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Special Reports

Narrative Medicine

Review Articles

Commentary

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Winter 2018/ Volume 22 No. 1

The Permanente Journal

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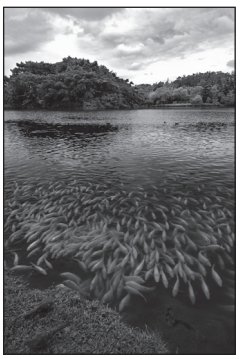

Koi Pond at Ho'omaluhia
photograph
By Jae Lim, MD, PhD

This photograph was taken at Ho'omaluhia Botanical Garden in Kaneohe, Oahu, HI. The 400-acre park boasts hiking trails, freshwater lakes and streams, and a campground.

Dr Lim is an Otolaryngologist for the Hawaii Permanente Medical Group. He is passionate about exploring and photographing the natural beauty of Hawaii. More of his work can be seen at www.lim-photography.com.

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TABLE OF CONTENTS

ORIGINAL RESEARCH & CONTRIBUTIONS

CME credits are available online at www.tpjcme.org. The mail-in CME form can be found on page 112.

ONLINE

Content available at:
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Impact of Asynchronous Training on Radiology Learning Curve among Emergency Medicine Residents and Clerkship Students.
Ali Pourmand, MD, MPH, RDMS; Christina Woodward, MD; Hamid Shokoohi, MD, MPH, RDMS; Jordan B King, PharmD, MS; M Reza Taheri, MD, PhD; Jackson King; Christopher Lawrence

A total of 131 Emergency Medicine clerkship students and 32 Emergency Medicine residents were enrolled in a Web-based learning module. There was a significant improvement in percentage of correctly classified computed tomography images after the training intervention. Among subsets by training level, all subgroups, except first-year residents, demonstrated a statistically significant increase in scores after the training.

Assessment of Pharmacy Department Patient Safety Culture with the Use of Validated Work Environment Survey Indices. Julia E Rawlings, PharmD; Sheryl J Herner, PharmD, MHSA; Thomas Delate, PhD, MS; Kelsey E Palmer, PharmD; Kelly A Swartzendruber, PharmD

This survey was conducted online in an ambulatory Pharmacy Department; 429 of 900 staff participated in an integrated health care delivery system. Although health care system personnel may prefer to measure patient safety culture with a survey instrument that assesses a variety of workplace environment measures, these findings suggest that use of nonvalidated work environment indices will not provide accurate assessment of patient safety culture in a Pharmacy Department.

A Randomized Controlled Trial of Financial Incentives for Medicaid Beneficiaries with Diabetes.
Ritabelle Fernandes, MD, MPH; Chuan C Chinn, PhD; Dongmei Li, PhD; Timothy B Frankland, MA; Christina MB Wang, MPH, RN; Myra D Smith, MPH; Rebecca Rude Ozaki, PhD

This study was conducted at Kaiser Permanente Hawaii with 320 participants (159 intervention group/161 control group). Participants could earn up to $320/y in financial incentives. Evaluation measures included 1) clinical outcomes of change in hemoglobin A_{1C}, blood pressure, and cholesterol; 2) compliance with American Diabetes Association standards; 3) cost-effectiveness; 4) quality of life; 5) self-management activities; and 6) satisfaction with incentives. Overall, this study found no conclusive evidence that financial incentives alone had beneficial effects on improving standards of medical care in diabetes.

SPECIAL REPORTS

NARRATIVE MEDICINE

REVIEW ARTICLES

SOUL OF THE HEALER

Contents continued on next page.

Contents continued from previous page.

CASE REPORTS

NARRATIVE MEDICINE

COMMENTARY

EDITORIAL

ADDITIONAL ONLINE

More content is available at: www.thepermanentejournal.org.

IMAGE DIAGNOSIS

NARRATIVE MEDICINE

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A Simple Model for Predicting Two-Year Risk of Diabetes Development in Individuals with Prediabetes

Harry Glauber, MD; William M Vollmer, PhD; Gregory A Nichols, PhD

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E-pub:12/28/2017

https://doi.org/10.7812/TPP/17-050

ABSTRACT

Context: Given the dramatic rise in the incidence of type 2 diabetes mellitus (T2DM) in recent decades, identifying individuals at increased risk of T2DM and validating methods to reduce their risk of disease progression is important. With more than one-third of US adults having prediabetes, a more precise stratification of absolute risk of T2DM incidence would help in prioritizing prevention efforts.

Objective: To develop a simple and clinically useful schema to stratify short-term (2-year) absolute risk of T2DM.

Design: Observational study of more than 77,000 adult members (age 18-75 years) from 3 Regions of the Kaiser Foundation Health Plan with prediabetes (hemoglobin A_{1C} [HbA_{1C}] = 5.7%-6.4%).

Main Outcome Measures: The 2-year probability for development of diabetes as a function of baseline HbA_{1C} and body mass index (BMI).

Results: The 2-year risk of diabetes diagnosis varied widely by HbA_{1C} and BMI. A small subset (5.2%) had a very high risk of T2DM developing within 2 years. Another 13.3% had a moderate 2-year risk of T2DM, whereas most (81.5%) of the population was at much lower risk. Thus, most Kaiser Foundation Health Plan members with prediabetes have only modest risk of progression to T2DM within 2 years.

Conclusion: Using HbA_{1C} and BMI, we created a simple stratification scheme to more precisely estimate risk of T2DM incidence. This will enable more efficient assignment of prevention interventions and clinical and laboratory follow-up to the small subset at highest risk, while minimizing the potentially negative effects of overdiagnosis among the majority with prediabetes who are not at high short-term risk of T2DM.

INTRODUCTION

In recent decades we have seen a dramatic increase in worldwide incidence and prevalence of type 2 diabetes mellitus (T2DM), particularly in low- and middle-income countries.[1] Diabetes currently affects 29 million people in the US—about 9% of the population—with a predicted increase to 30% by 2050,[2] although more recent data suggest that the growth in incidence has been slowing since 2009.[3] In 2010, diabetes was the seventh leading cause of death in the US, and in 2012 estimated diabetes costs in the US were $245 billion: $176 billion for direct medical costs and another $69 billion for indirect costs related to disability, work loss, and premature death.[4]

In response to these trends, much work has been conducted to identify individuals at increased risk of development of T2DM, and to intervene to prevent or delay this progression. This has led to the recognition of a dysglycemic state ("prediabetes") between normal glucose tolerance and T2DM. The Centers for Disease Control and Prevention[4] estimates that 37% of US adults aged 20 years and older with prediabetes are at increased risk of diabetes development. Prediabetes may be identified as a hemoglobin A_{1C} (HbA_{1C}) of 5.7% to 6.4%, a fasting plasma glucose level of 100 mg/dL to 125 mg/dL (impaired fasting glucose), or a plasma glucose level of 140 mg/dL to 199 mg/dL 2 hours after an oral glucose challenge (impaired glucose tolerance).[5] The HbA_{1C} test is increasingly being used to screen for the presence of T2DM or increased risk of T2DM because of improved standardization of the HbA_{1C} test, the increasing availability of rapid point-of-care testing, and the convenience of a nonfasting blood test.[6]

Fortunately, studies have shown that for many individuals with prediabetes, progression to T2DM may be prevented or delayed through improved diet, increased physical activity, and modest weight loss.[7-9] The lifestyle program tested in the Diabetes Prevention Program (DPP) study prevented or delayed almost 60% of new cases of T2DM in adults with prediabetes.[9] Recently published long-term outcomes of the DPP confirm a sustained effect of improved diet and physical activity to reduce progression to T2DM over 15 years.[10] Medication (metformin) can also reduce the incidence of T2DM (by 31% in the DPP study) and may be an attractive option for some patients.[11]

The sheer size of the at-risk population, however, is daunting—as many as 86 million people in the US have prediabetes.[12] Although several studies have indicated that diabetes prevention efforts such as those tested in the DPP are cost-effective,[13] the benefits of interventions are maximized when those efforts are targeted at the highest risk subset of the total prediabetes population.[14-17] In the prediabetic group, there is likely to be a spectrum of risk. Indeed, a recent article in the *British Medical Journal*[18] raised concerns about diagnosis creep, suggesting that we may be overdiagnosing prediabetes, and supporting differential

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intensity of prevention efforts focused on the subset at highest risk. A simple algorithm for stratifying the risk of progression to diabetes would allow for more efficient allocation of limited prevention resources, with individuals at highest risk receiving more intensive outreach and follow-up than those at lower risk.

We also know that not all people identified with prediabetes progress to T2DM. The long-term DPP outcomes data show that approximately 50% of subjects in the control group remained free of diabetes after 15 years. This is likely to be more common for those currently identified with prediabetes using the expanded range of HbA_{1C} of 5.7% to 6.4% vs 6.0% to 6.4%, because the DPP used a more stringent criterion to identify diabetes risk.

Nevertheless, substantial anxiety and increased utilization of medical resources may follow the identification of prediabetes. Although increased relative risk of diabetes incidence is typically reported, *absolute risk of diabetes development* may be more useful and actionable information for patients as well as for medical professionals.

We describe the development and validation of a simple algorithm for classification of absolute risk of progression to T2DM among individuals with prediabetes who were members of a large managed care organization in three different geographic regions of the US.

METHODS

This work was initially carried out as part of ongoing quality improvement efforts and was subsequently expanded under the Health Insurance Portability and Accountability Act (HIPAA) preparatory to research work for a research grant application. We subsequently applied for and received approval from the Kaiser Permanente (KP) Northwest (KPNW) institutional review board to publish these findings. Patient-level data were anonymized and deidentified before analysis.

Setting and Study Population

We carried out our study in 3 Regions of the KP Medical Care Program: KPNW, Hawaii (KPHI), and Georgia (KPGA). KP is a federally qualified, prepaid group-model integrated Health Plan. Currently, KPNW provides medical care to approximately 545,000 primarily white members in northwest Oregon and southwest Washington. The KPHI membership includes approximately 248,000 individuals: About 27% whites, 33% Asians, 12% native Hawaiians or Pacific Islanders, 24% of mixed heritage, about 1% combined American Indian/Alaska Native and Black or African American, and 3% unknown or not reported. Finally, KPGA provides care to approximately 295,000 members in the metropolitan Atlanta area. The membership is racially and socioeconomically similar to the surrounding geographic region: approximately 50% white, 45% African American, 4% Hispanic, and 1% other races and ethnicities.

Our analysis focused on KP members with HbA_{1C} levels between 5.7% and 6.4%. We focused solely on HbA_{1C} because, as noted earlier, it is becoming a commonly accepted test for classifying prediabetes and is likely to be more acceptable to patients as part of a large-scale screening program. A scheme based on use of HbA_{1C} would allow for immediate risk stratification without the need for patients to return for testing in a fasting state.

Development of Risk Index

Our risk classification system was originally developed as part of ongoing disease management efforts in KPNW. We selected patients with any HbA_{1C} measurement in 2011 that fell between 5.7% and 6.4%, using the first such value if multiple values were available as the index date. To ensure these patients did not already have a diagnosis of diabetes, we required 1 year of pre-index date eligibility with no indication of diabetes (diagnosis in the electronic medical record [EMR], use of an antihyperglycemic drug, or a laboratory value above diagnostic thresholds). Body mass index (BMI) was calculated using the mean of all height and weight values recorded in 2011. We assessed risk of development of diabetes for 1 year after the index HbA_{1C} value.

Validation of Risk Index

The initial risk index was refined and validated as part of the development of a diabetes prevention research proposal involving KPHI and KPGA as well as KPNW. We assessed the initial risk classification described earlier using data from all three KP Regions to determine the consistency of the risk strata, and then used this expanded dataset to develop final classification rules and corresponding risk levels associated with them.

Unlike the initial development work, which focused on 1-year diabetes risk, we calculated 2-year diabetes incidence and used this to estimate the 2-year risk (probability) of diabetes developing. This was done to be consistent with the proposed outcome of a study assessing the impact of diabetes prevention interventions. We also took a more pragmatic approach to defining the base population that reflected the screening guidelines we proposed to use for that study. Specifically, we classified an individual's prediabetes status using his or her most recent HbA_{1C} measurement in the previous 3 years, and we relied solely on a diabetes diagnosis code in the EMR to rule out diabetes in defining the at-risk cohort and in determining subsequent incidence of new diabetes. A single diagnosis code for diabetes can yield a positive predictive value of 86% to 95%.[19,20] Furthermore, we believe this is a realistic paradigm for how screening and risk classification might be done in the real world, and hence believe this gives added validity to our findings. Finally, whereas the initial development work looked at individuals aged 10 to 75 years, our validation work focused on adults, using a lower age limit of 18 years.

Statistical Methods

We calculated prospective risk from two perspectives, and for each perspective calculated two-year risk as defined here.

For what we term the *cross-sectional perspective*, we defined an at-risk population as of a given point in time and then followed individuals forward for 2 years to determine diabetes incidence. To evaluate 2-year incidence, we defined our starting population as KP members without diabetes as of January 1, 2012, and looked back 3 years from this date (2009-2011) to find the most recent HbA_{1C} measurement and BMI for purposes of

risk classification. We then followed each person forward in time from January 1, 2012, for up to 24 months. We defined length of follow-up as minimum of time to first diagnosis of diabetes or time to loss of Health Plan coverage, then computed the incidence rate as 100 × (total number of new cases of diabetes) ÷ (total person-years of follow-up). This is equivalent to the number of new cases per 100 person-years of follow-up. We then doubled the latter figure to estimate the number of new cases per 100 persons per 2 years of follow-up (ie, the cumulative 2-year incidence).

For what we term the *longitudinal perspective*, we defined our population not on the basis of a single fixed time point, but rather on the date of individuals' most recent HbA_{1C} measurement or BMI, and then followed individuals forward in time accordingly. That is, we still classified individuals on the basis of their most recent HbA_{1C} and BMI levels in the 3 years from 2009 to 2011, but we measured their 24-month follow-up from the date of the most recent HbA_{1C} level.

Finally, for each of these 2 approaches we estimated the absolute risk (ie, 2-year probability) of development of diabetes as $1 - e^{-H(2)}$, where H(2) is the cumulative 2-year incidence calculated as just described. Because not everyone had complete follow-up, the risks estimated in this manner tend to be somewhat larger than the observed proportions of individuals in whom diabetes actually developed over these same time frames.

RESULTS

Table 1 shows the results of the initial development work for the risk index. A total of 45,620 individuals aged 10 to 75 years with HbA_{1C} between 5.7% and 6.4% were cross-classified by BMI, and 1-year T2DM incidence probabilities were calculated. On the basis of these data, 3 risk strata (low, moderate, and high) were proposed. The BMI could not be calculated for a small proportion of members, usually because of absence of a measured weight in the EMR.

Table 2 shows the corresponding 2-year validation data for each of the 3 participating KP Regions separately and overall using the longitudinal perspective. The

Table 1. One-year probability (%) of diabetes developing, from initial development work[a]

	Body mass index, kg/m²				
Hemoglobin A_{1C}	Missing	< 25	25-30	30-35	≥ 36
5.7-5.8	0	0.1	0.1	0.1	0.4
5.9-6.0	0.5	0.4	0.4	0.9	1.4
6.1-6.2	1.8	0.8	1.9	3.2	4.3
6.3-6.4	6.4	6.7	12.6	12.5	15.7

[a] Estimates are based on data from 45,620 Kaiser Permanente Northwest members aged 10 to 75 years. No shading = low risk; gray shading = moderate risk; black shading = high risk.

Table 2. Two-year probability (%) of diabetes developing, longitudinal perspective[a]

		Body mass index,[b] kg/m²				
KP Region	HbA_{1C}	Missing	< 25	25-30	31-35	≥ 36
Northwest (n = 36,915)	5.7-5.8	0.8	0.6	0.5	0.9	2.0
	5.9-6.0	1.3	0.6	1.4	2.5	4.2
	6.1-6.2	7.6	2.4	3.4	6.9	9.3
	6.3-6.4	19.9	11.5	13.8	18.5	24.1
Hawaii (n = 31,906)	5.7-5.8	0.4	0.2	0.4	1.0	1.7
	5.9-6.0	1.1	0.8	1.0	1.5	3.1
	6.1-6.2	2.4	2.3	3.9	4.2	7.8
	6.3-6.4	8.6	4.9	7.9	11.5	15.5
Georgia (n = 8286)	5.7-5.8	3.0	1.2	0.3	2.4	3.4
	5.9-6.0	4.1	2.3	3.4	4.3	6.1
	6.1-6.2	9.3	4.8	4.5	9.3	8.9
	6.3-6.4	16.0	16.3	13.2	17.2	19.1
Total (N = 77,107)	5.7-5.8	1.2	0.4	0.5	1.1	2.1
	5.9-6.0	2.0	0.8	1.4	2.3	4.1
	6.1-6.2	5.8	2.5	3.8	6.3	8.8
	6.3-6.4	12.7	7.9	10.8	15.6	20.7

[a] Two-year probability was estimated as $1 - e^{-H(2)}$, where H(2) is the cumulative 2-year incidence. Data are based on percentage of members with prediabetes aged 18 to 75 years. For corresponding numbers of members, see Table 3. No shading = low risk; gray shading = moderate risk; black shading = high risk.
[b] Body mass index was rounded to the nearest whole number.
HbA_{1C} = hemoglobin A_{1C}; KP = Kaiser Permanente.

Table 3. Cell sizes for corresponding data in Table 2

		Body mass index,[a] kg/m²				
KP Region	HbA_{1C}	Missing	< 25	25-30	31-35	≥ 36
Northwest (n = 36,915)	5.7-5.8	312	2685	5964	3675	3515
	5.9-6.0	204	1539	3987	2921	3005
	6.1-6.2	125	605	1937	1659	1840
	6.3-6.4	49	218	843	754	1078
Hawaii (n = 31,906)	5.7-5.8	642	3458	4896	2107	1604
	5.9-6.0	508	2411	3806	1836	1510
	6.1-6.2	273	1192	2268	1215	1118
	6.3-6.4	185	462	1101	657	657
Georgia (n = 8286)	5.7-5.8	379	456	984	714	675
	5.9-6.0	293	240	780	522	647
	6.1-6.2	185	138	459	455	409
	6.3-6.4	109	63	266	219	293
Total (N= 77,107)	5.7-5.8	1333	6599	11844	6496	5794
	5.9-6.0	1005	4190	8573	5279	5162
	6.1-6.2	583	1935	4664	3329	3367
	6.3-6.4	343	743	2210	1630	2028

[a] Body mass index was rounded to nearest whole number.
HbA_{1C} = hemoglobin A_{1C}; KP = Kaiser Permanente.

corresponding number of subjects in each cell is shown in Table 3. The overall data are also shown in Figure 1. Corresponding data based on the cross-sectional perspective are included in Table 4. Collectively, Table 2 and Figure 1 represent data on more than 77,000 individuals. The risk strata suggested by each Region's data were more similar than dissimilar, although absolute levels of risk varied modestly from Region to Region. With a single exception, individuals whose HbA_{1C} value was 6.0% or less, as well as those with HbA_{1C} levels of 6.1% to 6.2% and BMI below 30 kg/m^2, consistently defined a low-risk category; those with HbA_{1C} of 6.1% to 6.2% and BMI of 30 kg/m^2 or higher were consistently classified as moderate risk; and those with HbA_{1C} of 6.3% to 6.4% and BMI of 30 kg/m^2 or higher were consistently classified as high risk. The remaining cells were generally classified as either moderate or high risk.

Table 5 shows, using the risk strata defined for the pooled sample at the bottom of Table 2, the proportion of individuals falling into each risk stratum and the associated 2-year risk of developing diabetes. Under this schema, 5.2% of the pooled sample is defined to be at high risk, with an estimated 2-year probability of diabetes development of 18.0%; 13.3% of the sample is defined to be at moderate risk, with a 2-year probability of development of diabetes of 8.2%; and 81.5% of the sample is defined to be at low risk, with a 2-year probability of diabetes development of just 1.6%.

Table 4. Two-year probability of diabetes developing, cross-sectional perspective[a]

KP Region	HbA_{1C}	Body mass index,[b] kg/m^2 (%)				
		Missing	< 25	25-30	31-35	≥ 36
Northwest (n = 36,915)	5.7-5.8	0.5	0.6	0.5	0.9	1.9
	5.9-6.0	1.5	0.7	1.3	2.4	4.2
	6.1-6.2	8.4	2.3	3.2	7.2	9.7
	6.3-6.4	16.7	12.3	14.4	18.9	25.1
Hawaii (n = 31,906)	5.7-5.8	0.5	0.2	0.4	0.9	1.7
	5.9-6.0	1.3	0.8	0.9	1.5	3.3
	6.1-6.2	1.7	1.9	3.8	4.2	8.0
	6.3-6.4	5.6	4.9	7.9	11.4	15.8
Georgia (n = 8286)	5.7-5.8	2.4	1.2	0.4	2.3	3.7
	5.9-6.0	4.7	2.5	3.6	4.5	6.0
	6.1-6.2	9.7	5.1	4.5	9.0	8.8
	6.3-6.4	12.9	15.7	14.0	17.2	20.9
Total (N = 77,107)	5.7-5.8	1.0	0.4	0.5	1.1	2.0
	5.9-6.0	2.3	0.8	1.3	2.3	4.2
	6.1-6.2	5.8	2.3	3.6	6.4	9.0
	6.3-6.4	9.6	8.1	11.2	15.7	21.6

[a] Two-year probability estimated as $1\text{-}e^{-H(2)}$, where H(2) is the cumulative 2-year incidence. Data are based on percentage of members with prediabetes aged 18 to 75 years. No shading = low risk; gray shading = moderate risk; and black shading = high risk.

[b] Body mass index was rounded to the nearest whole number.

HbA_{1C} = hemoglobin A_{1C}; KP = Kaiser Permanente.

DISCUSSION

The dramatic worldwide rise in incidence and prevalence of T2DM in recent decades has resulted in increased attention to prevention. Several studies have demonstrated the ability of lifestyle or medication interventions to prevent or delay the development of diabetes. Although cost-effective, such interventions are resource intensive and have limited effectiveness, which has led some to decry widespread population-level T2DM prevention efforts.[18] Diagnosing as many as one-third of the population as having prediabetes may not be useful if the resources to manage their diabetes risk are not available. Our results, summarized in Figure 1 and Table 5, indicate that in the category of prediabetes, there is a wide range of short-term risk of progression to incident T2DM, highlighting the importance of being able to more precisely estimate absolute risk of diabetes onset, and allowing for simple identification of the subset of patients at the greatest risk of progression.

Risk of T2DM is related to numerous clinical, historical, biochemical, genomic, metabolomic, and lifestyle factors.[21] Several predictive models have been proposed, but, to our knowledge, none are currently used in clinical practice. This may be because model performance when applied to alternative populations is poor.[22] The Framingham Offspring Study developed a relatively simple clinical model using only age, sex, parental history of diabetes, BMI, and levels of high-density lipoprotein cholesterol, triglycerides, and fasting plasma glucose to produce an area under the receiver operating characteristic curve of 0.852,[23] a model that was subsequently validated in KPNW (area under the curve = 0.824).[24] However, that model predated the use of HbA_{1C} as a diagnostic test and hence requires for its use fasting laboratory values that may not be available at the point of care. This, in turn, limits the model's utility for day-to-day clinical use. Patients, physicians, health plans, and public health agencies seeking more readily available and simpler ways of placing individuals with prediabetes along the spectrum of risk of diabetes onset may find our results useful.

Table 5. Two-year probability of diabetes developing, by risk strata, for individuals with prediabetes aged 18 to 75 years[a]

Risk stratum	No. (% of sample)	Probability of diabetes developing, %
Low	62,874 (81.5)	1.6
Moderate	10,232 (13.3)	8.2
High	4001 (5.2)	18.0
Total	77,107 (100.0)	

[a] The categorization shown in Table 5 matches that from Table 2. No shading = low risk; gray shading = moderate risk; black shading = high risk.

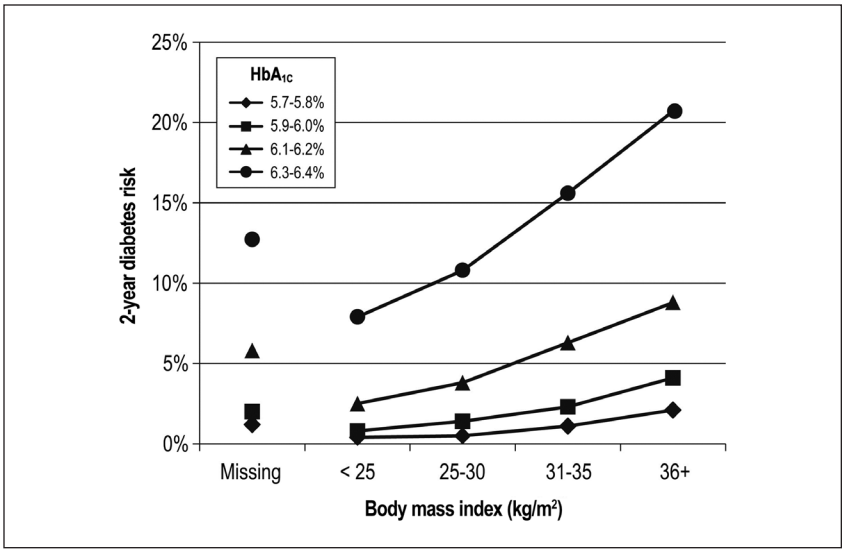

Figure 1. Two-year probability for progression from prediabetes to type 2 diabetes on the basis of hemoglobin A_{1C} (HbA_{1C}) and body mass index for 77,107 members, aged 18 to 75 years, of Kaiser Permanente Northwest, Hawaii, and Georgia.

CONCLUSION

With the increasingly widespread use of the HbA_{1C} test in the US to screen for T2DM,[6] a growing number of people are being recognized as having prediabetes (HbA_{1C} level = 5.7%-6.4%). Obesity, as assessed by BMI, is an additional readily available and important predictor of risk of incident T2DM. Using observational data from 3 demographically different Regions of KP, we have combined HbA_{1C} and BMI into a simple risk model to more precisely classify 2-year absolute risk of progression to T2DM that ranges from less than 0.5% for those with an HbA_{1C} of 5.7% to 5.8% who are not obese, to more than 20% in those with an HbA_{1C} of 6.3% to 6.4% who are obese. On the basis of this categorization of patients representing all age, sex, and race/ethnicities, only about 5% of individuals with prediabetes are at greater than 10% risk of diabetes developing in the next 2 years, whereas more than 80% are at much lower risk of T2DM (< 2%).

With a lifetime risk of occurrence of 40% in the US,[25] diabetes mellitus is a major public health problem that directly or indirectly affects the lives of nearly all Americans, as well as increasing numbers of people in low- and middle-income countries.[1] Lifestyle interventions can successfully delay or prevent onset of T2DM, but the cost-effectiveness of such programs is likely to depend on risk stratification that directs limited resources to the patients at greatest immediate risk.[16] The case has been made for use of HbA_{1C} as a diagnostic tool and risk stratifier.[26,27] Our additional use of BMI provides an enhanced estimator of short-term diabetes risk that is easy to implement and can intelligently inform targeted diabetes prevention efforts. Use of these prediction tables would be analogous to use of the FRAX (Fracture Risk Assessment Tool) model[28] to assess 10-year risk of osteoporotic fracture, or use of tools such as the Framingham Risk Score or the American Heart Association calculator to assess risk of cardiovascular events.[29] When a patient and his/her clinician have an idea of the absolute risk of the clinical event, in this case progressing from the prediabetic to the diabetic states, shared decision making regarding benefits, risks, cost, and indications for interventions is helped.

This simple approach of using readily available clinical (BMI) and laboratory (HbA_{1C}) measures to stratify risk of progression from prediabetes to diabetes mellitus could reduce anxiety as well as the intensity of interventions and follow-up laboratory testing for most individuals with prediabetes (ie, those in our low-risk group). At the same time, this approach could allow increased intensity of lifestyle change interventions and medication use and frequency of HbA_{1C} monitoring for the much smaller number of individuals in the high-risk group. Given the wide variation in diabetes incident rates among age, sex, and race/ethnicity categories,[6] refinements of this approach by studying the impact of these characteristics would be valuable, as would be longer-term and confirmatory studies in a range of populations. ❖

Disclosure Statement

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References

1. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes since 1980: A pooled analysis of 751 population-based studies with 4.4 million participants. Lancet 2016 Apr 9;387(10027):1513-30. DOI: https://doi.org/10.1016/s0140-6736(16)00618-8.
2. Boyle JP, Thompson TJ, Gregg EW, Barker LE, Williamson DF. Projection of the year 2050 burden of diabetes in the US adult population: Dynamic modeling of incidence, mortality, and prediabetes prevalence. Popul Health Metr 2010 Oct 22;8:29. DOI: https://doi.org/10.1186/1478-7954-8-29.
3. Diagnosed diabetes [Internet]. Atlanta, GA: Centers for Disease Control and Prevention (CDC); 2015 [cited 2017 Oct 3]. Available from: https://gis.cdc.gov/grasp/diabetes/DiabetesAtlas.html.
4. Centers for Disease Control and Prevention (CDC). National Diabetes Statistics Report, 2014: Estimates of diabetes and its burden in the United States [Internet]. Atlanta, GA: US Department of Health and Human Services; 2014 [cited 2017 Sep 1]. Available from: https://stacks.cdc.gov/view/cdc/23442.
5. American Diabetes Association. (2) Classification and diagnosis of diabetes. Diabetes Care 2015 Jan;38 Suppl:S8-S16. DOI: https://doi.org/10.2337/dc15-S005.

6. Nichols GA, Schroeder EB, Karter AJ, et al; SUPREME-DM Study Group. Trends in diabetes incidence among 7 million insured adults, 2006-2011: The SUPREME-DM project. Am J Epidemiol 2015 Jan 1;181(1):32-9. DOI: https://doi.org/10.1093/aje/kwu255.
7. Pan XR, Li GW, Hu YH, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. Diabetes Care 1997 Apr;20(4):537-44. DOI: https://doi.org/10.2337/diacare.20.4.537.
8. Tuomilehto J, Lindström J, Eriksson JG, et al; Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001 May 3;344(18):1343-50. DOI: https://doi.org/10.1056/NEJM200105033441801.
9. Knowler WC, Barrett-Connor E, Fowler SE, et al; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002 Feb 7;346(6):393-403. DOI: https://doi.org/10.1056/nejmoa012512.
10. Diabetes Prevention Program Research Group. Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: The Diabetes Prevention Program Outcomes Study. Lancet Diabetes Endocrinol 2015 Nov;3(11):866-75. DOI: https://doi.org/10.1016/s2213-8587(15)00291-0.
11. American Diabetes Association. Standards of medical care in diabetes—2014. Diabetes Care 2014 Jan;37 Suppl 1:S14-80. DOI: https://doi.org/10.2337/dc14-s014.
12. Cowie CC, Rust KF, Ford ES, et al. Full accounting of diabetes and pre-diabetes in the US population in 1988-1994 and 2005-2006. Diabetes Care 2009 Feb;32(2):287-94. DOI: https://doi.org/10.2337/dc08-1296.
13. Li R, Qu S, Zhang P, et al. Economic evaluation of combined diet and physical activity promotion programs to prevent type 2 diabetes among persons at increased risk: A systematic review for the Community Preventive Services Task Force. Ann Intern Med 2015 Sep 15;163(6):452-60. DOI: https://doi.org/10.7326/m15-0469.
14. Diabetes Prevention Program Research Group. The 10-year cost-effectiveness of lifestyle intervention or metformin for diabetes prevention: An intent-to-treat analysis of the DPP/DPPOS. Diabetes Care 2012 Apr;35(4):723-30. DOI: https://doi.org/10.2337/dc13-er12c.
15. Zhuo X, Zhang P, Kahn HS, Gregg EW. Cost-effectiveness of alternative thresholds of the fasting plasma glucose test to identify the target population for type 2 diabetes prevention in adults aged ≥ 45 years. Diabetes Care 2013 Dec;36(12):3992-8. DOI: https://doi.org/10.2337/dc13-0497.
16. Zhuo X, Zhang P, Selvin E, et al. Alternative HbA_{1C} cutoffs to identify high-risk adults for diabetes prevention: A cost-effectiveness perspective. Am J Prev Med 2012 Apr;42(4):374-81. DOI: https://doi.org/10.1016/j.amepre.2012.01.003.
17. Kahn R, Alperin P, Eddy D, et al. Age at initiation and frequency of screening to detect type 2 diabetes: A cost-effectiveness analysis. Lancet 2010 Apr 17;375(9723):1365-74. DOI: https://doi.org/10.1016/s0140-6736(09)62162-0.
18. Yudkin JS, Montori VM. The epidemic of pre-diabetes: The medicine and the politics. BMJ 2014 Jul 15;349:g4485. DOI: https://doi.org/10.1136/bmj.g4485. Erratum in: BMJ 2014;349:g4683. DOI: https://doi.org/10.1136/bmj.g4683.
19. Miller DR, Safford MM, Pogach LM. Who has diabetes? Best estimates of diabetes prevalence in the Department of Veterans Affairs based on computerized patient data. Diabetes Care 2004 May;27 Suppl 2:B10-21. DOI: https://doi.org/10.2337/diacare.27.suppl_2.b10.
20. Zgibor JC, Orchard TJ, Saul M, et al. Developing and validating a diabetes database in a large health system. Diabetes Res Clin Pract 2007 Mar;75(3):313-9. DOI: https://doi.org/10.1016/j.diabres.2006.07.007.
21. Glauber H, Karnieli E. Preventing type 2 diabetes mellitus: A call for personalized intervention. Perm J 2013 Summer;17(3):74-9. DOI: https://doi.org/10.7812/TPP/12-143.
22. Tanamas SK, Magliano DJ, Balkau B, et al. The performance of diabetes risk prediction models in new populations: The role of ethnicity of the development cohort. Acta Diabetol 2015 Feb;52(1):91-101. DOI: https://doi.org/10.1007/s00592-014-0607-x.
23. Wilson PW, Meigs JB, Sullivan L, Fox CS, Nathan DM, D'Agostino RB Sr. Prediction of incident diabetes mellitus in middle-aged adults: The Framingham Offspring Study. Arch Intern Med 2007 May 28;167(10):1068-74. DOI: https://doi.org/10.1001/archinte.167.10.1068.
24. Nichols GA, Brown JB. Validating the Framingham Offspring Study equations for predicting incident diabetes mellitus. Am J Manag Care 2008 Sep;14(9):574-80.
25. Gregg EW, Zhuo X, Cheng YJ, Albright AL, Narayan KM, Thompson TJ. Trends in lifetime risk and years of life lost due to diabetes in the USA, 1985-2011: A modelling study. Lancet Diabetes Endocrinol 2014 Nov;2(11):867-74. DOI: https://doi.org/10.1016/s2213-8587(14)70161-5.
26. International Expert Committee. International Expert Committee report on the role of the A_{1C} assay in the diagnosis of diabetes. Diabetes Care 2009 Jul;32(7):1327-34. DOI: https://doi.org/10.2337/dc09-9033.
27. Gregg EW, Geiss L, Zhang P, Zhuo X, Williamson DF, Albright AL. Implications of risk stratification for diabetes prevention: The case of hemoglobin A1c. Am J Prev Med 2013 Apr;44(4 Suppl 4):S375-80. DOI: https://doi.org/10.1016/j.amepre.2012.12.012.
28. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. FRAX and the assessment of fracture probability in men and women from the UK. Osteoporos Int 2008 Apr;19(4):385-97. DOI: https://doi.org/10.1007/s00198-007-0543-5.
29. Goff DC Jr, Lloyd-Jones DM, Bennett G, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014 Jun 24;129(25 Suppl 2):S49-73. DOI: https://doi.org/10.1161/01.cir.0000437741.48606.98. Erratum in: Circulation 2014 Jun 24;129(25 Suppl 2):S74-5. DOI: https://doi.org/10.1161/CIR.0000000000000067.

Die Young Late

Clearly, if disease is man-made, then it can be man prevented.
It should be the function of medicine to help people die young as late in life as possible.

Ernst Wynder, MD, 1922-1999, American epidemiologist and public health researcher

Association of Proteinuria with Central Venous Catheter Use at Initial Hemodialysis

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ABSTRACT

Context: Central venous catheter (CVC) use is associated with increased mortality and complications in hemodialysis recipients. Although prevalent CVC use has decreased, incident use remains high.

Objective: To examine characteristics associated with CVC use at initial dialysis, specifically looking at proteinuria as a predictor of interest.

Design: Retrospective cohort of 918 hemodialysis recipients from Kaiser Permanente Northwest who started hemodialysis from January 1, 2004, to January 1, 2014.

Main Outcome Measures: Multivariable logistic regression was used to examine an association of proteinuria with the primary outcome of CVC use.

Results: More than one-third (36%) of patients in our cohort started hemodialysis with an arteriovenous fistula, and 64% started with a CVC. Proteinuria was associated with starting hemodialysis with a CVC (likelihood ratio test, $p < 0.001$) after adjustment for age, peripheral vascular disease, congestive heart failure, diabetes, sex, race, and length of predialysis care. However, on pairwise comparison, only patients with midgrade proteinuria (0.5-3.5 g) had lower odds of starting hemodialysis with a CVC (odds ratio = 0.39, 95% confidence interval = 0.24-0.65).

Conclusion: Proteinuria was associated with use of CVC at initial hemodialysis. However, a graded association did not exist, and only patients with midgrade proteinuria had significantly lower odds of CVC use. Our findings suggest that proteinuria is an explanatory finding for CVC use but may not have pragmatic value for decision making. Patients with lower levels of proteinuria may have a higher risk of starting dialysis with a CVC.

INTRODUCTION

Patients with end-stage renal disease (ESRD) have a mortality rate that is higher than that for cancer, heart disease, heart failure, or diabetes.[1] The 1-year mortality rate for patients with ESRD is estimated to be 17%.[1] One major reason for higher mortality rates in ESRD is the high rate of central venous catheter (CVC) use. Several studies have shown that patients who dialyze with a CVC have a 50% to 70% increased risk of dying compared with patients who dialyze with an arteriovenous fistula (AVF).[2-6] For this reason, several national initiatives have targeted increasing AVF use. The Fistula First campaign[7] was started in 2003 to increase AVF placement and to decrease use of CVCs to improve morbidity and mortality. Fistula First has been credited with a reduction in prevalent CVC use from 27.7% in 2007 to 16.3% in 2014.[1] However, despite reduction in prevalent CVC use, its use remains high at initial hemodialysis. This remains a concern because patients starting hemodialysis with CVCs have been shown to have a higher mortality and higher risk of sepsis.[5,8] One of the goals in Healthy People 2020,[9] a national initiative involving the US Department of Health and Human Services, is to increase use of AVF or presence of a maturing AVF at the start of hemodialysis to a target of 34.5%. Despite meeting Healthy People 2020 targets, more than 80% of patients with ESRD dialyze with CVCs at initial treatment.[1] Even with optimal predialysis care under the supervision of a nephrologist, about 50% of patients start dialysis with a CVC.[10] This statistic suggests that this is an area requiring further improvement.

Several factors have been found to be associated with CVC use at initial hemodialysis treatment, including elderly age,[11] black race,[4] female sex,[12,13] diabetes,[14] peripheral vascular disease,[14] late referrals to a nephrologist,[15] and cardiac disease.[4] Reasons for higher CVC use include rates of primary AVF failures (defined as an AVF that is never usable) of between 20% and 50%[16] and delayed AVF placement.[11] Elderly age, peripheral vascular disease, and coronary artery disease have been associated with primary AVF failures.[17,18] Older age, black race, female sex, and shorter pre-ESRD nephrology care have been associated with delayed AVF placement.[19]

Proteinuria has been shown to be associated with mortality and progression of chronic kidney disease (CKD).[20] In addition, after AVF placement, patients with proteinuria had a higher likelihood of AVF use[21] or initiation of hemodialysis.[22] However, to the best of our knowledge, the association of proteinuria with CVC use at initial hemodialysis has not been examined. The aim of this study was to look at factors associated with CVC use at time of dialysis initiation specifically looking at proteinuria as a primary variable of interest. Our hypothesis was that higher grades of proteinuria were associated with higher rates of CVC use at initial hemodialysis. Proteinuria may be helpful in identifying patients who may benefit from earlier referral for AVF placement or closer monitoring for failure of an AVF to mature after placement, to decrease the rate of CVC use at initial hemodialysis.

METHODS

Study Population

We created a retrospective cohort from the Kaiser Permanente Northwest (KPNW) dialysis registry, a large integrated health care system with approximately 500,000 members in Oregon and

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Washington. Eligible patients were adults aged 18 years or older who started hemodialysis from January 1, 2004, to January 1, 2014. Patients were excluded if they recovered renal function, started dialysis with an arteriovenous graft, had a peritoneal dialysis catheter present, had less than 6 months of continuous membership at KPNW, or had transferred to KPNW with a previous diagnosis of ESRD. Variables were obtained through review of electronic health records and databases that included outpatient laboratory values. This study was reviewed and approved by the institutional review board of KPNW and conducted in accordance with the ethical standards laid down in the Declaration of Helsinki.

Primary Outcome

Our primary outcome was the use of CVC at initial hemodialysis. This was obtained through chart review of vascular surgery notes in the electronic health record. Use of CVCs was defined as patients in which a CVC was used at first hemodialysis regardless of whether an AVF was present. Patients who started hemodialysis with an AVF but required placement of a CVC within 30 days were also included in this category. We chose to classify these patients in the CVC group on the basis of prior studies using successful cannulation of an AVF during a 30-day time frame to define successful use of an AVF.[17]

Predictors

Proteinuria was divided into 4 categories by the highest level of spot urine protein/creatinine ratio, urine albumin/creatinine ratio, or urinalysis noted according to KDIGO (Kidney Disease: Improving Global Outcomes) staging.[23] *Absent* (no proteinuria present) was defined as less than 0.2 g of protein per gram of creatinine, a urine albumin/creatinine ratio below 30 mg/g, or 0 on urinalysis; *low grade,* 0.2 to 0.5 g of protein per gram of creatinine, urine albumin/creatinine ratio of 30 to 300 mg/g, or 1+ on urinalysis; *midgrade,* 0.5 to 3.5 g of protein per gram of creatinine, urine albumin/creatinine ratio of 301 to 2200 mg/g, or 2+ or greater on urinalysis; and *high grade,* above 3.5 g of protein per gram of creatinine or urine albumin/creatinine ratio greater than 2200 mg/g.[23]

Other variables studied included presence of congestive heart failure, diabetes, peripheral vascular disease, history of acute kidney injury in the prior 2 years, sex, race, age at start of hemodialysis, length of predialysis care in months, and number of hospitalizations in the 2-year period before the start of hemodialysis. When race was missing or unknown (about 22% of the cohort), patients were labeled as white because this was the most common race among our members. Age was divided into categories of younger than 50 years, 50 to 70 years, and older than 70 years. Among patients who had an AVF present at the time of initial dialysis, variables recorded

Table 1. Baseline characteristics of patients with central venous catheter with arteriovenous fistula vs arteriovenous fistula at initial dialysis

Variable	CVC with immature AVF (n = 152)	AVF (n = 329)	p value[a]
Sex (men), %	50	62	0.03
Mean age, y	65.8	64.1	0.19
PVD, %	28.9	21.5	0.10
CHF, %	49	37.9	0.02
Diabetes, %	72.3	67.2	0.30
History of AKI, %	36.2	45	0.10
Hospitalizations, median no.	5.7	4.6	0.01
Proteinuria grade, %[b]			
Absent	13.1	7.5	0.10
Low grade	9.2	10.3	0.83
Midgrade	33.5	52.2	< 0.001
High grade	44.1	29.8	0.006
Race, %			
Asian	3.3	5.1	0.49
Black	7.8	8.8	0.87
White	87.5	83.3	0.29
Native American	1.3	2.7	0.52
Length of predialysis care, %			
None	—	—	—
0-6 mo	17.1	4.2	< 0.001
6-12 mo	11.8	8.5	0.43
12-24 mo	15.8	14.3	0.77
> 24 mo	55.2	72.9	< 0.001
AVF, %			
Radiocephalic location	13.8	15.5	0.73
Brachiocephalic location	69.1	76.6	0.15
Brachiobasilic location	15.8	7.0	0.01
Early start	38	41	0.32
Access revised	23	24	0.84
Timing of AVF placement, %			
0-3 mo	55.6	17	< 0.001
3-6 mo	13.1	19.8	0.15
6-9 mo	4.6	15.5	0.002
9-12 mo	5.3	8.2	0.33
12-24 mo	12.5	16.4	0.33
> 24 mo	9.8	23.1	0.002

[a] Unadjusted comparisons between AVF vs CVC with immature AVF group.

[b] Low grade was defined as urine protein/creatinine ratio 0.2 to 0.5, urine albumin/creatinine ratio of 30 to 300 mg/g, or 1+ on urinalysis; midgrade as urine protein/creatinine ratio of 0.5 to 3.5, urine albumin/creatinine ratio > 300 to 2200 mg/g, or 2+ or greater on urinalysis; and high grade as urine protein/creatinine ratio > 3.5 or urine albumin/creatinine ratio > 2200 mg/g.

AKI = acute kidney injury; AVF = arteriovenous fistula; CHF = congestive heart failure; CVC = central venous catheter; PVD = peripheral vascular disease.

included location of the AVF, whether the AVF was revised before dialysis (defined as requiring additional surgical or interventional procedures), and timing of AVF placement before initial dialysis. Location of the AVF was divided into radiocephalic, brachiocephalic, or brachiobasilic. Time of the AVF placement before the start of dialysis was divided into categories: 0 to 3 months, 3.1 to 6 months, 6.1 to 9 months, 9.1 to 12 months, 12.1 to 24 months, and greater than 24 months.

Estimated glomerular filtration rate (eGFR) was calculated using the CKD-Epidemiology Collaboration equation[24] after 2010 and by the Modification of Diet in Renal Disease equation[24] in 2010 and earlier. Last outpatient eGFR available within 31 days of dialysis initiation was recorded (available in 63.6% of the cohort). Patients were classified as "early start" of dialysis if the last recorded outpatient eGFR was greater than 10 mL/min. The eGFR at the time of AVF placement was available in 38% of patients with AVFs placed.

Table 2. Baseline characteristics of study cohort by access type at initial dialysis

Variable	Entire sample (N = 918)	CVC (n = 589)	AVF (n = 329)	p value[a]
Sex (men), %	59	57	62	0.10
Mean age, y	63.8	63.6	64.1	0.60
PVD, %	25.6	28	21.5	0.04
CHF, %	42.8	45	37.9	0.03
Diabetes, %	66.2	66	67.2	0.70
History of AKI, %	42.2	40	45	0.25
Hospitalizations, median no.	4.0	6.1	4.6	< 0.001
Proteinuria grade, %[b]				
Absent	11.5	13.7	7.5	0.009
Low grade	11.5	12.2	10.3	0.45
Midgrade	40.4	33.7	52.2	< 0.001
High grade	36.5	40.2	29.8	0.004
Race, %				
Asian	5.0	4.9	5.1	0.89
Black	8.1	7.6	8.8	0.63
White	84.3	84.9	83.3	0.52
Native American	2.6	2.5	2.7	0.86
Length of predialysis care, %				
None	9.5	14.9	NA	< 0.001
0-6 mo	12.4	17	4.2	< 0.001
6-12 mo	8.8	9	8.5	0.89
12-24 mo	13.3	12.7	14.3	0.72
> 24 mo	55.9	46.3	72.9	< 0.001
AVF, %				
Radiocephalic location	NA	NA	15.5	NA
Brachiocephalic location	NA	NA	76.6	NA
Brachiobasilic location	NA	NA	7.0	NA
Early dialysis start	37.3	35	41	0.13
Access revised	NA	NA	24	NA
Timing of AVF placement, %				
0-3 mo	NA	NA	17	NA
3-6 mo	NA	NA	19.8	NA
6-9 mo	NA	NA	15.5	NA
9-12 mo	NA	NA	8.2	NA
12-24 mo	NA	NA	16.4	NA
> 24 mo	NA	NA	23.1	NA

[a] Unadjusted comparisons between AVF vs CVC.

[b] Low grade was defined as urine protein/creatinine ratio of 0.2 to 0.5, urine albumin/creatinine ratio of 30 to 300 mg/g, or 1+ on urinalysis; midgrade as urine protein/creatinine ratio of 0.5 to 3.5, urine albumin/creatinine ratio > 300 to 2200 mg/g, or 2+ or greater on urinalysis; and high grade as urine protein/creatinine ratio > 3.5 or urine albumin/creatinine ratio > 2200 mg/g.

AKI = acute kidney injury; AVF = arteriovenous fistula; CHF = congestive heart failure; CVC = central venous catheter; NA = not applicable; PVD = peripheral vascular disease.

Statistical Analysis

Patients were divided into 2 groups on the basis of access used at first hemodialysis: AVF and CVC. Baseline characteristics were compared between AVF vs CVC using the χ^2 test for categorical variables and the *t*-test for continuous variables. A logistic regression model was used to determine which variables were associated with the outcome for CVC. Odds ratio (OR) with 95% Wald confidence intervals (CIs) were calculated. For categorical variables with multiple categories (including proteinuria grade, race, age, and time of AVF placement), the likelihood ratio test was calculated using logistic regression. If the overall test was statistically significant ($p < 0.05$), then pairwise differences for categories were calculated. The multivariable logistic regression model was repeated after removing nonsignificant variables using backward stepwise selection. Statistical significance was defined as $p < 0.05$. All calculations were done using R Version 3.1.0 (The R Foundation, Free Software Foundation, Boston, MA) and SAS Version 9.2 (SAS Institute Inc, Cary, NC).

Patients who started hemodialysis with CVC were further divided into subgroups by whether or not they had an immature AVF present. Baseline characteristics were compared between patients starting hemodialysis with AVF vs CVC with AVF present (Table 1). Logistic regression models were used to determine which variables were associated with the outcome of CVC with AVF present.

RESULTS

Our final dialysis cohort consisted of 918 patients, of which 35.9% started dialysis with an AVF and 64.1% started with a CVC. Of the 64% that started with a CVC, 25% had an immature AVF present (Table 2). The average age at initial hemodialysis was 63.8 years, with a range of 18 to 94 years, and 40.2% of the cohort was older than age 70 years. The average

last outpatient eGFR before the start of hemodialysis was 12.9 mL/min, with an interquartile range of 9 to 15 mL/min (data missing in 36% of the sample). In patients who had an AVF placed before hemodialysis, 29% had an AVF placed less than 3 months beforehand. Only 9.5% of patients were not seen by a nephrologist, whereas most patients (69.3%) had greater than 1 year of follow-up with a nephrologist before hemodialysis.

Measurement of proteinuria was present in the health records of the entire cohort. Most patients (77%) had overt proteinuria (> 0.5 g); 36% had high-grade proteinuria, (> 3.5 g) whereas 40.4% had midgrade proteinuria (0.5 to 3.5 g). Patients with high-grade proteinuria were more likely to be younger, have diabetes, and be less likely to have predialysis nephrology care of greater than 2 years compared with patients with midgrade proteinuria (Table 3). Patients with low-grade or absent proteinuria were more likely to be older, have congestive heart failure, be white, have no predialysis care, and start hemodialysis at a higher eGFR, and were less likely to have diabetes. Compared with patients with low-grade or absent proteinuria and those with midgrade proteinuria, patients with high-grade proteinuria were more likely to have their AVF placed later, at less than 90 days, and at a lower eGFR.

Proteinuria grade was associated with CVC use vs AVF use at initial hemodialysis in univariate analysis using the global likelihood ratio test ($p < 0.001$; Table 4, Model 1). However, on pairwise comparison, only patients with midgrade proteinuria remained with a statistically significant association and had the lowest odds of 0.36 for starting hemodialysis with a CVC (95% CI = 0.21-0.58) compared with patients with absent proteinuria. Patients with low-grade and high-grade proteinuria had higher odds of starting with a CVC compared with patients with midgrade proteinuria (low grade: OR = 0.65, 95% CI = 0.35-1.10; high grade: OR = 0.75, 95% CI = 0.44-1.22), but the difference was not statistically significant.

After adjustment with logistic regression with all variables (Table 4, Model 2) and removal of nonsignificant variables (Table 4, Model 3), proteinuria grade was still associated with CVC use (likelihood ratio test, $p < 0.001$). However, this association was statistically significant only in patients with midgrade proteinuria, who had the lowest odds of starting hemodialysis with a CVC (OR = 0.39, 95% CI = 0.24-0.65). Proteinuria grade was also associated with presence of an AVF in patients starting hemodialysis with a CVC in multivariate analysis compared with patients starting dialysis with AVF. Patients with midgrade proteinuria had the lowest odds of starting hemodialysis with a CVC with an AVF present (Table 5).

Table 3. Unadjusted comparisons in baseline characteristics between patients divided by proteinuria grade

Variable	Proteinuria grade		
	< 0.5 g (n = 212)	0.5-3.5 g (n = 371)	> 3.5 g (n = 335)
Sex (men), %	58	60.4	57.6
PVD, %	22.2	28.8	24.2
CHF, %	56[a]	41	36
Diabetes, %	50.1[a]	64.4	78.2[a]
History of AKI, %	44.3	45.8	36.4[a]
eGFR at start of dialysis, median mL/min	15.4[a]	12.9	11.7
Early dialysis start, %	42	38.5	33.1
Time of AVF placement, median d	214	277	130[a]
eGFR at AVF placement, median mL/min	19[a]	16	15
AVF placed < 90 d before first dialysis, %	21.5	22.8	41.6[a]
Access type, %			
CVC	56.1[a]	39.9	50.7[a]
AVF	27.8[a]	46.4	29.3[a]
CVC with immature AVF	16	13.7	20
Age groups (y), %			
< 50	8	13.7	24.2[a]
50-70	35.3[a]	49.3	54.9
> 70	56.6[a]	36.9	20.9[a]
Race, %			
Asian	2.4	4.9	6.8
Black	4.7	9.2	9.3
White	92[a]	83.8	80
Length of predialysis care, %			
None	18.9[a]	7.5	6
0-6 mo	10.4	10.8	15.5
6-12 mo	7.5	6.2	12.5[a]
12-24 mo	9.4	12.7	16.4
> 24 mo	53.8	62.8	49.6[a]

[a] Denotes group with significant p value with 0.5 to 3.5 g of proteinuria as comparator group.
AKI = acute kidney injury; AVF = arteriovenous fistula; CHF = congestive heart failure; CVC = central venous catheter; eGFR = estimated glomerular filtration rate; PVD = peripheral vascular disease.

DISCUSSION

Our findings demonstrate that midgrade proteinuria is associated with lower CVC use at initial hemodialysis. Our results did not support our hypothesis that higher levels of proteinuria were associated with higher rates of CVC use. Surprisingly, we found that patients with midgrade proteinuria had the lowest odds (ie, best outcome) of starting dialysis with CVC compared with other levels of proteinuria, including absent and low-grade proteinuria. When we looked at differences in patient characteristics between proteinuria grades, we found that patients with high-grade proteinuria had the shortest time from AVF placement until starting hemodialysis, the lowest eGFR at the time of AVF placement, and the highest percentage of an AVF placed 90 days or less before starting dialysis, compared with other grades of proteinuria. This suggests that one reason

for higher rates of CVC use in the high proteinuria group was delay in referral for AVF placement. This group may benefit from earlier referral for access placements or closer monitoring by a nephrologist.

Interestingly, patients with absent or low-grade proteinuria were also more likely to start dialysis with a CVC compared with patients with midgrade proteinuria. We found these patients were more likely to have a diagnosis of congestive heart failure, were more likely to have a higher eGFR before starting dialysis, and were less likely to have been followed-up by a nephrologist before dialysis. We theorize that this group included patients in whom acute kidney injury occurred or patients who had previously stable CKD but experienced acute kidney injury and did not recover. In addition, this group included a higher number of elderly patients. Elderly patients present a challenge to the nephrologist for dialysis preparation because of the competing risk of death,[25] lower incidence of proteinuria than in younger patients with CKD,[26] and slower rate of CKD progression,[25] which will often result in later referral for AVF placement.[11]

Another important finding in our study was that even with optimal nephrology care before dialysis, CVC use remains high. This finding was illustrated in our cohort of whom approximately 60% of patients starting hemodialysis with CVCs had seen a nephrologist for at least 12 months. This has been shown in other studies to be partly because of late AVF placement.[11,27] In our cohort, almost 30% of AVFs were placed less than 90 days before the start of dialysis, and longer predialysis care was not associated with decreased rates of immature AVF use at initial dialysis. A major challenge comes from predicting which patients will progress to ESRD and when to place an AVF. Placing an AVF too early will result in patients undergoing unnecessary procedures who may die before progressing to ESRD or requiring more interventions to maintain patency,[28] whereas placing an AVF too late will result in higher CVC use. Several conflicting guidelines have been published regarding the optimal timing for AVF placement. The National Kidney Foundation Kidney Disease Outcome Quality Initiative[29] recommends placement of an AVF at least 6 months before initiation of hemodialysis. However, the Canadian Society of Nephrology suggests referral for AVF placement at an eGFR of 15 mL/min to 20 mL/min,[30] and the European Renal Best Practice guidelines recommends referral when the eGFR is below 30 mL/min.[31] Hod et al[32] examined the timing of AVF placement in elderly patients from the United States Renal Data System and suggests that the optimal timing is 6 to 9 months before dialysis. With the current recommended threshold of 20 mL/min for eGFR, about 40% of patients in our cohort would have had their AVF placed less than 6 months before starting hemodialysis.

Several prediction models have been recently published predicting risk of progression to ESRD in patients with CKD.[33,34] In addition, two recent studies found that higher levels of proteinuria predicted which patients would go on to start hemodialysis

Table 4. Logistic regression model for central venous catheter vs arteriovenous fistula at initial dialysis

	Model 1[a]			Model 2[b]			Model 3[c]		
Variable	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value
Sex (men, reference)	1.27	0.96-1.68	0.09	1.23	0.91-1.66	0.18	—	—	—
CHF	1.36	1.04-1.80	0.03	1.20	0.86-1.66	0.28	—	—	—
Diabetes	0.94	0.70-1.25	0.65	0.75	0.54-1.04	0.08	—	—	—
History of AKI	0.85	0.64-1.11	0.22	1.07	0.79-1.44	0.68	—	—	—
PVD	1.40	1.02-1.93	0.04	1.38	0.96-1.98	0.08	—	—	—
Hospitalizations	1.07	1.04-1.10	< 0.001	1.07	1.04-1.11	< 0.001	1.07	1.04-1.11	< 0.001
Length of predialysis care (mo)	0.98	0.98-0.99	< 0.001	0.99	0.98-0.99	< 0.001	0.99	0.98-0.99	< 0.001
Proteinuria[d]	—	—	< 0.001	—	—	< 0.001	—	—	< 0.001
Absent (reference)	—	—	—	—	—	—	—	—	—
Low grade	0.65	0.35-1.19	0.17	0.78	0.42-1.48	0.45	0.72	0.39-1.34	0.30
Midgrade	0.36	0.21-0.58	< 0.001	0.44	0.26-0.75	0.002	0.39	0.24-0.65	< 0.001
High grade	0.75	0.44-1.22	0.26	0.94	0.54-1.64	0.84	0.76	0.45-1.28	0.30
Age groups, y[d]	—	—	0.06	—	—	0.11	—	—	—
< 50	1.16	0.76-1.77	0.50	1.10	0.68-1.79	0.70	—	—	—
50-70	0.76	0.57-1.03	0.08	0.76	0.54-1.06	0.10	—	—	—
> 70 (reference)	—	—	—	—	—	—	—	—	—
Race[d]	—	—	0.78	—	—	0.52	—	—	—
White (reference)	—	—	—	—	—	—	—	—	—
Native American	0.91	0.40-2.20	0.83	0.66	0.27-1.66	0.35	—	—	—
Asian	0.93	0.51-1.76	0.83	0.81	0.42-1.62	0.55	—	—	—
Black	0.85	0.52-1.40	0.52	0.96	0.56-1.65	0.89	—	—	—

[a] Model 1: Univariate logistic regression.
[b] Model 2: Multivariate logistic regression with all variables.
[c] Model 3: Multivariate logistic regression after removal of nonsignificant variables.
[d] Likelihood ratio test between model with categorical variable and model without.
AKI = acute kidney injury; CHF = congestive heart failure; CI = confidence interval; OR = odds ratio; PVD = peripheral vascular disease.

after AVF placement.[21,22] These models and studies suggest that factors other than eGFR, such as proteinuria, age, and diabetes status, may help in individualizing which patients should be prepared for dialysis and possibly determining the timing of AVF placement. However, our study suggests that these models, in which patients who are younger and have higher levels of proteinuria are more likely to have higher risk scores, may miss older patients with lower levels of proteinuria who progress to ESRD and may be more likely to start with a CVC. An important future study would look at performance of these models in predicting which of these patients are at risk of progression to ESRD.

Our study had some limitations. The observational study design shows association rather than causation. Factors in other studies, including obesity, cerebrovascular disease, smoking, and malignancy were not included in our analysis, which may have altered our findings regarding proteinuria because of confounding. Outcome of access used at dialysis was based on a review of vascular surgery notes, which may have been incomplete or documented incorrectly. The applicability of this study to the general population may be limited because patients were members of an integrated health care system, which may result in different practice patterns because of more integrated delivery. Patients were predominantly white, so applicability to other racial groups will be limited. We chose to divide proteinuria as a categorical rather than continuous variable because of the variability of proteinuria in our dataset. Glomerular filtration data were missing for more than one-third of our dataset, which could have altered those findings. In patients with an eGFR available, about 60% started hemodialysis at an eGFR above 10 mL/min. The IDEAL (Initiating Dialysis Early and Late) trial showed no improved outcomes with initiation of dialysis at a higher eGFR.[35] It is possible that these associations may be different in a more contemporary cohort of patients starting dialysis at a lower eGFR. Finally, the small size of our cohort may

Table 5. Logistic regression model for central venous catheter with arteriovenous fistula present vs arteriovenous fistula at initial dialysis

	Model 1[a]			Model 2[b]			Model 3[c]		
Variable	**OR**	**95% CI**	**p value**	**OR**	**95% CI**	**p value**	**OR**	**95% CI**	**p value**
Sex (men, reference)	1.67	1.14-2.47	0.009	1.73	1.10-2.71	0.02	1.76	1.14- 2.72	0.01
CHF	1.59	1.08-2.35	0.02	1.06	0.64-1.74	0.83	—	—	—
Diabetes	1.28	0.84-1.97	0.25	1.05	0.63-1.75	0.85	—	—	—
History of AKI	0.70	0.47-1.04	0.08	0.86	0.54-1.37	0.53	—	—	—
PVD	1.48	0.95-2.29	0.08	1.14	0.67-1.95	0.63	—	—	—
Hospitalizations	1.05	1.01-1.10	0.02	1.04	0.99-1.09	0.11	—	—	—
Length of predialysis care, mo	0.99	0.98-0.99	0.003	1.00	0.99-1.01	0.67	—	—	—
Proteinuria[d]	—	—	0.01	—	—	0.01	—	—	0.02
Absent (reference)	—	—	—	—	—	—	—	—	—
Low grade	0.51	0.21-1.20	0.13	0.71	0.28-1.84	0.48	0.71	0.28-1.81	0.48
Midgrade	0.37	0.19. 0.73	0.003	0.38	0.18-0.82	0.01	0.37	0.18-0.78	0.009
High grade	0.85	0.44-1.67	0.64	0.77	0.34-1.71	0.51	0.65	0.31-1.36	0.25
Age groups, y[d]	—	—	0.12	—	—	0.12	—	—	—
< 50	0.79	0.43-1.43	0.46	0.77	0.36-1.63	0.49	—	—	—
50-70	0.65	0.43-0.99	0.04	0.59	0.36-0.98	0.04	—	—	—
> 70 (reference)	—	—	—	—	—	—	—	—	—
Race[d]	—	—	0.23	—	—	0.23	—	—	—
White (reference)	—	—	—	—	—	—	—	—	—
Native American	0.46	0.07-1.81	0.32	0.36	0.05-1.82	0.26	—	—	—
Asian	0.61	0.20-1.57	0.34	0.60	0.17-1.83	0.40	—	—	—
Black	0.85	0.41-1.68	0.66	0.89	0.39-2.03	0.78	—	—	—
Timing of AVF placement, mo[d]	—	—	< 0.001	—	—	< 0.001	—	—	< 0.001
0-3	7.51	4.01-14.80	< 0.001	7.00	3.26-15.03	< 0.001	7.21	3.64-14.26	< 0.001
3-6	1.56	0.74-3.34	0.24	1.49	0.65-3.38	0.34	1.42	0.66-3.08	0.37
6-9	0.70	0.25-1.77	0.46	0.62	0.22-1.71	0.36	0.64	0.24-1.71	0.37
9-12	1.50	0.55-3.87	0.41	1.61	0.57-4.53	0.37	1.63	0.61-4.38	0.33
12-24	1.78	0.84-3.87	0.14	1.79	0.80-4.01	0.16	1.76	0.80-3.85	0.16
> 24 (reference)	—	—	—	—	—	—	—	—	—

[a] Model 1: Univariate logistic regression.
[b] Model 2: Multivariate logistic regression with all variables.
[c] Model 3: Multivariate logistic regression with only covariates after removing nonsignificant variables in step wise selection.
[d] Likelihood ratio test between model with categorical variable and model without.
AKI = acute kidney injury; AVF = arteriovenous fistula; CHF = congestive heart failure; CI = confidence interval; OR = odds ratio; PVD = peripheral vascular disease.

have limited our ability to find statistical significance for certain variables found to be significant in other studies.

CONCLUSION

We found that proteinuria was associated with starting dialysis with a CVC and with patients who had midgrade proteinuria having the best vascular access outcome for starting dialysis. However, we did not find that increasing proteinuria was associated with higher CVC rates as we had expected. Surprisingly, patients with low or absent proteinuria also had higher rates of CVC use comparable to patients with high-grade proteinuria. Our findings suggest that the relationship of proteinuria with CVC use is more complex, and current prediction models may miss older patients with lower-grade proteinuria who progress to ESRD. Future prospective studies looking at refinement of these models in this group of patients would be of interest in helping reduce CVC rates at initial dialysis. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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References

1. United States Renal Data System. USRDS 2015 annual data report: Atlas of chronic kidney disease and end-stage renal disease in the United States [Internet]. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2015 [cited 2017 Aug 29]. Available from: www.usrds.org/2015/view/Default.aspx.
2. Pisoni RL, Arrington CJ, Albert JM, et al. Facility hemodialysis vascular access use and mortality in countries participating in DOPPS: An instrumental variable analysis. Am J Kidney Dis 2009 Mar;53(3):475-91. DOI: https://doi.org/10.1053/j.ajkd.2008.10.043.
3. Lee T, Barker J, Allon M. Associations with predialysis vascular access management. Am J Kidney Dis 2004 Jun;43(6):1008-13. DOI: https://doi.org/10.1053/j.ajkd.2004.02.013.
4. Hod T, Desilva RN, Patibandla BK, Vin Y, Brown RS, Goldfarb-Rumyantzev AS. Factors predicting failure of AV "fistula first" policy in the elderly. Hemodial Int 2014 Apr;18(2):507-15. DOI: https://doi.org/10.1111/hdi.12106.
5. Xue JL, Dahl D, Ebben JP, Collins AJ. The association of initial hemodialysis access type with mortality outcomes in elderly Medicare ESRD patients. Am J Kidney Dis 2003 Nov;42(5):1013-9. DOI: https://doi.org/10.1053/S0272-6386(03)01015-1.
6. Dhingra RK, Young EW, Hulbert-Shearon TE, Leavey SF, Port FK. Type of vascular access and mortality in US hemodialysis patients. Kidney Int 2001 Oct;60(4):1443-51. DOI: https://doi.org/10.1046/j.1523-1755.2001.00947.x.
7. CMS; ESRD Network. Fistula first breakthrough initiative. Arteriovenous fistula first: The first choice for hemodialysis [Internet]. Baltimore, MD: Centers for Medicare & Medicaid Services; 2003 Jul [cited 2016 Dec 18]. Available from: www.fistulafirst.org.
8. Oliver MJ, Rothwell DM, Fung K, Hux JE, Lok CE. Late creation of vascular access for hemodialysis and increased risk of sepsis. J Am Soc Nephrol 2004 Jul;15(7):1936-42. DOI: https://doi.org/10.1097/01.ASN.0000131524.52012.F8.
9. Chronic Kidney Disease, HealthyPeople.gov [Internet]. Washington, DC: US Department of Health and Human Services, Office of Disease Prevention and Health Promotion; updated 2017 Aug 29 [cited 2016 Dec 18]. Available from: www.healthypeople.gov/2020/topics-objectives/topic/chronic-kidney-disease/objectives.
10. United States Renal Data System. USRDS 2013 annual data report: Atlas of chronic kidney disease and end-stage renal disease in the United States [Internet]. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2013 [cited 2017 Aug 30]. p 1-26. Available from: www.usrds.org/atlas13.aspx.
11. Lee T, Thamer M, Zhang Y, Zhang Q, Allon M. Outcomes of elderly patients after predialysis vascular access creation. J Am Soc Nephrol 2015 Dec;26(12):3133-40. DOI: https://doi.org/10.1681/ASN.2014090938.
12. Allon M, Ornt DB, Schwab SJ, et al. Factors associated with the prevalence of arteriovenous fistulas in hemodialysis patients in the HEMO study. Hemodialysis (HEMO) Study Group. Kidney Int 2000 Nov;58(5):2178-85. DOI: https://doi.org/10.1111/j.1523-1755.2000.00391.x.
13. Peterson WJ, Barker J, Allon M. Disparities in fistula maturation persist despite preoperative vascular mapping. Clin J Am Soc Nephrol 2008 Mar;3(2):437-41. DOI: https://doi.org/10.2215/CJN.03480807.
14. Hirth RA, Turenne MN, Woods JD, et al. Predictors of type of vascular access in hemodialysis patients. JAMA 1996 Oct 23-30;276(16):1303-8. DOI: https://doi.org/10.1001/jama.1996.03540160025028.
15. Astor BC, Eustace JA, Powe NR, et al. Timing of nephrologist referral and arteriovenous access use: The CHOICE Study. Am J Kidney Dis 2001 Sep;38(3):494-501. DOI: https://doi.org/10.1053/ajkd.2001.26833.
16. Allon M, Robbin ML. Increasing arteriovenous fistulas in hemodialysis patients: Problems and solutions. Kidney Int 2002 Oct;62(4):1109-24. DOI: https://doi.org/10.1111/j.1523-1755.2002.kid551.x.
17. Lok CE, Allon M, Moist L, Oliver MJ, Shah H, Zimmerman D. Risk equation determining unsuccessful cannulation events and failure to maturation in arteriovenous fistulas (REDUCE FTM I). J Am Soc Nephrol 2006 Nov;17(11):3204-12. DOI: https://doi.org/10.1681/ASN.2006030190.
18. DeSilva RN, Patibandla BK, Vin Y, et al. Fistula first is not always the best strategy for the elderly. J Am Soc Nephrol 2013 Jul;24(8):1297-304. DOI: https://doi.org/10.1681/ASN.2012060632.
19. Patibandla BK, Narra A, Desilva R, et al. Disparities in arteriovenous fistula placement in older hemodialysis patients. Hemodial Int 2014 Jan;18(1):118-26. DOI: https://doi.org/10.1111/hdi.12099.
20. Levey AS, de Jong PE, Coresh J, et al. The definition, classification, and prognosis of chronic kidney disease: A KDIGO Controversies Conference report. Kidney Int 2011 Jul;80(1):17-28. DOI: https://doi.org/10.1038/ki.2010.483.
21. Stoumpos S, Stevens KK, Aitken E, et al. Predictors of sustained arteriovenous access use for haemodialysis. Am J Nephrol 2014;39(6):491-8. DOI: https://doi.org/10.1159/000362744.
22. Al-Balas A, Lee T, Young CJ, Barker-Finkel J, Allon M. Predictors of initiation for predialysis arteriovenous fistula. Clin J Am Soc Nephrol 2016 Oct 7;11(10):1802-8. DOI: https://doi.org/10.2215/CJN.00700116.
23. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney International Supplements 2013 Jan;1(3):1-150.
24. Levey AS, Stevens LA, Schmid CH, et al; CKD-EPI (Chronic Kidney Diseae Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med 2009 May 5;150(9):604-12. DOI: https://doi.org/10.7326/0003-4819-150-9-200905050-00006. Erratum in: Ann Intern Med 2011 Sep 20;155(6):408. DOI: https://doi.org/10.7326/0003-4819-155-6-201109200-00024.
25. O'Hare AM, Choi AI, Bertenthal D, et al. Age affects outcomes in chronic kidney disease. J Am Soc Nephrol 2007 Oct;18(10):2758-65. DOI: https://doi.org/10.1681/ASN.2007040422.
26. O'Hare AM, Kaufman JS, Covinsky KE, Landefeld CS, McFarland LV, Larson EB. Current guidelines for using angiotensin-converting enzyme inhibitors and angiotensin II-receptor antagonists in chronic kidney disease: Is the evidence base relevant to older adults? Ann Intern Med 2009 May 19;150(10):717-24. DOI: https://doi.org/10.7326/0003-4819-150-10-200905190-00010.
27. Al-Jaishi AA, Lok CE, Garg AX, Zhang JC, Moist LM. Vascular access creation before hemodialysis initiation and use: A population-based cohort study. Clin J Am Soc Nephrol 2015 Mar 6;10(3):418-27. DOI: https://doi.org/10.2215/CJN.06220614.
28. Richardson AI 2nd, Leake A, Schmieder GC, et al. Should fistulas really be first in the elderly patient? J Vasc Access 2009 Jul-Sep;10(3):199-202. DOI: https://doi.org/10.5301/JVA.2009.3240.
29. National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) [Internet]. New York, NY: National Kidney Foundation; c2017 [cited 2017 Aug 30]. Available from: www.kidney.org/professionals/guidelines.
30. Canadian Society of Nephrology home [Internet]. Montreal, Quebec, Canada: Canadian Society of Nephrology; c2017 [cited 2017 Aug 30]. Available from: www.csnscn.ca/.
31. ERBP (European Renal Best Practice) [Internet]. Glasgow, Scotland: European Renal Best Practice; c2017 [cited 2017 AAug 30]. Available from: www.european-renal-best-practice.org/.
32. Hod T, Patibandla BK, Vin Y, Brown RS, Goldfarb-Rumyantzev AS. Arteriovenous fistula placement in the elderly: When is the optimal time? J Am Soc Nephrol 2015 Feb;26(2):448-56. DOI: https://doi.org/10.1681/ASN.2013070740.
33. Schroeder EB, Yang X, Thorp ML, et al. Predicting 5-year risk of RRT in stage 3 or 4 CKD: Development and external validation. Clin J Am Soc Nephrol 2017 Jan 6;12(1):87-94. DOI: https://doi.org/10.2215/CJN.01290216.
34. Tangri N, Stevens LA, Griffith J, et al. A predictive model for progression of chronic kidney disease to kidney failure. JAMA 2011 Apr 20;305(15):1553-9. DOI: https://doi.org/10.1001/jama.2011.451.
35. Cooper BA, Branley P, Bulfone L, et al; IDEAL study. A randomized, controlled trial of early versus late initiation of dialysis. N Engl J Med 2010 Aug 12;363(7):609-19. DOI: https://doi.org/10.1056/NEJMoa1000552.

Rectal Cancer Survivors' Participation in Productive Activities

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ABSTRACT

Context: Rectal cancer and its treatment impair survivors' productivity.

Objective: To assess determinants of market and nonmarket employment, job search, volunteering, and homemaking among survivors five years or longer after diagnosis.

Design: We mailed questionnaires to 1063 survivors who were members of Kaiser Permanente (Northern California, Northwest) during 2010 and 2011.

Main Outcome Measures: Productive activities, functional health status, and bowel management at the time of the survey.

Results: Response rate was 60.5% (577/953). Higher comorbidity burdens were associated with lower productivity for men and women rectal cancer survivors. Productive survivors were younger and had lower disease stage and age at diagnosis, higher household income and educational attainment, and fewer comorbidity burdens and workplace adjustments than did nonproductive survivors ($p < 0.05$ each; 2-sided). Productive rectal cancer survivors were evenly split by sex.

Conclusion: Staying productive is associated with better mental health for rectal cancer survivors. Rectal cancer survivors with multiple chronic conditions, higher disease stage, lower productive activities, and older age need better access to medical care and closer monitoring of the quality of their care, including self-care. To capture the full extent of the involvement of survivors in all types of productive activities, research should routinely include measures of employment, searching for employment, homemaking, and volunteering. Counting market and nonmarket productive activities is innovative and recognizes the continuum of contributions survivors make to families and society. Health care systems should routinely monitor rectal cancer survivors' medical care access, comorbidities, health-related quality of life, and productive activities.

INTRODUCTION

Cancer imposes substantial productivity losses caused by morbidity and the intangible burden of illness, even among those who have survived well beyond 5 years after diagnosis.[1] Survivors of cancer have an elevated disability rate compared with cancer-free patients after adjustment for age, sex, and other factors.[2] In addition, cancer significantly reduces labor force participation by female survivors compared with women without cancer,[3] and both male and female survivors have lower employment rates and work fewer hours than similarly aged adults do.[4,5] For male survivors, annual labor-market earnings drop by almost 40% within 2 years after diagnosis and remain low; total family income declines by 20%, although it recovers within 4 years after the diagnosis.[6]

The per capita mean annual incremental lost productivity from all patients with cancer (compared with cancer-free patients of similar age and sex) in the US was recently estimated at $1459 in 2011 dollars.[7] The sources of loss were employment disability, missed workdays among employed persons, and lost household productivity. In a meta-analysis of 26 articles, cancer survivors—particularly gastrointestinal cancer survivors—were more likely to be unemployed than healthy control participants were.[8]

More specifically, compared with an age- and sex-matched cancer-free population, colorectal cancer survivors experience significantly more fatigue and report more problems with thinking clearly, even up to 10 years after diagnosis.[9] Survivors with ostomies face prominent physical and psychosocial concerns regarding daily activities, work ability, and employment that are also distressing, although less well understood.[10-12] They report persistent deficits in health-related quality of life (HRQOL), including pain, insomnia, and psychological distress.[13-39] The ability of patients and survivors with rectal cancer to resume paid and unpaid labor is in the interest of both the individual and society. A study published in 2005 of rectal cancer survivorship found adverse effects on paid and unpaid labor continuing through 2 years of follow-up.[40] To update and extend the findings from that study, we examined the composition and correlates of productive status—employment (paid work), volunteering (unpaid work), and homemaking (household production)—among patients with rectal cancer who had survived for 5 or more years after their diagnosis.

METHODS

Participants

Long-term rectal cancer survivors (≥ 5 years after diagnosis) who were members of the Kaiser Permanente Northern

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California (KPNC) and Kaiser Permanente Northwest (KPNW) Regions with permanent ostomy (N = 183) or sphincter-sparing (anastomosis) surgery (N = 394) completed the survey during 2010 and 2011 (60.5% response rate). The study was coordinated at the University of Arizona Cancer Center, Tucson, AZ, and was approved by the institutional review boards at all sites. Details of the study design are available from a methods article by Wendel and colleagues.[41]

Surveys

Mailed surveys included the City of Hope Quality of Life Colorectal Cancer tool, which assesses HRQOL in the physical, psychological, social, and spiritual domains.[42-45] The tool consists of 47 forced-choices and open-ended items as well as 43 HRQOL items evaluated using 11-point scales and multiple items related to physical and behavioral adjustments. Validity analysis was conducted using content, construct, discriminant, and criterion-related approaches.[42]

Our survey also applied the Memorial Sloan Kettering Cancer Center Bowel Function Index[43] to assess the bowel function of patients with rectal cancer undergoing surgery. The 18-item questionnaire contains 3 subscales (frequency, dietary, and soilage) with published test-retest reliability of 0.74, 0.62, and 0.87, respectively, and 0.84 for the overall instrument.[43] The Bowel Function Index demonstrated discriminant validity among survivors with preoperative radiation therapy, postoperative radiation therapy, or no radiation therapy; among local excision, low anterior resection, and coloanal anastomosis; and between hand-sewn and stapled anastomosis. It further demonstrated consistency with all 4 of the Fecal Incontinence Quality of Life subscales and 9 of the 17 European Organization for Research and Treatment of Cancer (EORTC) subscales.[43] The Bowel Function Index had previously been adapted and validated by our team for use by patients with rectal cancer and intestinal ostomies.[41]

Our survey instruments contained three employment-related items from the American Cancer Society Studies of Cancer Survivors[44]: 1) "What do you consider your current employment?" (possible responses were full time, part time, retired and not working another job, homemaker, temporarily laid off, unemployed and looking for work, unemployed and not looking for work, on disability, or other); 2) "Do you volunteer on a regular basis?"; and if the answer was "yes," 3) "About how many hours per week did you spend on volunteer activities in the past four weeks?"[44,45]

We mailed questionnaires to 1063 rectal cancer survivors (≥ 5 years after diagnosis). Eligible patients were identified in tumor registries in September 2009. Study enrollment dates ranged from January 2010 to December 2011. The CONSORT (Consolidated Standards of Reporting Trials) diagram of our recruitment is available in a previous publication.[41] Survey packets included scannable forms programmed with TeleForms 10.3 (Digital Vision, Highland Park, IL) and developed at the University of Arizona Cancer Center, which were sent to potential participants by their respective Kaiser Permanente sites (KPNC, KPNW). Two weeks after a survey packet was mailed, a potential subject who had not yet returned the study questionnaire was contacted by phone (up to 10 attempts). Individuals interested in participating were asked to complete the questionnaire and return it in the postage-paid envelope, or they could answer the questionnaire items by phone. Patients refusing participation were no longer contacted.

Comprehensive information on demographic characteristics and medical history were obtained via the patient survey and the extraction of electronic medical record data. Both KPNC and KPNW maintain a decentralized, standardized virtual data warehouse for research uses.[46] A variety of definitions have been developed for a wide range of variables from major health plan informatics systems, such as electronic medical record data, enrollment data, hospital discharge abstract systems, medication dispensing systems, outside claims, and referral systems. The Virtual Data Warehouse enabled us to concatenate data from the 2 participating health systems. Multiple demographic parameters were collected: Age, sex, race, Hispanic ethnicity, number of survival years, household income, educational attainment, marital status, and smoking status. Medical history items included weight, height, type of cancer surgery, length of time since cancer surgery; Surveillance, Epidemiology, and End Results general summary stage; and comorbidities, including the Charlson-Deyo comorbidity index for the 12 months before the survivor survey.[47]

Our primary dichotomous outcome measure was whether rectal cancer survivors were engaged in productive activities at the time of the survey.

Table 1. Productivity status of study participants, by sex

Productivity status	Men, no. (%) (n = 330)[a]	Women, no. (%) (n = 233)[a]	Total, no. (%) (N = 563)
Productive			
Total employed: full time + part time + unemployed and looking for work + homemaker	94 (48.7)	99 (51.3)	193 (34.3)
Volunteer, but not employed or homemaker	39 (52.0)	36 (48.0)	75 (13.3)
Total productive: employed and/or homemaker and/or volunteer	133 (49.6)	135 (50.4)	268 (47.6)
Nonproductive			
Retired + not employed + not looking for work + not volunteering + not homemaking	174 (67.7)	83 (32.3)	257 (45.7)
On disability + not employed + not volunteering + not homemaking	7 (63.6)	4 (36.4)	11 (2.0)
Unemployed and not looking for work	2 (40.0)	3 (60.0)	5 (0.9)
Other nonproductive	14 (63.6)	8 (36.4)	22 (3.9)
Total nonproductive	197 (66.8)	98 (33.2)	295 (52.4)

[a] Percentages for Men and Women columns are by row. Percentages may not total to 100 because of rounding.

Statistical Analysis

From our previous research, we learned that male and female survivors report different profiles of challenges because of rectal cancer.[23] Therefore, in the current study we analyzed HRQOL outcomes and productive activity patterns for men and women separately. We compared demographic and clinical characteristics between male and female productive and nonproductive rectal cancer survivors by using the 2-sided Student *t*-test for statistically significant differences in continuous measures and the 2-sided χ^2 test for significance of differences in categorical measures at $p < 0.05$. We analyzed engagement in productive activities (yes/no) using multiple logistic regression models. Statistical significance of regression coefficients was set at $p < 0.05$. All analyses were performed with the SAS statistical package Version 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

Productive Status of Respondents

Our sample contained more male survivors (59%). About 50% of both male and female rectal cancer survivors were engaged in productive activities (Table 1). Approximately two-thirds of nonproductive respondents were men. Of the *nonproductive* respondents, 88% of men and 85% of women were fully retired (ie, not employed, not looking for work, not volunteering, not homemaking, and not

Table 2. Characteristics of study participants, by sex and productivity[a]

Characteristics	Men (n = 330)			Women (n = 233)		
	Productive (n = 133)	Nonproductive (n = 197)	p value	Productive (n = 135)	Nonproductive (n = 98)	p value
Demographic characteristics						
Age (y), mean	68.20	76.07	< 0.05	68.67	77.57	< 0.05
Number of survival y, mean	11.78	13.58	< 0.05	12.42	13.03	0.49
Married or partnered, %	81.15	78.79	0.76	45.93	37.89	0.23
Hispanic ethnicity, %	3.79	9.60	< 0.05	5.88	6.19	0.92
Nonwhite race, %	15.27	12.69	0.51	15.44	18.75	0.51
Household income ≥ $30,000, %	61.42	40.98	< 0.05	44.35	22.09	< 0.05
Some college education or higher, %	76.67	66.67	0.06	77.34	56.32	< 0.05
Rectal cancer treatments, %						
Surgery: anastomosis	59.09	46.46	< 0.05	66.18	55.67	0.10
Surgery: temporary ostomy	12.88	12.12	0.84	8.82	13.40	0.27
Surgery: permanent ostomy	25.00	38.38	< 0.05	22.79	27.84	0.38
Radiotherapy for rectal cancer	49.24	43.43	0.30	33.82	25.77	0.19
Chemotherapy for rectal cancer	57.58	51.01	0.24	50.00	43.30	0.31
Health status at time of survey						
Overweight/obese (body mass index ≥ 25 kg/m^2), mean	23.85	21.43	0.61	31.34	29.47	0.76
Charlson-Deyo comorbidity score, mean	0.59	1.04	< 0.05	0.45	1.20	< 0.05
Any other pelvic cancer, %	12.88	17.17	0.29	9.56	6.19	0.35
COH physical well-being (0 = low; 10 = high), mean	7.77	7.42	0.10	7.44	7.16	0.28
COH social well-being (0 = low; 10 = high), mean	7.45	7.19	0.31	7.98	7.72	0.36
COH psychological well-being (0 = low;10 = high), mean	7.95	7.50	< 0.05	7.76	7.28	< 0.05
COH spiritual well-being (0 = low; 10 = high), mean	7.37	7.09	0.22	7.43	7.27	0.55
Is support from family and friends sufficient to meet your needs? (0 = not at all; 10 = extremely), mean	8.74	8.07	< 0.05	8.53	7.59	< 0.05
Current smoker, %	40.00	27.69	< 0.05	58.21	52.63	0.40
Bowel function at time of survey						
How often had soilage in undergarments during the day in past 4 wk (1 = never, 5 = always), mean	2.13	2.21	0.52	1.95	2.03	0.56
How often had loose stool in past 4 wk (1 = never, 5 = always), mean	2.65	2.84	0.11	2.58	2.47	0.45
How often altered activities because of bowel function in past 4 wk (1 = never, 5 = always), mean	2.08	2.19	0.35	2.04	2.03	0.98
Highest number of bowel movements or bag emptying per d in past 4 wk, mean	5.79	6.39	0.45	6.37	4.55	< 0.05
Lowest number of bowel movements or bag emptying per d in last 4 wk, mean	1.58	2.09	0.19	1.80	1.28	≤ 0.05

[a] Productive = employed (full time, part time, unemployed and looking for work), and/or volunteer, and/or homemaker.
COH = City of Hope.

disabled). Fourteen respondents did not provide answers to the productive activities questions.

Descriptive Statistics for Rectal Cancer Respondents

Demographic Characteristics

Average age of the rectal cancer survivor cohort was 73.1 years, and 63% were married or partnered at the time of survey. Sex composition was 59.1% men and 40.9% women. More male than female rectal cancer respondents were likely to be married or partnered (80% vs 42%, $p < 0.05$) or to have an annual household income of $30,000 or more (50% vs 35%, $p < 0.05$).

Rectal Cancer Treatment

Compared with male rectal cancer survivors, female survivors were more likely to have had anastomoses as surgical treatment (61% vs 52.5%, $p < 0.05$) and less likely to have received radiotherapy (30.6% vs 45.5%, $p < 0.05$).

Health Status at Time of Survey

More female than male rectal cancer survivors were overweight or obese (30% vs 23%, $p < 0.05$), were smokers (55% vs 33%, $p < 0.05$), and had higher social well-being scores (7.9 vs 7.3, $p < 0.05$). Male rectal cancer survivors were nearly twice as likely as female rectal cancer survivors to have experienced another pelvic cancer (primarily prostate cancer among men; 15% vs 8%, $p < 0.05$).

Bowel Function at Time of Survey

For the 4 weeks before completing the survey, male rectal cancer survivors reported substantially higher frequency of soilage in undergarments ($p < 0.05$) and loose stools ($p < 0.05$) than female rectal cancer survivors did.

Characteristics of Productive and Nonproductive Rectal Cancer Survivors, by Sex

Demographic Characteristics of Productive and Nonproductive Rectal Cancer Survivors

For both men and women, productive rectal cancer survivors were significantly younger than nonproductive rectal cancer survivors (men: 8 years, $p < 0.05$; women: 9 years, $p < 0.05$), and were more likely to have an annual household income of $30,000 or greater (men: 61% vs 41%, $p < 0.05$; women: 44% vs 22%, $p < 0.05$; Table 2). Productive female rectal cancer survivors had higher educational attainment than nonproductive female survivors (77% vs 56%, $p < 0.05$). Nonproductive male rectal cancer survivors had significantly longer survivorship periods than their male productive counterparts did (by 1.8 years, $p < 0.05$). Productive male rectal cancer survivors were less likely to be Hispanic compared with nonproductive male survivors (3.79% vs 9.60%, $p < 0.05$).

Rectal Cancer Treatments

Among productive male rectal cancer survivors, surgical treatment with an anastomosis was more prevalent compared with nonproductive male survivors (59% vs 46%, $p < 0.05$), and, conversely, treatment with a permanent ostomy was less prevalent (24% vs 38%, $p < 0.05$; Table 2). Types of rectal cancer treatments were not significantly related to productivity status for female survivors. Rates of receipt of radiotherapy and chemotherapy between productive and nonproductive rectal cancer survivors were not significantly different for both men and women survivors.

Health Status at Time of Survey

Both male and female nonproductive rectal cancer survivors had higher comorbidity scores than productive rectal cancer survivors did ($p < 0.05$ for men and women), whereas both productive male and female rectal cancer survivors had higher psychological well-being scores than nonproductive survivors did ($p < 0.05$ for both men and women; Table 2). Both productive male and female survivors reported receiving higher levels of support from family and friends than nonproductive survivors (men: 8.74 vs 8.07, $p < 0.05$; women: 8.53 vs 7.59, $p < 0.05$). Among male rectal cancer survivors, productive men were more likely to smoke than nonproductive men (40% vs 28%, $p < 0.05$).

Bowel Function at Time of Survey

Productive female rectal cancer survivors had a higher average number of bowel movements or colostomy bag emptyings per day than did nonproductive female survivors for both the highest (6.4 vs 4.6 movements or bag emptyings per day, $p < 0.05$) and lowest (1.8 vs 1.3, $p < 0.05$) frequency days (Table 2). No statistically significant differences in bowel function between productive and nonproductive male rectal cancer survivors were found.

Multiple Logistic Regression

Women

Altogether, the independent variables included in the logistic regression for female rectal cancer survivors explained a statistically significant portion of the variance in the odds of being productive ($p < 0.05$). However, the only individual variable to reach statistical significance was the Charlson-Deyo comorbidity index for the 12 months before the survey; the higher the comorbidity burden, the lower the odds of female rectal cancer survivors participating in productive activities ($p < 0.05$; Table 3).

Men

All the independent variables included in the logistic regression for male rectal cancer survivors explained a statistically significant portion of the variance in the odds of being productive ($p < 0.05$; Table 3). Eight variables predicting participation in productive activities by male rectal cancer survivors were statistically significant. Those male survivors whose rectal cancer was diagnosed at regional or distant stages or had a higher Charlson-Deyo comorbidity index score in the year before the survey had lower odds of participating in productive activities at the time of the survey ($p < 0.05$ for both). Longer rectal cancer survival periods, receipt of chemotherapy, higher current body mass index, current smoker, annual household incomes of $30,000 or greater, and receipt of positive on-the-job feedback and flexible working conditions after rectal cancer diagnosis or surgery were associated with significantly higher odds of being productive ($p < 0.05$ for each).

DISCUSSION

We sought to understand the determinants of being engaged in productive activities—employment, volunteering, and homemaking—among long-term rectal cancer survivors. Compared with their nonproductive counterparts, productive male and female rectal cancer survivors were on average eight to nine years younger, and had higher educational attainment and incomes. In addition, survivors with anastomoses were

more likely to be productive than those with permanent ostomies. In the logistic regressions, higher comorbidity burden was associated with lower levels of productive activities among *both* men and women. These results reinforce findings from our previous research in veterans with ostomies[48] as well as other research on the general population of rectal cancer survivors[49] that high comorbidity burden is significantly associated with lower HRQOL and affects more domains than having an ostomy. Survivors with above-average and/or increasing comorbidity burdens should be regularly evaluated for medical care, care management, and support service needs. Survivorship care plans for patients with rectal cancer should include routine monitoring and evaluation for decreasing engagement in nonmarket productive activities—volunteering and homemaking. Productive rectal cancer survivors should be monitored for increasing difficulties in sustaining their productive roles and activities; those identified should receive help to resolve barriers to remaining productive at the same level, adjusting productive activities in the workplace and home to transition to fewer and/or easier productive activities. The goal is for these transitions to be perceived as planned, not unexpected. Integrated health care systems with a single electronic medical record system have a structural advantage in implementing coordinated management of multiple comorbidities.

With the total number of cancer survivors increasing and living longer after diagnosis,[50] understanding the long-term effects of cancer and cancer treatments on patients and their families is imperative for formulating health care delivery reforms and policy initiatives.[51] Previous research has demonstrated that the consequences of anastomosis or colostomy for rectal cancer can manifest for many years, and include psychological problems[14,52-56] and interference with work.[57-60] Cancer-related fatigue can affect up to one-third of survivors and is associated with much higher levels of disability compared with persons without cancer.[36] Having a permanent ostomy appears to inhibit rectal cancer survivors, especially women, from seeking and holding jobs.[58-60] Many ostomates report feeling stigmatized by their appliance and being more likely to avoid situations where they must interact with others and use bathrooms in their workplaces and other locations outside their homes.[19,51] Ostomies are also associated with multiple HRQOL difficulties, including those related to travel, social situations, and appearance.[14,52,53,61-65] Rectal cancer survivors experiencing challenges could benefit from coordinated support of health and vocational professionals regarding remaining productive, coping, managing self-care, and maintaining social networks and personal relationships.[52-55] Unmet information needs are

Table 3. Multiple logistic regression results: Participation in work and/or volunteer and/or homemaking activities of men and women rectal cancer survivors

	Men				Women			
Parameter	Estimate	Standard error	Wald χ^2	p value	Estimate	Standard error	Wald χ^2	p value
Intercept	-122.60	53.29	4.46	< 0.05	-39.38	67.20	0.34	0.56
Ileostomy for rectal cancer	-0.33	0.82	0.16	0.68	13.35	1262.0	0.0001	0.99
Permanent ostomy for rectal cancer	-0.43	0.35	1.54	0.21	0.45	0.45	1.03	0.31
Rectal cancer regional stage or higher	-0.93	0.38	6.12	< 0.05	-0.05	0.44	0.01	0.91
Years since rectal cancer surgery	0.05	0.03	4.13	< 0.05	0.02	0.03	0.31	0.58
Receipt of radiotherapy for rectal cancer	0.12	0.40	0.09	0.77	0.63	0.49	1.63	0.20
Receipt of chemotherapy for rectal cancer	0.87	0.45	3.69	< 0.05	-0.80	0.54	2.21	0.14
Any other pelvic cancer	0.07	0.40	0.03	0.85	0.59	0.74	0.63	0.43
Prior year Charlson-Deyo comorbidity index	-0.39	0.14	7.76	< 0.05	-0.59	0.19	10.03	< 0.05
Current body mass index (kg/m^2)	0.06	0.03	4.10	< 0.05	0.03	0.03	1.22	0.27
Current smoker	0.87	0.32	7.44	< 0.05	0.25	0.37	0.47	0.49
Physical well-being	0.18	0.11	2.58	0.11	0.07	0.12	0.33	0.56
Social well-being	-0.11	0.10	1.21	0.27	-0.07	0.13	0.26	0.61
Psychological well-being	0.21	0.16	1.66	0.20	0.28	0.21	1.65	0.20
Spiritual well-being	0.00	0.09	0.00	0.98	-0.15	0.13	1.43	0.23
Married or partnered	-0.16	0.38	0.18	0.67	-0.06	0.38	0.03	0.87
Hispanic ethnicity	-1.24	0.67	3.42	0.06	0.75	0.84	0.80	0.37
Nonwhite race	-0.45	0.45	1.01	0.32	0.13	0.53	0.06	0.81
Some college education or higher	0.18	0.34	0.29	0.59	0.60	0.41	2.16	0.14
Household income ≥ $30,000	0.73	0.32	5.27	< 0.05	0.55	0.43	1.65	0.20
Receipt of positive job action because of cancer	1.20	0.39	9.69	< 0.05	0.12	0.55	0.05	0.82
Receipt of negative job action because of cancer	-0.08	0.45	0.03	0.86	-0.12	0.68	0.03	0.86
Model χ^2 (df = 21)			63.84	< 0.05			35.21	< 0.05

prevalent in 36% to 48% of cancer survivors; furthermore, patients who were less satisfied with information received and had more unmet information needs reported more anxiety, more depression, and lower quality of life.[56]

We considered homemaking as a productive activity—unpaid nonmarket production of household services, which, if not performed by a household member, would have to be purchased on the market. We found that female rectal cancer survivors were engaged in all types of productive activities at a higher rate than male survivors were (59% vs 42%). Overall, women were more likely to be employed, volunteering, and/or homemaking; men were more likely to report being retired. One consideration is that male survivors may underreport their homemaking activities. Some husbands may have gradually taken on more homemaking activities but did not perceive or report themselves as homemakers, especially if their spouses were also performing homemaking tasks. Also, female spouses or partners tend to take on caregiving responsibilities for their partners (60% of caregivers who care for someone aged 50 years or older are female, and most provide care for a relative).[52]

Compared with nonproductive female rectal cancer survivors, productive female rectal cancer survivors had significantly more daily bowel movements per day than did nonproductive women. We do not interpret this association to mean that more bowel movements generate more productivity; rather, women survivors who face the demands of balancing employment, volunteering, and/or housekeeping may be more focused on their bowel function. Working female rectal cancer survivors often find their employment situations demotivating and emotionally stressful.[58-60,64,65] Survivors who continue to expose themselves to productive activities and the associated physical and social environments (employment and volunteering can reduce access to bathrooms and greater involvement in social groups) may find that any amount of bowel dysfunction is disruptive and socially embarrassing. This may reduce their tolerance of bowel problems and increase their propensity to report bowel problems. Moreover, survivors who need the income from employment to meet their daily needs may be more likely to continue working despite poor bowel function.

The major strengths of our study are as follows: 1) having the data to treat volunteering and homemaking as productive activities equivalent to employment, 2) combining social survey and electronic medical record data, and 3) having a defined Health Plan population with continuing enrollment patterns. We were able to define and identify our study population before we administered our survey. By using a target population of cancer survivors enrolled in an integrated managed care system with sophisticated informatics resources, we captured nearly all medical care use of our survey respondents during their cancer treatment and survivorship. We also measured comorbidity burden, health insurance coverage, and cancer status and achieved a good response rate to our lengthy mailed survey, in part because of our considerable experience of more than 50 years in conducting research in our managed care system. However, except for use of medical care, our cross-sectional design was restricted to participant recall for historical self-reported data, which are subject to reinterpretation in light of subsequent events.

CONCLUSION

Counting both *market and nonmarket* activities as productive is innovative and recognizes the continuum of contributions survivors make to their families and communities. We have confirmed our previous finding that comorbidity burden reduces the ability of male rectal cancer survivors to sustain productive activities, and we now know that it similarly affects female rectal cancer survivors.[48] Our findings also suggest that physicians caring for rectal cancer survivors should be monitoring for manifestations of multiple interacting diseases, including the physical, social, emotional, and cognitive components of HRQOL. Rectal cancer survivors with multiple chronic conditions may benefit from periodic social surveys of HRQOL to identify self-reported functional impairments that may not be visible during routine office visits. Time plots of HRQOL scores could reveal erosion of functional status as comorbidities progress and additional diseases emerge.

Cancer reduces the economic well-being of affected adults and their families. Male rectal cancer survivors with advanced disease are more likely to be restricted from participating in both market and nonmarket productive activities during their survivorship periods than those with less advanced disease. Future research should examine whether this subgroup of survivors could benefit from additional health coaching and environmental support to cope with their changes in bowel function and external appearance, thereby facilitating their productive activities.

Finally, we found evidence that supportive work environments can sustain productive activities among male rectal cancer survivors in particular. This assistance could include emotional support from supervisors, co-workers, and family members. It could also include environmental modifications, such as reducing business travel and modifying workplace bathrooms to make it more convenient for ostomates to empty, clean, or change their ostomy bags. ❖

Disclosure Statement

Dr Herrinton has had research contracts in the past three years with MedImmune Inc, Gaithersburg, MD, that were unrelated to this study. The other authors and their immediate family members, including spouses or partners, have no financial relationships relevant to the content of this report, and they have no conflicts of interest to disclose.

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All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

This study was approved by the University of Arizona Institutional Review Board (IRB) and the IRBs at both Kaiser Permanente sites in accordance with assurances filed with and approved by the US Department of Health and Human Services. Informed consent was considered to be received by return of the completed survey.

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References

1. Yabroff KR, Guy GP Jr, Ekwueme DU, et al. Annual patient time costs associated with medical care among cancer survivors in the United States. Med Care 2014 Jul;52(7):594-601. DOI: https://doi.org/10.1097/mlr.0000000000000151.
2. Short PF, Vasey JJ, Belue R. Work disability associated with cancer survivorship and other chronic conditions. Psychooncology 2008 Jan;17(1):91-7. DOI: https://doi.org/10.1002/pon.1194.
3. Moran JR, Short PF. Does cancer reduce labor market entry? Evidence for prime-age females. Med Care Res Rev 2014 Jun;71(3):224-42. DOI: https://doi.org/10.1177/1077558713510359.
4. Farley Short P, Vasey JJ, Moran JR. Long-term effects of cancer survivorship on the employment of older workers. Health Serv Res 2008 Feb;43(1 Pt 1):193-210. DOI: https://doi.org/10.1111/j.1475-6773.2007.00752.x.
5. Moran JR, Short PF, Hollenbeak CS. Long-term employment effects of surviving cancer. J Health Econ 2011 May;30(3):505-14. DOI: https://doi.org/10.1016/j.jhealeco.2011.02.001.
6. Zajacova A, Dowd JB, Schoeni RF, Wallace RB. Employment and income losses among cancer survivors: Estimates from a national longitudinal survey of American families. Cancer 2015 Dec 15;121(24):4425-32. DOI: https://doi.org/10.1002/cncr.29510.
7. Ekwueme DU, Yabroff KR, Guy GP Jr, et al; Centers for Disease Control and Prevention (CDC). Medical costs and productivity losses of cancer survivors—United States, 2008-2011. MMWR Morb Mortal Wkly Rep 2014 Jun 13;63(23):505-10.
8. de Boer AG, Frings-Dresen MH. Employment and the common cancers: Return to work of cancer survivors. Occup Med (Lond) 2009 Sep;59(6):378-80. DOI: https://doi.org/10.1093/occmed/kqp087.
9. Thong MS, Mols F, Wang XS, Lemmens VE, Smilde TJ, van de Poll-Franse LV. Quantifying fatigue in (long-term) colorectal cancer survivors: A study from the population-based patient reported outcomes following initial treatment and long term evaluation of survivorship registry. Eur J Cancer 2013 May;49(8):1957-66. DOI: https://doi.org/10.1016/j.ejca.2013.01.012.
10. Mehnert A. Employment and work-related issues in cancer survivors. Crit Rev Oncol Hematol 2011 Feb;77(2):109-30. DOI: https://doi.org/10.1016/j.critrevonc.2010.01.004.
11. Mehnert A, de Boer A, Feuerstein M. Employment challenges for cancer survivors. Cancer 2013 Jun 1;119 Suppl 11:2151-9. DOI: https://doi.org/10.1002/cncr.28067.
12. Aaronson NK, Mattioli V, Minton O, et al. Beyond treatment—psychosocial and behavioural issues in cancer survivorship research and practice. EJC Suppl 2014 Jun;12(1):54-64. DOI: https://doi.org/10.1016/j.ejcsup.2014.03.005.
13. Schmidt CE, Bestmann B, Küchler T, Longo WE, Kremer B. Prospective evaluation of quality of life of patients receiving either abdominoperineal resection or sphincter-preserving procedure for rectal cancer. Ann Surg Oncol 2005 Feb;12(2):117-23. DOI: https://doi.org/10.1245/aso.2005.12.036.
14. McKenzie F, White CA, Kendall S, Finlayson A, Urquhart M, Williams I. Psychological impact of colostomy pouch change and disposal. Br J Nurs 2006 Mar 23-Apr 12;15(6):308-16. DOI: https://doi.org/10.12968/bjon.2006.15.6.20678.
15. Vironen JH, Kairaluoma M, Aalto AM, Kellokumpu IH. Impact of functional results on quality of life after rectal cancer surgery. Dis Colon Rectum 2006 May;49(5):568-78. DOI: https://doi.org/10.1007/s10350-006-0513-6.
16. Krouse R, Grant M, Ferrell B, Dean G, Nelson R, Chu D. Quality of life outcomes in 599 cancer and non-cancer patients with colostomies. J Surg Res 2007 Mar;138(1):79-87. DOI: https://doi.org/10.1016/j.jss.2006.04.033.
17. Mao JJ, Armstrong K, Bowman MA, Xie SX, Kadakia R, Farrar JT. Symptom burden among cancer survivors: Impact of age and comorbidity. J Am Board Fam Med 2007 Sep-Oct;20(5):434-43. DOI: https://doi.org/10.3122/jabfm.2007.05.060225.
18. Mitchell KA, Rawl SM, Schmidt CM, et al. Demographic, clinical, and quality of life variables related to embarrassment in veterans living with an intestinal stoma. J Wound Ostomy Continence Nurs 2007 Sep-Oct;34(5):524-32. DOI: https://doi.org/10.1097/01.won.0000290732.15947.9e.
19. McMullen CK, Hornbrook MC, Grant M, et al. The greatest challenges reported by long-term colorectal cancer survivors with stomas. J Support Oncol 2008 Apr;6(4):175-82.
20. Baldwin CM, Grant M, Wendel C, et al. Influence of intestinal stoma on spiritual quality of life of US veterans. J Holist Nurs 2008 Sep;26(3):185-94. DOI: https://doi.org/10.1177/0898010108315185.
21. Altschuler A, Ramirez M, Grant M, et al. The influence of husbands' or male partners' support on women's psychosocial adjustment to having an ostomy resulting from colorectal cancer. J Wound Ostomy Continence Nurs 2009 May-Jun;36(3):299-305. DOI: https://doi.org/10.1097/won.0b013e3181a1a1dc.
22. Baldwin CM, Grant M, Wendel C, et al. Gender differences in sleep disruption and fatigue on quality of life among persons with ostomies. J Clin Sleep Med 2009 Aug 15;5(4):335-43.
23. Krouse RS, Herrinton LJ, Grant M, et al. Health-related quality of life among long-term rectal cancer survivors with an ostomy: Manifestations by sex. J Clin Oncol 2009 Oct 1;27(28):4664-70. DOI: https://doi.org/10.1200/jco.2008.20.9502.
24. Liu L, Herrinton LJ, Hornbrook MC, Wendel CS, Grant M, Krouse RS. Early and late complications among long-term colorectal cancer survivors with ostomy or anastomosis. Dis Colon Rectum 2010 Feb;53(2):200-12. DOI: https://doi.org/10.1007/dcr.0b013e3181bdc408.
25. Popek S, Grant M, Gemmill R, et al. Overcoming challenges: Life with an ostomy. Am J Surg 2010 Nov;200(5):640-5. DOI: https://doi.org/10.1016/j.amjsurg.2010.07.009.
26. Grant M, McMullen CK, Altschuler A, et al. Gender differences in quality of life among long-term colorectal cancer survivors with ostomies. Oncol Nurs Forum 2011 Sep;38(5):587-96. DOI: https://doi.org/10.1188/11.onf.587-596.
27. Hornbrook MC, Wendel CS, Coons SJ, et al. Complications among colorectal cancer survivors: SF-6D preference-weighted quality of life scores. Med Care 2011 Mar;49(3):321-6. DOI: https://doi.org/10.1097/mlr.0b013e31820194c8.
28. McMullen CK, Wasserman J, Altschuler A, et al. Untreated peristomal skin complications among long-term colorectal cancer survivors with ostomies. Clin J Oncol Nurs 2011 Dec;15(6):644-50. DOI: https://doi.org/10.1188/11.cjon.644-650.
29. Grant M, McMullen CK, Altschuler A, et al. Irrigation practices in long-term survivors of colorectal cancer with colostomies. Clin J Oncol Nurs 2012 Oct;16(5):514-9. DOI: https://doi.org/10.1188/12.cjon.514-519.
30. Bulkley J, McMullen CK, Hornbrook MC, et al. Spiritual well-being in long-term colorectal cancer survivors with ostomies. Psychooncology 2013 Nov;22(11):2513-21. DOI: https://doi.org/10.1002/pon.3318.
31. Skeps R, McMullen CK, Wendel CS, et al. Changes in body mass index and stoma related problems in the elderly. J Geriatr Oncol 2013 Jan;4(1):84-9. DOI: https://doi.org/10.1016/j.jgo.2012.10.172.
32. Sun V, Grant M, McMullen CK, et al. Surviving colorectal cancer: Long-term, persistent ostomy-specific concerns and adaptations. J Wound Ostomy Continence Nurs 2013 Jan-Feb;40(1):61-72. DOI: https://doi.org/10.1097/won.0b013e3182750143.
33. McMullen CK, Schneider J, Altschuler A, et al. Caregivers as healthcare managers: Health management activities, needs, and caregiving relationships for colorectal cancer survivors with ostomies. Support Care Cancer 2014 Sep;22(9):2401-8. DOI: https://doi.org/10.1007/s00520-014-2194-3.
34. Sun V, Grant M, McMullen CK, et al. From diagnosis through survivorship: Health-care experiences of colorectal cancer survivors with ostomies. Support Care Cancer 2014 Jun;22(6):1563-70. DOI: https://doi.org/10.1007/s00520-014-2118-2.
35. Sun V, Grant M, Wendel CS, et al. Dietary and behavioral adjustments to manage bowel dysfunction after surgery in long-term colorectal cancer survivors. Ann Surg Oncol 2015 Dec;22(13):4317-24. DOI: https://doi.org/10.1245/s10434-015-4731-9.
36. Jones JM, Olson K, Catton P, et al. Cancer-related fatigue and associated disability in post-treatment cancer survivors. J Cancer Surviv 2016 Feb;10(1):51-61. DOI: https://doi.org/10.1007/s11764-015-0450-2.
37. Jansen L, Koch L, Brenner H, Arndt V. Quality of life among long-term (≥ 5 years) colorectal cancer survivors—systematic review. Eur J Cancer 2010

Nov;46(16):2879-88. DOI: https://doi.org/10.1016/j.ejca.2010.06.010.

38. Jansen L, Herrmann A, Stegmaier C, Singer S, Brenner H, Arndt V. Health-related quality of life during the 10 years after diagnosis of colorectal cancer: A population-based study. J Clin Oncol 2011 Aug 20;29(24):3263-9. DOI: https://doi.org/10.1200/jco.2010.31.4013.
39. Ness S, Kokal J, Fee-Schroeder K, Novotny P, Satele D, Barton D. Concerns across the survivorship trajectory: Results from a survey of cancer survivors. Oncol Nurs Forum 2013 Jan;40(1):35-42. DOI: https://doi.org/10.1188/13.onf.35-42.
40. van den Brink M, van den Hout WB, Kievit J, et al. The impact of diagnosis and treatment of rectal cancer on paid and unpaid labor. Dis Colon Rectum 2005 Oct;48(10):1875-82. DOI: https://doi.org/10.1007/s10350-005-0120-y.
41. Wendel CS, Grant M, Herrinton L, et al. Reliability and validity of a survey to measure bowel function and quality of life in long-term rectal cancer survivors. Qual Life Res 2014 Dec;23(10):2831-40. DOI: https://doi.org/10.1007/s11136-014-0724-6.
42. Grant M, Ferrell B, Dean G, Uman G, Chu D, Krouse R. Revision and psychometric testing of the City of Hope Quality of Life-Ostomy Questionnaire. Qual Life Res 2004 Oct;13(8):1445-57. DOI: https://doi.org/10.1023/b:qure.0000040784.65830.9f.
43. Temple LK, Bacik J, Savatta SG, et al. The development of a validated instrument to evaluate bowel function after sphincter-preserving surgery for rectal cancer. Dis Colon Rectum 2005 Jul;48(7):1353-65. DOI: https://doi.org/10.1007/s10350-004-0942-z.
44. Smith T, Stein KD, Mehta CC, et al. The rationale, design, and implementation of the American Cancer Society's studies of cancer survivors. Cancer 2007 Jan 1;109(1):1-12. DOI: https://doi.org/10.1002/cncr.22387.
45. Lerro CC, Stein KD, Smith T, Virgo KS. A systematic review of large-scale surveys of cancer survivors conducted in North America, 2000-2011. J Cancer Surviv 2012 Jun;6(2):115-45. DOI: https://doi.org/10.1007/s11764-012-0214-1.
46. Ross TR, Ng D, Brown JS, et al. The HMO Research Network virtual data warehouse: A public data model to support collaboration. EGEMS (Wash DC) 2014 Mar 24;2(1):1049. DOI: https://doi.org/10.13063/2327-9214.1049.
47. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992 Jun;45(6):613-9. DOI: https://doi.org/10.1016/0895-4356(92)90133-8.
48. Krouse RS, Grant M, Wendel CS, et al. A mixed-methods evaluation of health-related quality of life for male veterans with and without intestinal stomas. Dis Colon Rectum 2007 Dec;50(12):2054-66. DOI: https://doi.org/10.1007/s10350-007-9004-7.
49. Jain S, McGory ML, Ko CY, et al. Comorbidities play a larger role in predicting health-related quality of life compared to having an ostomy. Am J Surg 2007 Dec;194(6):774-9. DOI: https://doi.org/10.1016/j.amjsurg.2007.08.020.
50. DeSantis CE, Lin CC, Mariotto AB, et al. Cancer treatment and survivorship statistics, 2014. CA Cancer J Clin 2014 Jul-Aug;64(4):252-71. DOI: https://doi.org/10.3322/caac.21235.
51. de Moor JS, Mariotto AB, Parry C, et al. Cancer survivors in the United States: Prevalence across the survivorship trajectory and implications for care. Cancer Epidemiol Biomarkers Prev 2013 Apr;22(4):561-70. DOI: https://doi.org/10.1158/1055-9965.epi-12-1356.
52. Weber-Raley L, Smith E; Greenwald & Associates. Caregiving in the US: 2015 report [Internet]. Bethesda, MD: National Alliance for Caregiving (NAC); 2015 [cited 2017 Jul 25]. Available from: www.caregiving.org/wp-content/uploads/2015/05/2015_CaregivingintheUS_Final-Report-June-4_WEB.pdf.
53. Lundy JJ, Coons SJ, Wendel C, et al. Exploring household income as a predictor of psychological well-being among long-term colorectal cancer survivors. Qual Life Res 2009 Mar;18(2):157-61. DOI: https://doi.org/10.1007/s11136-008-9432-4.
54. Black PK. Hidden problems of stoma care. Br J Nurs 1994 Jul 28-Aug 10;3(14):707-11. DOI: https://doi.org/10.12968/bjon.1994.3.14.707.
55. Aron S, Carrareto R, Prazeres SM, de Cerqueira AP, Santos VL. Self-perceptions about having an ostomy: A postoperative analysis. Ostomy Wound Manage 1999 Apr;45(4):46-50, 52-4, 56 passim.
56. Berndtsson I, Lindholm E, Ekman I. Thirty years of experience living with a continent ileostomy: Bad restrooms—not my reservoir—decide my life. J Wound Ostomy Continence Nurs 2005 Sep-Oct;32(5):321-6. DOI: https://doi.org/10.1097/00152192-200509000-00010.
57. Stergiou-Kita M, Grigorovich A, Tseung V, et al. Qualitative meta-synthesis of survivors' work experiences and the development of strategies to facilitate return to work. J Cancer Surviv 2014 Dec;8(4):657-70. DOI: https://doi.org/10.1007/s11764-014-0377-z.
58. Bains M, Munir F, Yarker J, Steward W, Thomas A. Return-to-work guidance and support for colorectal cancer patients: A feasibility study. Cancer Nurs 2011 Nov-Dec;34(6):E1-12. DOI: https://doi.org/10.1097/ncc.0b013e31820a4c68.
59. Bains M, Munir F, Yarker J, et al. The impact of colorectal cancer and self-efficacy beliefs on work ability and employment status: A longitudinal study. Eur J Cancer Care (Engl) 2012 Sep;21(5):634-41. DOI: https://doi.org/10.1111/j.1365-2354.2012.01335.x.
60. Bains M, Yarker J, Amir Z, Wynn P, Munir F. Helping cancer survivors return to work: What providers tell us about the challenges in assisting cancer patients with work questions. J Occup Rehabil 2012 Mar;22(1):71-7. DOI: https://doi.org/10.1007/s10926-011-9330-4.
61. Faller H, Koch U, Brähler E, et al. Satisfaction with information and unmet information needs in men and women with cancer. J Cancer Surviv 2016 Feb;10(1):62-70. DOI: https://doi.org/10.1007/s11764-015-0451-1.
62. Burch J. Psychological problems and stomas: A rough guide for community nurses. Br J Community Nurs 2005 May;10(5):224-7. DOI: https://doi.org/10.12968/bjcn.2005.10.5.18051.
63. Brown H, Randle J. Living with a stoma: A review of the literature. J Clin Nurs 2005 Jan;14(1):74-81. DOI: https://doi.org/10.1111/j.1365-2702.2004.00945.x.
64. Downing A, Morris EJ, Richards M, et al. Health-related quality of life after colorectal cancer in England: A patient-reported outcomes study of individuals 12 to 36 months after diagnosis. J Clin Oncol 2015 Feb 20;33(6):616-24. DOI: https://doi.org/10.1200/jco.2014.56.6539.
65. Pachler J, Wille-Jørgensen P. Quality of life after rectal resection for cancer, with or without permanent colostomy. Cochrane Database Syst Rev 2012 Dec 12;12:CD004323. DOI: https://doi.org/10.1002/14651858.cd004323.pub4.

Care and Heal

The physician takes care, nature heals.

— Hippocrates of Kos, 460 BC – 370 BC, Greek physician of the Age of Pericles

On Becoming Trauma-Informed: Role of the Adverse Childhood Experiences Survey in Tertiary Child and Adolescent Mental Health Services and the Association with Standard Measures of Impairment and Severity

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ABSTRACT

Context: There is a movement toward trauma-informed, trauma-focused psychiatric treatment.

Objective: To examine Adverse Childhood Experiences (ACE) survey items by sex and by total scores by sex vs clinical measures of impairment to examine the clinical utility of the ACE survey as an index of trauma in a child and adolescent mental health care setting.

Design: Descriptive, polychoric factor analysis and regression analyses were employed to analyze cross-sectional ACE surveys (N = 2833) and registration-linked data using past admissions (N = 10,400) collected from November 2016 to March 2017 related to clinical data (28 independent variables), taking into account multicollinearity.

Results: Distinct ACE items emerged for males, females, and those with self-identified sex and for ACE total scores in regression analysis. In hierarchical regression analysis, the final models consisting of standard clinical measures and demographic and system variables (eg, repeated admissions) were associated with substantial ACE total score variance for females (44%) and males (38%). Inadequate sample size foreclosed on developing a reduced multivariable model for the self-identified sex group.

Conclusion: The ACE scores relate to independent clinical measures and system and demographic variables. There are implications for clinical practice. For example, a child presenting with anxiety and a high ACE score likely requires treatment that is different from a child presenting with anxiety and an ACE score of zero. The ACE survey score is an important index of presenting clinical status that guides patient care planning and intervention in the progress toward a trauma-focused system of care.

INTRODUCTION

The movement toward trauma-informed and trauma-focused psychiatric treatment is an important consideration that requires considerable professional education and adjustment in the system of care. For example, psychiatric treatment generally focuses on specific diseases, disorders, and syndromes, whereas, in actuality, from the perspective of developmental psychopathology, the gateways to diagnostic entities—whether idiopathic or constitutional—are invariably influenced by environmental factors such as early experiences. In the future, the ability to understand and contextualize the report of early adverse or traumatic experiences will fundamentally influence the approach to diagnosis and treatment of all psychiatric entities.[1] This proposition is reminiscent to some extent of the longstanding distinction between the categorical and dimensional approaches to conceptualization. For example, adolescent depression may be efficiently measured as a multidimensional entity.[2] Such arguments represent a false dichotomy, and more modern algorithmic approaches to diagnosis and treatment take into account the multiaxial nature of mental disorders.[3-7]

In this article, we examine the relationship between Adverse Childhood Experiences (ACE) Study survey scores as an index of trauma and measures of impairment typically used systemwide locally to evaluate the clinical severity of referrals and admissions to the regional Child and Adolescent Addiction, Mental Health and Psychiatry Program (CAAMHPP) in Alberta, Canada. The main purpose of this study was to establish an evidence base, as the first step for becoming trauma-informed and ultimately trauma-focused at a system level vis-à-vis the implementation of the ACE survey.

Even though the link between trauma, human development, and subsequent lifespan adaptation has long been established, a focus on child health policy formation[8-18] to guide the development of trauma-informed and trauma-focused intervention is only beginning to take shape as a standard of care in mental health systems.[19] Although many regional institutions in Canada are moving toward developing policies, guidelines, and education, implementation at the level of patient care lags.

One of the most influential bodies of work advancing the importance of the

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impact of early adversity in relationship to developmental psychopathology has been the ACE Study,[20-23] especially in respect to overall health status during the lifespan.[24-26] Nevertheless, children's health and mental health systems' responses continue to plod, as at the time of the seminal Kirby Report,[27] especially within our own catchment. For example, there is evidence of local systemic stigma based on population data analysis, in that children registered in tertiary mental health services receive less emergency and inpatient treatment for their physical disorders after psychiatric diagnosis than do children with no mental disorder, even though they have more physical and biomedical diagnoses at the levels of ambulatory and provincial physician billing.[28]

We report on the development of the evidence base by examining the ACE survey scores in relationship to the established clinical measures of clinical severity, global function, and problem severity collected routinely for children and adolescents referred and accepted for treatment.[29,30] Systemwide implementation of the ACE survey, as a first step, positions CAAMHPP to become an evidence-based, trauma-informed service organization, because ACE survey scores necessarily must relate to clinical outcomes in order to evaluate the effect of trauma-focused interventions in clinical practice. We hypothesized that ACE scores would be positively associated with our standard measures of clinical severity and impairment in addition to demographics (age, sex, family composition) and system variables (repeated admissions). Through this examination, we set the stage for evaluating clinical interventions in relationship to ACE scores and treatment outcomes that may inform our long-term goal of developing effective trauma-focused care.

METHODS

This research was conducted under The University of Calgary Research Ethics Board approval (REB15-1057).

Staff Training and Data Collection

After participation in the Alberta Family Wellness Initiative 2014 Accelerating Innovation Symposium, the CAAMHPP administration decided in December 2014 to implement the ACE survey. After 2 formal staff orientations (N = 300) and dissemination of a plan for electronic survey data collection, voluntary implementation of the ACE survey commenced in November 2015, and mandatory implementation of the ACE survey for each registration began in September 2016.

Staff orientation and training about the ACE Study and survey criteria continued biannually between 2014 and 2017. An online presentation and training manual were developed and disseminated in September 2016, and ACE training was embedded in new staff orientation, ensuring a minimal level of consistency in survey completion and thereby enhancing the potential for collecting reliable and valid data. The ACE total score was entered into the regional information system commencing in November 2015. Subsequently in April 2016, all 10 ACE survey items were embedded in the information system, which also contained the clinical profile, outcomes, and demographic and system-level data from which the data for this study were extracted and analyzed.

Each clinical area collected the data and completed the survey as best fit its practice model. For example, some areas might complete the survey on admission if this fit with their model of engagement or, alternatively, gather the ACE survey information during the course of treatment. Training feedback indicated that the ACE survey items represented information normally collected in the course of assessment and treatment, and the survey presented a way to formalize data collection to inform clinical treatment via the ten nominal categories of early childhood adversity as embedded in the ACE survey. The main message disseminated was that the implementation was not gathering new information; rather the ACE survey represented a novel way of organizing clinical information in relation to patient care. The training process also presented the opportunity to disseminate the education developed by the Alberta Family Wellness Initiative.

Participants

Eligible participants included all postimplementation active-treatment enrollments (not consults or assessments; N = 9329 registrations to the regional tertiary child addiction and adolescent mental health services [CAAMHPP, Alberta Health Services, Calgary Zone, Alberta, Canada]). The registrations consisted of 2464 unique males (mean age = 12.3 years), 3268 unique females (mean age = 14.7 years), and 77 unique others (self-identified sex; mean age = 18.8 years).

Instruments

Measurement of clinical profiles of patient referrals and enrollments in the regional tertiary child addiction and adolescent mental health services are well described; valid and reliable measures collected on referral, admission, and discharge have been employed at CAAMHPP since April 2002, and the admission and discharge Strength/Concern scale were implemented in 2008.[30] The following measures constituted the independent variables:

1. Admission and discharge ratings of global function were included, as were admission and discharge ratings of problem severity (Strength/Concern scale), which constitute the measurable treatment plan.[29,30] Improving function and reducing problem severity represent the core objectives of any intervention, and employing long-established published measures of these domains is value added.
2. The Western Canada Waiting List Children's Mental Health-Priority Criteria Score (WCWL-CMH-PCS) form has been completed regularly for first-time admissions since 2002 regionally.[30] The WCWL-CMH-PCS form consists of 18 clinical items capturing the clinician raters' assessment of urgency and has been described in detail elsewhere.[30,31] This measure of clinical urgency prioritizes clients' relative position on waiting lists in clinics. The items sum to a total score of 100; however, each item is a relatively independent domain of measurement highly relevant to providing a detailed clinical picture when employed to compare clinically distinct groups or, in this study, the relationship to ACE survey scores.
3. Demographic data (age, sex, family composition) and system variables were collected. For demographics, family

composition by increasing clinical risk consisted of 3 groups: a) blended/biological families; b) single parent; and c) blood relatives, foster care, or ward of the government. The system variables were repeated admissions and length of stay. (Other system variables, such as the reason for referral, and diagnosis were not included because these variables did not map efficiently onto the sample construction employed in the final analysis.)

4. The ACE survey total score, the dependent variable in analyses, was the sum of 10 items describing distinct categories of early adversity (http://ACEstudy.org/the-ace-score.html). Many studies testify to the validity of the ACE survey.[21-23,32-34] Two forms of ACE survey total scores (cross-sectional and registration-linked) were employed as detailed in the next 2 sections.

Sample Construction

The present model of care employed in the regional child and adolescent mental health service is episodic, meaning that once enrolled in the system of care, a patient may have a single admission or, depending on need, multiple admissions (eg, emergency, inpatient, ambulatory services, or specialized services). The unit of analysis in the present study was each patient, and patients at CAAMHPP tend to have on average three admissions. One assumption supporting the validity of this approach is that early adversity—measured using the ACE survey—preceded mental disorder and the need for services. Many patients in the served population had been admitted before the implementation of the ACE survey. In construction of the dataset under analysis, baseline (first admission) clinical profiles and demographics were linked to last-admission outcomes data (global function and Strength/Concern ratings). These data were then linked to the ACE survey data (cross-sectional data). Exploratory analyses were conducted to examine the relationship between the models of ACE survey data on the basis of cross-sectional admissions with data linked to all registrations for each patient (registration-linked data).

Data Analysis

Demographic variables were examined regarding potential modification and confounding effects. Sex was found to have a significant relationship with both dependent and independent variables, and hence sexes were analyzed separately. Descriptive statistics included mean, median, count of subsample size, lower 95% confidence interval, and upper 95% confidence interval. Significant differences were identified in the bivariate and multivariable analyses employing factor loadings, regression analysis p values, and, where applicable, comparisons of 95% confidence intervals (z set to 1.96).

Polychoric Factor Analysis

We validated the sample construction and examined the relationship between ACE items and total ACE scores (dependent variables) and important independent variables using polychoric factor analyses (designed for binary data) of the ACE survey items' factor structure. We also compared the results for the bivariate and multivariable hierarchical models-based ACE survey data linked with clinical profile data on the basis of cross-sectional unique individuals and the registration-linked samples.

Polychoric factor analysis of males (cross-sectional ACE items: n = 831) produced one factor (eigenvalue = 4.98) that accounted for 83% of the variance in the ACE score items for males. For the polychoric factor analysis of registration-linked ACE items for males (n = 3004), one factor (eigenvalue = 4.75) accounted for 77% of the variance in the ACE score items for males.

Polychoric factor analysis of females (cross-sectional ACE items: n = 1387) produced one factor (eigenvalue = 5.23) that accounted for 84% of the variance in the ACE score items for females. The polychoric factor analysis of females' registration-linked ACE items (n = 5196) had one factor (eigenvalue = 5.51) that accounted for 85% of the variance in the ACE score items for females.

For others (cross-sectional ACE items: n = 39), the sample size was not sufficient to calculate the polychoric factor structure. For registration-linked ACE score item data (ACE items: n = 513), one factor (eigenvalue = 5.62) accounted for 77% of the variance in the ACE score items for others.

Collinearity

In addition to descriptive statistics and bivariate and multivariable hierarchical linear regression analyses, collinearity among the variables was examined because of the high degree of correlation between the continuous and discrete independent variables. Potential collinearity of the independent variables was examined by comparing bivariate and multivariable analyses. Collinearity is indicated in the comparison by sign reversal and inflated standard errors in the β-coefficient in the regression on the dependent variable.[35]

Multivariable hierarchical regression analysis was selected as the optimum method to identify for each sex the most parsimonious model while controlling for collinearity. Multivariable hierarchical regression permits grouping of related variables (as described earlier in the "Instruments" section), which are then added successively to the model. Examination of independent variables contributing significantly to the full models at each stage permitted selection of the reduced parsimonious models. Both full and reduced models were examined for potential collinearity.

There were 400 possible pairwise correlations including the dependent ACE score totals variable, and 361 with the dependent variable omitted. Of these correlations, there were 290 significant correlations ($p < 0.05$) including the dependent variable and 267 significant correlations omitting the independent variable, indicating a high degree of potential collinearity. An examination of collinearity was undertaken comparing changes in the standard errors and magnitude and sign (positive or negative) of the bivariate analyses results with the standard bivariate regression models for each sex and the full hierarchical regression models.

For each case, in comparison within variables between the bivariate and multivariable models, the standard errors were within 10% and βs were within 20%. Sign changes were observed for both males and females on the WCWL-CMH-PCS items: Danger to self-2, School and/or work-2 and Comorbid medical conditions-2. Sign changes were observed for females on the

WCWL-CMH-PCS items: Does the child/adolescent (patient) have problems in the context of the home?-2, Female Prognosis without further intervention-2, Female Children's global assessment of functioning scale-2, Female Internalize symptoms-2, Female Externalize symptoms/disruptive behavior-2, and Female Comorbid psychiatric conditions-2.

All the independent variables measure a single construct (psychopathy); hence, it may be expected that these would be intercorrelated. Hierarchical linear regression provided a means of grouping the variables in a meaningful way. For example, Strength/Concern and function ratings are composites of the measurable treatment plan (Group 1) and the WCWL-CMH-PCS items (Group 2) groups; additionally, demographic and system variables (Group 3) were grouped for convenience to examine the potential effects of collinearity. Of all the independent variables, when we compared hierarchical regression models (full and reduced) with bivariate regression results, only 2 variables in the full hierarchical model for females provided evidence of collinearity in sign reversal and magnitude change. Externalizing symptoms/disruptive behavior-2 and Comorbid psychiatric conditions-2 shifted from significant in the bivariate model to nonsignificant in the full hierarchical model, but they were not in the final model. On the basis of this examination and approach to modeling,[35] multicollinearity was deemed to have minimal effect in respect to the final models. The potential effect of multicollinearity was possible given the high level of intercorrelation among all of the variables. Evidence of the effective multicollinearity comparing bivariate and multivariable models was examined in detail, finding a minimal influence, particularly in the hierarchical regression analysis.

Table 1. Description of Adverse Childhood Experiences item scores by sex

	Cross-sectional		Registration-linked	
ACE item	Observed	Proportions (LCI, UCI)	Observed	Proportions[a] (LCI, UCI)
Male				
1. Emotional abuse[b,c]	831	0.28 (0.25, 0.31)	3004	0.36 (0.34, 0.38)
2. Physical abuse[b]	831	0.15 (0.12, 0.17)	3004	0.19 (0.18, 0.21)
3. Sexual abuse[c]	831	0.04 (0.03, 0.06)	3004	0.06 (0.05, 0.07)
4. Lack of love/support[b,c]	831	0.27 (0.24, 0.3)	3004	0.34 (0.32, 0.35)
5. Neglect[b]	831	0.1 (0.08, 0.12)	3004	0.16 (0.15, 0.18)
6. Parental divorce/separation[b]	831	0.5 (0.46, 0.53)	3004	0.56 (0.54, 0.58)
7. Spousal abuse of parent	831	0.2 (0.17, 0.23)	3004	0.24 (0.23, 0.26)
8. Parental substance abuse	831	0.25 (0.22, 0.28)	3004	0.28 (0.27, 0.3)
9. Parental mental illness[a,b,c]	831	0.48 (0.45, 0.52)	3004	0.55 (0.53, 0.57)
10. Parental incarceration	831	0.07 (0.05, 0.09)	3004	0.09 (0.08, 0.1)
Female				
1. Emotional abuse[b]	1387	0.35 (0.33, 0.38)	5196	0.43 (0.42, 0.45)
2. Physical abuse[a]	1387	0.18 (0.16, 0.2)	5196	0.25 (0.23, 0.26)
3. Sexual abuse[a]	1387	0.15 (0.13, 0.17)	5196	0.2 (0.19, 0.21)
4. Lack of love/support[a]	1387	0.41 (0.38, 0.44)	5196	0.5 (0.49, 0.51)
5. Neglect[a]	1387	0.12 (0.1, 0.13)	5196	0.15 (0.15, 0.17)
6. Parental divorce/separation	1387	0.48 (0.46, 0.51)	5196	0.54 (0.53, 0.56)
7. Spousal abuse of parent	1387	0.21 (0.19, 0.24)	5196	0.26 (0.25, 0.28)
8. Parental substance abuse	1387	0.29 (0.27, 0.32)	5196	0.34 (0.32, 0.35)
9. Parental mental illness[b]	1387	0.56 (0.54, 0.59)	5196	0.64 (0.62, 0.65)
10. Parental incarceration	1387	0.08 (0.07, 0.1)	5196	0.1 (0.09, 0.11)
Other (self-identified sex)				
1. Emotional abuse	39	0.44 (0.28, 0.6)	536	0.38 (0.33, 0.42)
2. Physical abuse	39	0.33 (0.19, 0.5)	536	0.19 (0.16, 0.23)
3. Sexual abuse	39	0.28 (0.15, 0.45)	536	0.18 (0.15, 0.22)
4. Lack of love/support	39	0.56 (0.4, 0.72)	536	0.47 (0.42, 0.51)
5. Neglect	39	0.28 (0.15, 0.45)	536	0.23 (0.19, 0.27)
6. Parental divorce/separation	39	0.54 (0.37, 0.7)	536	0.51 (0.47, 0.55)
7. Spousal abuse of parent	39	0.41 (0.26, 0.58)	536	0.33 (0.29, 0.38)
8. Parental substance abuse	39	0.33 (0.19, 0.5)	536	0.33 (0.29, 0.37)
9. Parental mental illness	39	0.64 (0.47, 0.79)	536	0.56 (0.51, 0.6)
10. Parental incarceration	39	0.23 (0.11, 0.39)	536	0.14 (0.11, 0.17)

[a] Proportion refers to the number of observations endorsing the ACE item.
[b] Within sex cross-sectional vs registration-linked nonoverlapping 95% confidence interval.
[c] Between sex (male vs female) nonoverlapping 95% confidence interval.
ACE = Adverse Childhood Experiences; LCI = lower 95% confidence interval; UCI = upper 95% confidence interval.

RESULTS

Table 1 compares the proportional distributions of responses for each ACE item collected in cross-section for a single admission (at the time of and during the course of admission) or on the basis of data linkage by each individual patient registration to the clinical profile data with baseline data from the first admission and outcomes data from the last discharge. From Table 1, higher proportions indicate a greater number of the group is closer to the value 1 compared with the value 0. All differences in proportions (sex, ACE item number, proportion) between linked and cross-sectional data were less than 9% within each sex (maximum 8% for item 8 for males and maximum 9% for item 3 for females), notwithstanding that there were a number of within sex (ACE items 1, 2, 4, 6, 9 for males and females) and between sex differences (ACE items 1, 3, 4, 9). Note that there were very few cross-sectional ACE surveys completed for the Other category, but that these linked with 536 unique patient registrations, a ratio of 13.7 compared with 3.6 for males and 3.7 for females. Comparison of the unlinked cross-sectional and registration-linked data groups indicated that the data linkage was reliable for analyzing the relationship of the ACE survey data and the standard clinical measures employed. The clinical relevance of this approach is presented in the Discussion section.

Table 2. Polychoric factor analysis results by sex

ACE item from registration-linked data	Male (n = 3004) (uniqueness)	Female (n = 5196) (uniqueness)	Other[a] (n = 513) (uniqueness)
1. Emotional abuse	0.87 (0.24)	0.83 (0.32)	0.77 (0.41)
2. Physical abuse	0.81 (0.34)	0.83 (0.32)	0.78 (0.4)
3. Sexual abuse	0.34 (0.89)	0.62 (0.61)	0.57 (0.68)
4. Lack of love/support	0.69 (0.52)	0.76 (0.42)	0.77 (0.4)
5. Neglect	0.71 (0.5)	0.86 (0.27)	0.85 (0.28)
6. Parental divorce/separation	0.65 (0.58)	0.72 (0.49)	0.76 (0.42)
7. Spousal abuse of parent	0.76 (0.42)	0.8 (0.37)	0.81 (0.35)
8. Parental substance abuse	0.71 (0.5)	0.75 (0.44)	0.77 (0.41)
9. Parental mental illness	0.65 (0.58)	0.57 (0.67)	0.6 (0.64)
10. Parental incarceration	0.57 (0.68)	0.64 (0.58)	0.78 (0.39)

[a] Self-identified sex.
ACE = Adverse Childhood Experiences.

Table 2 shows the polychoric factor structure for the registration-linked ACE item data. All item loadings on factors ranged between 2% and 17% of each other. There were greater differences between the sex-based groups: ACE Item 3 (sexual abuse) loads on the factor for females 45% more than for males, and comparable to others (self-identified sex), sexual abuse loads on the factor for others 40% more than for males. This observation indicates that the factor structure of the cross-sectional and linked data was stable and comparable and that females and others reported sexual abuse more than males did.

The sample of patients with ACE scores on at least 1 admission since implementation consisted of 1098 males of an average age of 11.6 years (standard deviation = 4.6 years), 1686 females of average age 13.9 years (standard deviation = 6.1 years), and 49 others of average age 17.3 years (standard deviation = 7.1 years). The total numbers admitted with outcome measures since implementation was 3727 males, 6133 females, and 560 others.

Sex and family composition were associated (3 groups: biological/stepparent; single parent; and adoptive or foster parent, ward, or blood relative; $\chi^2 = 48.9$, $p < 0.0001$). Table 3 describes all the dependent and independent variables underpinning the development of a final parsimonious model describing the relationship between 3 groups of independent variables and individual ACE survey score totals. Sexes were considered separately for clarity of comparison on the basis of between-group differences within ACE score and within independent variable distributions.

Table 3 also shows (indicated by a superscript b) the independent variables that were not significantly related to the ACE total score in cross-sectional or linked bivariate analysis. Overall, for the significant bivariate regression relationships, compared with the bivariate regression results of unique patient cross-sectional ACE score totals on the independent variable, the results were similar to the regression on the registration-linked data variables. For males, 29 variables significantly predicted cross-sectional ACE score totals, and 27 variables significantly predicted registration-linked ACE score totals. For females, 28 variables significantly predicted cross-sectional ACE scores, and 26 variables significantly predicted registration-linked ACE score totals. For others, the sample size for cross-sectional examination was too sparse to reliably examine the relationship between ACE scores and the independent variables. For the others with registration-linked ACE score data, 16 variables significantly predicted registration-linked ACE score totals. The results of the bivariate analysis for registration-linked and cross-sectional data indicated that the registration-linked data results are stable and representative compared with cross-sectional data. More importantly, these results indicate that most clinical and system measures were related to the ACE score total, a finding that underpins the centrality of the ACE survey in clinical assessment and potentially treatment.

Model Summary

A hierarchical multivariable regression model was developed to describe the relationship of ACE survey total scores to the independent variables. Table 4 provides a summary of the final model, and the details of the independent variables in relation to the ACE total scores for each sex are shown in Table 5. Model development commenced with 3 groups of registration-linked independent variables resulting in the final reduced model, which differed for males and females: Group 1: Minimum admission and maximum discharge global function and Strength/Concern ratings; Group 2: WCWL-CMH-PCS items; and Group 3: The system variable of number of repeated admissions and the demographic variable of family composition. Overall, the variables remaining in the models accounted for 38% of the ACE total score variance for males and 44% of the variance for females.

Results Summary

1. The proportional distributions of the ACE items (Table 1) and the factor structure of the ACE items (Table 2) were consistent comparing by sex the unique patient ACE scores linked in cross-section with first admissions and last discharges to all patient registration-linked ACE item survey data. For example, there was only one factor and although a number of items were significantly different probably owing to sample size (nonoverlapping 95% confidence intervals), the proportions differed by less than 9%. Differences between males and females were observed in cross-section in Table 1 for ACE items 1, 3, 4, 9; there was only one uniqueness value in Table 2 for ACE item 3 sexual abuse. There were insufficient data to include the cross-sectional data for the Other category, but there were sufficient linked data to examine the ACE survey item factor structure in the registration-linked data. Females and others were distinct from males in the factor loading structure, specifically on Item 3 relating to sexual abuse.
2. Comparison of bivariate cross-sectional and linked dependent and independent variable data indicated that

Table 3. Descriptions by sex of the patient by dependent variable (ACE scores) and all independent variables

	Male		Female		Other (self-identified sex)	
Variable[a]	Observed	Mean (LCI, UCI)	Observed	Mean (LCI, UCI)	Observed	Mean (LCI, UCI)
ACE score total, cross-sectional	1098	2.46 (2.32, 2.6)	1686	2.89 (2.77, 3.01)	49	4.1 (3.27, 4.94)
Strength/concern admission-1	3727	2.99 (2.91, 3.06)	6113	3.49 (3.43, 3.56)	560	3.31 (3.07, 3.54)
Strength/concern discharge-1	1146	3.16 (3.06, 3.26)	2004	3.27[b] (3.2, 3.33)	65	3.23 (2.89, 3.56)
Admission CGAS (add label for cross-sectional)-1	1146	5.63 (5.46, 5.8)	2004	5.55 (5.43, 5.67)	65	5.36 (4.82, 5.9)
Discharge CGAS-1	2403	45.6 (45.15, 46.06)	4193	46.49 (46.16, 46.81)	100	48.7 (45.86, 51.54)
First admission CGAS-1	1146	3.47 (3.35, 3.59)	2004	3.29 (3.2, 3.37)	65	3.43 (2.93, 3.93)
Last admission CGAS-1	3572	38.4 (38, 38.79)	5902	38.45 (38.15, 38.75)	144	35.56 (33.85, 37.26)
First admission strength/concern-1	3525	59.03 (58.66, 59.4)	5732	61.68 (61.41, 61.95)	144	68.26 (66.3, 70.23)
Last discharge strength/concern-1	2936	2.42 (2.36, 2.47)	4949	2.49 (2.45, 2.53)	138	1.88 (1.73, 2.04)
No. of repeated admissions-3	2936	6.5 (6.4, 6.6)	4949	6.52 (6.45, 6.59)	138	7.42 (7.09, 7.75)
Danger to self-2	3727	5.45 (5.29, 5.6)	6113	7.3 (6.97, 7.62)	144	10.74 (9.66, 11.82)
Danger to others-2	1872	1.02 (0.93, 1.11)	2658	1.31[b] (1.22, 1.4)	95	1.07 (0.94, 1.21)
Psychotic symptoms-2	1872	0.25 (0.23, 0.28)	2658	0.09[b] (0.08, 0.1)	95	0.19 (0.07, 0.31)
Global age-appropriate developmental progress-2	1872	0.39 (0.32, 0.46)	2658	0.39[b] (0.34, 0.44)	95	0.06 (0.01, 0.13)
Children's global assessment of function scale (CGAS)-2	1872	0.22 (0.21, 0.24)	2658	0.11 (0.1, 0.12)	95	0.17 (0.09, 0.25)
Internalize symptoms-2	1872	7.39[b] (7.24, 7.54)	2658	6.89 (6.77, 7)	95	6.27 (5.6, 6.94)
Externalizing symptoms/disruptive behavior-2	1872	5.76 (5.56, 5.97)	2658	6.99 (6.84, 7.14)	95	5.28 (4.65, 5.92)
Comorbid medical conditions-2	1872	1.79[b] (1.72, 1.86)	2658	0.93[b] (0.88, 0.98)	95	0.86 (0.59, 1.13)
Comorbid psychiatric conditions-2	1872	0.24[b] (0.22, 0.27)	2658	0.33[b] (0.31, 0.36)	95	0.48 (0.35, 0.62)
Harmful substance use/misuse-2	1872	1.08 (1, 1.16)	2658	0.88 (0.83, 0.93)	95	1.2 (1, 1.4)
Significant biological family history of mental illness-2	1872	0.05 (0.04, 0.06)	2658	0.07 (0.06, 0.08)	95	0 (0, 0)
School and/or work-2	1872	1.38 (1.33, 1.42)	2658	1.48 (1.45, 1.52)	95	1.73 (1.59, 1.87)
Social/friendships/community functioning-2	1872	0.32 (0.3, 0.34)	2658	0.22 (0.2, 0.23)	95	0 (0, 0)
Does the child/adolescent (patient) have problems in the context of the home?-2	1872	0.75 (0.73, 0.77)	2658	0.57 (0.55, 0.59)	95	0.54 (0.43, 0.64)
Family functioning or factors affecting child-2	1872	3.79 (3.71, 3.87)	2658	3.37 (3.3, 3.44)	95	2.97 (2.59, 3.35)
Prognosis without further intervention-2	1872	0.67 (0.65, 0.69)	2658	0.6 (0.58, 0.62)	95	0.4 (0.3, 0.5)
Degree of likely benefit with further intervention-2	1872	6.37[b] (6.15, 6.59)	2658	5.38[b] (5.2, 5.56)	95	7.74 (6.79, 8.68)
Global urgency-2	1869	8.42 (8.31, 8.54)	2649	8.33 (8.24, 8.42)	95	8.4 (7.9, 8.9)
WCWL-CMH-PCS total score registration-linked-2	1872	67.42 (66.43, 68.41)	2658	67.99 (67.26, 68.72)	95	67.85 (64.85, 70.86)
Cross-sectional length of stay-3	1869	38.21 (37.61, 38.82)	2649	35.98 (35.52, 36.43)	95	33.83 (32.01, 35.65)
First admission to last discharge length of stay-3	2705	91.6 (86.15, 97.06)	4450	83.68 (79.42, 87.94)	101	87.45 (55.39, 119.5)
ACE score total, registration-linked	3647	1020.88 (986.79, 1054.97)	5933	853.96 (832.19, 875.73)	144	1336.24 (1178.44, 1494.03)

[a] 1 = MTP variables; 2 = WCWL-CMH-PCS items; 3 = system and demographic variables; $p < 0.05$ between one or more sexes.

[b] Not significant.

ACE = Adverse Childhood Experiences; CGAS = Children's Global Assessment Scale; LCI = lower 95% confidence interval; MTP = measurable treatment plan; UCI = upper 95% confidence interval; WCWL-CMH-PCS = Western Canada Waiting List Children's Mental Health-Priority Criteria Score.

using linked data is acceptable from a statistical perspective.

3. There were insufficient registration-linked data in the Other category to develop a multivariate model. Two final reduced models were presented that identified the most important independent variables related to higher ACE total scores for males and females.
4. The results illustrate that the ACE survey was central to the clinical process of care planning and clinical outcomes.

Table 4. Reduced multivariable hierarchical regression model summaries for males and females describing relationship between ACE score totals and registration-linked independent variables

Model	R^2	*F* (df)	p value	R^2 change *F* (df)	Change (df)	p value
Male						
1	0.14	54.092 (4, 1400)	0.0001	—	—	—
2	0.35	69.169 (14, 1390)	0.0001	0.21	44.452 (10, 1390)	0.0001
3	0.38	79.116 (16, 1388)	0.0001	0.31	34.426 (2, 1388)	0.0001
Female						
1	0.07	100.079 (2, 1936)	0.00001	—	—	—
2	0.23	78.745 (9, 1929)	0.00001	0.15	54.811 (7, 1929)	0.00001
3	0.44	470.799 (12, 1926)	0.00001	0.21	238.965 (3, 1926)	0.00001

ACE = Adverse Childhood Experiences; df = degrees of freedom.

Table 5. Final reduced model details of independent variables by sex

ACE score total, registration-linked (dependent variable)	Males		Females	
	Coef[a]	SE	Coef[a]	SE
1. CGAS admission	-0.02	0.01	—	—
1. CGAS discharge	-0.04	0.01	—	—
1. Strength/concern admission	-0.19	0.05	-0.08	0.04
1. Strength/concern discharge	0.07	0.02	-0.15	0.02
2. Danger to self	-0.15	0.04	0.06	0.02
2. Danger to others	0.83	0.12	—	—
2. Psychotic symptoms[b]	0.1	0.04	—	—
2. Global age-appropriate developmental progress on referral[b]	—	—	-0.34	0.14
2. Children's global assessment of function scale on referral	—	—	0.06	0.02
2. Internalize symptoms	—	—	0.03	0.01
2. Comorbid medical conditions[b]	-0.22	0.09	—	—
2. Comorbid psychiatric conditions	—	—	—	—
2. Harmful substance use/misuse[b]	1.47	0.38	—	—
2. Significant biological family history of mental illness	0.3	0.06	—	—
2. School and/or work	-0.63	0.12	—	—
2. Social/friendships/community functioning	0.62	0.12	—	—
2. Does the child/adolescent (patient) have problems in the context of the home?	—	—	-0.20	0.04
2. Family functioning or factors affecting child	1.59	0.12	1.14	0.11
2. Prognosis without further intervention	—	—	0.04	0.01
2. Global urgency	-0.02	0	—	—
3. Single parent (compared with biological parent/stepparent)	0.83	0.13	1.85	0.11
3. Foster, ward, blood relative (compared with biological parent/stepparent)	1.07	0.15	2.65	0.19
3. Number of repeated admissions	—	—	0.03	0.002
Constant[c]	4.98	0.41	2.5	0.21

[a] All other variables < 0.0001.
[b] $p < 0.05$.
[c] The constant represents the n-dimensional intercept and is the baseline from which estimates are calculated in the complex regression equation: it is the 'b' in the simple algebraic equation y = mx + b, where m is the slope and b the y axis intercept.
ACE = Adverse Childhood Experiences; CGAS = Children's Global Assessment Scale; Coef = coefficient; SE = standard error.

DISCUSSION

ACEs are undeniably a developmental risk[36] and, by corollary, are central to mental health care, especially for children. Largely because of the ACE Study, many organizations have recognized the importance of trauma-informed and trauma-focused care. Incorporating these features into care systems requires a shift in organizational perspective. This is a shift that translates into the relational space extant between recipients and providers of care. The ability to measure assessment and treatment effectiveness is also a core feature pointing to success or failure.

A palpable relationship exists between ACE scores and independent variables measuring clinical impairment and outcomes. This step of examining ACE scores in relation to clinical profiles and outcomes was important in establishing the evidence base for the clinical utility of the ACE survey. The ability to measure outcomes in relation to ACE score totals as well as ACE items will form the basis for establishing in the future which interventions are effective for particular types of early trauma or adversity.

One advantage is that our system of care has a comprehensive regional information system that integrates valid and reliable measurement of clinical profiles and the effects of interventions.[29,30] By employing this established measurement system, we could test validity and hence the potential utility of the ACE survey. We demonstrated that patients with higher ACE scores also had clinical profiles indicative of greater clinical severity and impairment when analyzed using both bivariate and multivariable methods that took into account the specific nature of the data—cross-sectional patient and registration-linked data.

Implications

The main purpose of this study was to validate the potential clinical use of ACE surveys in the formation and execution of clinical intervention plans that might help not only to focus clinical

interventions but also to measure their effects differentially in relation to patients' particular ACE profiles. In our regional children's mental health and addiction services, ACE survey scores are now an integral component of assessment and treatment. It will become important to log the types of interventions that are being used with children to gauge the progress in the short-term transition to trauma-informed therapy in view of the long-term (five-year) transition to trauma-focused therapy. Fortunately, we possess an extensive evidence base of clinical information to serve as a background against which interventions and strategies may be compared.[29,30] Implementing mandatory ACE survey completion for every admission provides a mechanism for shifting from a diagnosis-driven, reductionist, medical treatment model to include the trauma-focused dimension of care that is more tuned to the individual's needs.

Traditionally, psychiatry, like other divisions of medicine, has been driven by diagnostic categories and disease-focused models of care.[2] On the basis of the present results, trauma-informed and trauma-focused care must be a turnstile upstream of diagnosis and care planning. For example, a child presenting with attention-deficit/hyperactivity disorder or anxiety and a high ACE score will likely require treatment that is different from a child presenting with the same disorder and an ACE score of zero. One practical shift that the process of implementing the ACE survey has led to in our system is the a priori concept among staff that treatment is about "what happened" to a child, rather than "what is wrong" with that child.

Limitations

Clinical profiles based on completion of the WCWL-CMH-PCS form are required only on an individual's first admission from the community. As a result, and together with incomplete data in some variables across subjects, the sample sizes for variables in the bivariate and multivariable analyses were less than those for the completed number of cross-sectional and registration-linked ACE score profiles. Yet, the final sample sizes were sufficient and representative of the served population.

The results remained relatively stable in relationship to the independent variables, and multicollinearity was evaluated and found to have minimal influence. There are no set or universally accepted ways to manage collinearity.[35]

The sample construction inflated the sample size. Normally studies simply collect baseline and outcome measures ad hoc. The approach used here is novel in some respects and is therefore unfamiliar, yet it has a basis not only for the clinical model of episodic care but also in the emergence of childhood mental disorder generally as a consequence of adversity.

Using the ACE survey, in and of itself, does not make a system of care trauma informed. There is also a great deal of ongoing education and support required. The ACE survey does provide a linchpin for action that can facilitate trauma-informed and trauma-focused care in a health system.

Last, there were insufficient data to represent the Other category. This group had high ACE scores, and, in the future, it will be important to assess and develop interventions specific to these patients with self-identified sex.

CONCLUSION

The ACE survey score is significantly related to clinical impairment measured on entry to tertiary mental health services. As such, the ACE survey score is an important index of past trauma related to presenting clinical status. Additionally, CAAMHPP has successfully implemented the ACE survey, moving closer to becoming an evidence-based trauma-informed system of care—a necessary step on the path to universal trauma-focused care. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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References

1. LeTendre ML, Reed MB. The effect of adverse childhood experience on clinical diagnosis of a substance use disorder: Results of a nationally representative study. Subst Use Misuse 2017 May 12;52(6):689-97. DOI: https://doi.org/10.1080/10826084.2016.1253746.
2. Nurcombe B, Seifer R, Scioli A, Tramontana MG, Grapentine WL, Beauchesne HC. Is major depressive disorder in adolescence a distinct diagnostic entity? J Am Acad Child Adolesc Psychiatry 1989 May;28(3):333-42. DOI: https://doi.org/10.1097/00004583-198905000-00006.
3. Ferrafiat V, Raffin M, Freri E, et al. A causality algorithm to guide diagnosis and treatment of catatonia due to autoimmune conditions in children and adolescents. Schizophr Res 2017 Jun 25 [forthcoming]. DOI: https://doi.org/10.1016/j.schres.2017.06.036.
4. Eisman HD, Fogel J, Lazarovich R, Pustilnik I. Empirical testing of an algorithm for defining somatization in children. J Can Acad Child Adolesc Psychiatry 2007;16(3):124-31.
5. Postilnik I, Eisman HD, Price R, Fogel J. An algorithm for defining somatization in children. J Can Acad Child Adolesc Psychiatry 2006 May;15(2):64-74.
6. Emerson RW, Adams C, Nishino T, et al. Functional neuroimaging of high-risk 6-month-old infants predicts a diagnosis of autism at 24 months of age. Sci Transl Med 2017 Jun 7;9(393):eaag2882. DOI: https://doi.org/10.1126/scitranslmed.aag2882.
7. Kamp-Becker I, Poustka L, Bachmann C, et al. Study protocol of the ASD-Net, the German research consortium for the study of Autism Spectrum Disorder across the lifespan: From a better etiological understanding, through valid diagnosis, to more effective health care. BMC Psychiatry 2017 Jun 2;17(1):206. DOI: https://doi.org/10.1186/s12888-017-1362-7.
8. Black JE, Greenough WT, Anderson BJ, Isaacs KR. Environment and the aging brain. Can J Psychol 1987 Jun;41(2):111-30.
9. Cicchetti D, Toth SL. A developmental psychopathology perspective on child abuse and neglect. J Am Acad Child Adolesc Psychiatry 1995 May;34(5):541-65. DOI: https://doi.org/10.1097/00004583-199505000-00008.
10. Cicchetti D, Richters JE. Examining the conceptual and scientific underpinnings of research in developmental psychopathology. Dev Psychopathol 1997 Spring;9(2):189-91.
11. Cicchetti D, Cannon TD. Neurodevelopmental processes in the ontogenesis and epigenesis of psychopathology. Dev Psychopathol 1999 Summer;11(3):375-93. DOI: https://doi.org/10.1017/s0954579499002114.
12. Cicchetti D, Toth SL. Social policy implications of research in developmental psychopathology. Dev Psychopathol 2000 Autumn;12(4):551-4.
13. Cicchetti D, Blender JA. A multiple-levels-of-analysis perspective on resilience: Implications for the developing brain, neural plasticity, and preventive

interventions. Ann N Y Acad Sci 2006 Dec;1094:248-58. DOI: https://doi.org/10.1196/annals.1376.029.

14. Cicchetti D. Gene-environment interaction. Dev Psychopathol 2007 Fall;19(4):957-9. DOI: https://doi.org/10.1017/s0954579407000466.
15. Greenough WT, Black JE, Wallace CS. Experience and brain development. Child Dev 1987 Jun;58(3):539-59. DOI: https://doi.org/10.2307/1130197.
16. Perry BD, Pollard R. Homeostasis, stress, trauma, and adaptation. A neurodevelopmental view of childhood trauma. Child Adolesc Psychiatr Clin N Am 1998 Jan;7(1):33-51.
17. Perry BD, Azad I. Posttraumatic stress disorders in children and adolescents. Curr Opin Pediatr 1999 Aug;11(4):310-6. DOI: https://doi.org/10.1097/00008480-199908000-00008.
18. Phillips SP, Carver L. Early parental loss and self-rated health of older women and men: A population-based, multi-country study. PLoS One 2015 Apr 1;10(4):e0120762. DOI: https://doi.org/10.1371/journal.pone.0120762. Erratum in: PLoS One 2015 May 21;10(5):e0128168. DOI: https://doi.org/10.1371/journal.pone.0128168.
19. Shern DL, Blanch AK, Steverman SM. Toxic stress, behavioral health, and the next major era in public health. Am J Orthopsychiatry 2016 Mar;86(2):109-23. DOI: https://doi.org/10.1037/ort0000120.
20. Anda RF, Dong M, Brown DW, et al. The relationship of adverse childhood experiences to a history of premature death of family members. BMC Public Health 2009 Apr 16;9:106. DOI: https://doi.org/10.1186/1471-2458-9-106.
21. Felitti VJ. Adverse childhood experiences and adult health. Acad Pediatr 2009 May-Jun;9(3):131-2. DOI: https://doi.org/10.1016/j.acap.2009.03.001.
22. Felitti VJ. Long-term medical consequences of incest, rape, and molestation. South Med J 1991 Mar;84(3):328-31. DOI: https://doi.org/10.1097/00007611-199103000-00008.
23. Felitti VJ, Anda RF, Nordenberg D, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. Am J Prev Med 1998 May;14(4):245-58. DOI: https://doi.org/10.1016/s0749-3797(98)00017-8.
24. Cawthorpe D, Wilkes TC, Guyn L, Li B, Lu M. Association of mental health with health care use and cost: A population study. Can J Psychiatry 2011 Aug;56(8):490-4. DOI: https://doi.org/10.1177/070674371105600807.
25. Cawthorpe D. A novel population-based health index for mental disorder. Perm J 2013 Spring;17(2):50-4. DOI: https://doi.org/10.7812/TPP/12-081.
26. Chartier G, Cawthorpe D. From 'Big 4' to 'Big 5': A review and epidemiological study on the relationship between psychiatric disorders and World Health Organization preventable diseases. Curr Opin Psychiatry 2016 Sep;29(5):316-21. DOI: https://doi.org/10.1097/yco.0000000000000270.
27. Chodos H, MacLeod JJ. Romanow and Kirby on the public/private divide in healthcare: Demystifying the debate. Healthc Pap 2004;4(4):10-25. DOI: https://doi.org/10.12927/hcpap..16849.
28. Ghuttora HK, Cawthorpe D. Treatment of physical disorder in children with mental disorder: A health care utilization study. J Hosp Adm 2014;3(2):24-31. DOI: https://doi.org/10.5430/jha.v3n2p24.
29. Novick J, Cawthorpe D, McLuckie A. A measurable treatment plan: Using the Children's Global Assessment and the Problem Severity scales as outcomes of clinical treatment. J Hosp Adm 2017;6(1):9-15. DOI: https://doi.org/10.5430/jha.v6n1p9.
30. Novick J, Cawthorpe D, McLuckie A. The validation of the Western Canada Waiting List Children's Mental Health-Priority Criteria Score Instrument: 2002-2015 results. J Hosp Adm 2016;5(4):1-8. DOI: https://doi.org/10.5430/jha.v5n4p1.
31. Cawthorpe D, Wilkes TC, Rahman A, et al. Priority-setting for children's mental health: Clinical usefulness and validity of the priority criteria score. J Can Acad Child Adolesc Psychiatry 2007 Feb;16(1):18-26.
32. Exley D, Norman A, Hyland M. Adverse childhood experience and asthma onset: A systematic review. Eur Respir Rev 2015 Jun;24(136):299-305. DOI: https://doi.org/10.1183/16000617.00004114.
33. Fang L, Chuang DM, Lee Y. Adverse childhood experiences, gender, and HIV risk behaviors: Results from a population-based sample. Prev Med Rep 2016 May 31;4:113-20. DOI: https://doi.org/10.1016/j.pmedr.2016.05.019.
34. Felitti VJ. [The relationship of adverse childhood experiences to adult health: Turning gold into lead]. [Article in German]. Z Psychosom Med Psychother 2002;48(4):359-69. DOI: https://doi.org/10.13109/zptm.2002.48.4.359.
35. Dormann CF, Elith J, Bacher S, et al. Collinearity: A review of methods to deal with it and a simulation study evaluating their performance. Ecography 2013 Jan;36(1):27-46. DOI: https://doi.org/10.1111/j.1600-0587.2012.07348.x.
36. Teicher MH, Samson JA. Annual research review: Enduring neurobiological effects of childhood abuse and neglect. J Child Psychol Psychiatry 2016 Mar;57(3):241-66. DOI: https://doi.org/10.1111/jcpp.12507.

Illness of the Nerves and Brain

Psychiatry has undergone a transformation in its relationship to the rest of the medicine … .
This transformation rests principally on the realization that patients with
so-called "mental illnesses" are really individuals with illnesses of the nerves and brain.

— Wilhelm Griesinger, MD, 1817-1868, German neurologist and psychiatrist

MicroWorld Butterflies
mixed media collage

Shenshen Dou, MS

This piece is part of the artist's larger MicroWorld collage series,
which is inspired by her research experiences as a molecular biologist.

An assemblage of bioform images was applied in this collage, as trees and as butterflies (chromosomes).
Butterflies are the result of metamorphosis, and also a symbol of transformation of life.

Ms Dou is an artist living in West Linn, OR.

CME credits available for this article — see page 112

ORIGINAL RESEARCH & CONTRIBUTIONS

Real-World Effectiveness of a Medically Supervised Weight Management Program in a Large Integrated Health Care Delivery System: Five-Year Outcomes

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ABSTRACT

Context: There are insufficient data on the long-term, nonsurgical, nonpharmacologic treatment of obesity.

Objective: To determine changes in weight over 5 years in participants enrolled between April 1, 2007, and December 31, 2014, in a medically supervised weight management program at Kaiser Permanente Northern California Medical Centers. The program consisted of 3 phases: Complete meal replacement for 16 weeks; transition phase, 17 to 29 weeks; and lifestyle maintenance phase, 30 to 82 weeks.

Design: Retrospective observational study of 10,693 participants (2777 available for analysis at 5 years); no comparator group.

Main Outcome Measures: Average change in weight from baseline to follow-up.

Results: Average age was 51.1 (standard deviation = 12.4) years, and 72.8% were women. Average baseline weight in the entire cohort was 112.9 kg (standard error [SE] = 0.23). Weight (kg) significantly changed over time: 4 months, -17.3 (SE = 0.12); 1 year, -14.2 (SE = 0.12); 2 years, -8.6 (SE = 0.14); 3 years, -6.9 (SE = 0.17); 4 years, -6.5 (SE = 0.16), and 5 years, -6.4 (SE = 0.29); $p < 0.0001$). In those with 5-year follow-up, weight loss between 5.0 and 9.9% below baseline occurred in 16.3% (SE = 0.004, 95% CI = 15.3% - 17.2%) and weight loss of 10.0% or more of baseline occurred in 35.2% (SE = 0.01, 95% CI = 33.6% - 36.7%).

Conclusion: The average weight change of obese adults who participated in a medically supervised weight management program, with available 5-year data, was a statistically and clinically significant 5.8% weight loss from baseline.

INTRODUCTION

Obesity increases the risk of type 2 diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease, and other chronic diseases. It correspondingly raises the risk of all-cause mortality and cardiovascular mortality.[1] The 2009 US National Health and Nutrition Examination Survey demonstrated that approximately 80 million adults age 20 years or older were obese, with a slightly higher female preponderance (41% women vs 38% men),[2] making obesity a dominant contributor to the nation's public health decay. Moreover, the societal economic costs, in 2008 dollars, were an astounding $147 billion.[3] It is therefore imperative that accountable care organizations and others strive to meet the obesity epidemic using creative and thoughtful methods.

A US Congressional review in 1990 highlighted the need for formal evaluation of the effectiveness of weight management programs[4] because of rampant false advertising during that time. An appraisal of studies conducted during that period points to their limited scope and applicability to modern practice owing to small sample sizes and large losses to follow-up.[5-7] More recent, well-conducted systematic reviews have continued to yield a paucity of information supporting the long-term effectiveness of nonsurgical, nonpharmacologic, weight management programs affecting clinically significant weight loss[8,9] defined as 5% weight loss or greater from baseline.[1]

In January 2002, the Kaiser Permanente Care Management Institute in Oakland, CA, launched a weight management and obesity initiative to tackle pressing issues surrounding obesity care within the organization.[10,11] In response to this and other perceived needs,[12] several of the study authors (RA, MO, BK, WS, SP), along with contributions from the leadership team, initiated a medically supervised weight management program (MSWMP) across Kaiser Permanente Northern California (KPNC) Bay Area Medical Centers. The MSWMP was initially started at four medical centers (San Jose, CA; Sacramento, CA; Fremont, CA; and Oakland, CA) in 2007, with the primary aim of improving long-term weight management outcomes for KPNC members. The program was designed to include an initial period of complete meal replacement therapy along with a behaviorally based lifestyle modification curriculum that aimed to enhance weight loss, with the exclusion of pharmacologic agents.

The current report is an evaluation of the effectiveness of the MSWMP on weight loss and lipid changes in KPNC Medical Centers during a five-year period. We used a retrospective, cohort study design to determine the average short-term and long-term weight loss and lipid concentration changes of participants in this program.

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METHODS

Overview of Weight Management Program

The goal of the program was to offer a long-term behavior management program, on a fee-for-service basis, to treat obesity in KPNC members. At the start of the current study, there were 21 programs across the Northern California Bay Area, with all locations following the same protocol to ensure consistency. Prospective participants were self-referred or referred by KPNC physicians. To be considered for the program, participants had to be age 18 years or older and have a body mass index (BMI) of 30 kg/m^2 or higher or a BMI of 28 kg/m^2 or higher with 2 or more comorbid conditions. Exclusion criteria included severe medical or mental illness, current malignancy, pregnancy or lactation, type 1 diabetes, active substance abuse, and unwillingness to participate in group meetings and physical activity.

An initial one-hour information session was mandatory before the program start. Interested participants were then screened (using chart review, clinic visits, laboratory data, and electrocardiograms) to ensure they met program criteria. The final decision to admit screened participants was at the discretion of the supervising medical director. Participants were then enrolled in the program after patient agreements, and informed consents were obtained.

Program Phases

The 82-week program was composed of 3 phases: Complete meal replacement for 16 weeks; transition phase from 17 to 29 weeks; and lifestyle maintenance phase from 30 to 82 weeks. The duration of the program was based on a perceived need to extend behavioral treatment beyond the acute weight loss phase.[13,14] The active weight loss period consisted of complete meal replacement therapy, weekly closed-group behavior change sessions, and monthly medical and laboratory monitoring. The number of participants in the closed-group behavior change sessions was kept between 16 and 25. Most sessions were led by the same facilitator (educators trained to deliver guideline-based behavioral counseling), to ensure consistency.

The meal replacement phase was initiated in Week 2 of the program. The duration of the meal replacement phase was chosen on the basis of prior efficacy and safety data.[5,7,15,16] During this active weight loss phase (16 weeks), all participants were prescribed a minimum of 960 kcal/d (6 meal replacements per day). Most meal replacement products used were Optifast (Nestlé HealthCare Nutrition Inc, Florham Park, NJ) shakes (160 kcal) or soups (160 - 170 kcal). Robard bars (160 kcal, Robard Corp, Mount Laurel, NJ) were also used. Participants were expected to have a minimum of 4 Optifast meal replacement products with the option of the other 2 being Optifast products or Robard bars. Additional kilocalories were added for BMI above 40 kg/m^2 in a scaled manner.

Beginning Week 17, the transition to regular food was initiated. Meal replacement products were reduced by 1 every week until Week 20. By Week 21, all participants were expected to be off complete meal replacement or could continue using up to 3 partial meal replacements per day. The total caloric intake during this transition was gradually increased to approximately 1200 kcal/d. Additional kilocalories were added if BMI was 40 kg/m^2 or higher. Participants were expected to continue their attendance at weekly closed-group behavior change sessions during this period.

The maintenance (also called lifestyle) phase began at Week 31 and ended at Week 82. The focus at the weekly group behavior change sessions during this period was on attendance, accountability, and problem solving. During the maintenance phase, sessions were open to all participants who completed the initial 30 weeks. Furthermore, participants were strongly encouraged to participate in the weekly open-group sessions beyond 82 weeks.

Behavioral Intervention and Exercise Counseling

For the first 30 weeks, the group behavior change sessions were weekly, in-person, closed-group meetings conducted by trained facilitators with the specific purpose of aiding participants to change their eating and exercise behaviors. A closed group ensured that the same participants and facilitators stayed together for these first 30 weeks. Each session lasted between 60 and 90 minutes. From Weeks 31 to 82, meetings were open to all participants who had completed the first 30 weeks. These sessions were guided by the behavioral change framework originally described by Fisher and Fisher[17] in 1992, the information, motivation, behavioral skills model. The model, validated in other clinical scenarios,[18] was based on providing accurate information and motivation to initiate change, with the premise being that this will lead to acquisition of a self-management skill set that can lead to behavioral change over time. The topics of the behavioral sessions were focused on the appropriate caloric reduction needed for weight loss and the amount of physical activity needed for maintenance of weight loss. These were constantly reinforced along with strategies for long-term adherence. A set of SMART self-management skills (goal setting, self-monitoring, environmental control, social support, and reward/reinforcement) were also tailored to individual participants' unique situations.[19]

Participants were educated on targeted methods of physical activity, inclusion of exercise into daily routines, direct and indirect health effects of exercise, and exercise risk avoidance with strategies and techniques.[20] Exercise was defined as activity above the daily baseline activity. Participants were counseled on exercise methods and goals by the group facilitator, with a focus on increasing daily activity early in the program for the development of this behavior to become a long-term habit. Participants were also given the long-term goal of reaching 60 min/d to 90 min/d of exercise. The goal of 10,000 steps daily was reinforced during group sessions and quantified with use of a pedometer or equivalent means.[21-23]

Study Design and Population

This study was an observational, retrospective study of participants who were enrolled in the KPNC MSWMP between April 1, 2007, and December 31, 2014. Participants were followed up for five years or until they died. They were censored when they met any of the following criteria: End of the study follow-up period or disenrollment from the Health Plan (loss to follow-up). The study was approved by the Kaiser Foundation Research Institute's institutional review board. The requirement for informed consent was waived on the basis of the observational nature of the study because there was no contact with participants for study purposes.

The source population for the current study was made up of members of KPNC, a large prepaid integrated health care delivery system thought to be representative of the surrounding population.[24] The target population comprised of adults enrolled in the MSWMP who attended at least the first two weeks of the program.

Outcome Measures

The primary outcome was the average change in weight (in kilograms) from baseline to follow-up. The secondary outcome was the average change in lipid concentrations, specifically total cholesterol, triglycerides, and low-density lipoprotein (LDL)-cholesterol (all in milligrams per deciliter). Follow-up was obtained at four months and at one, two, three, four, and five years ± three months. Participant weights at baseline and follow-up were obtained using standard digital weighing equipment[25] and were captured using the KPNC electronic health records. Available lipid concentrations were captured using the KPNC electronic health records and the laboratory databases.

Primary Exposure and Baseline Covariates

The primary exposure was enrollment in the MSWMP. No control group was obtained for this study.

The baseline covariates collected were patient demographics, comorbidities (up to five years earlier), medications, and laboratory data (up to three months earlier). The baseline demographics collected for the current study included age at the time of enrollment, sex, race, BMI, and average neighborhood-level income. The baseline clinical comorbidities were obtained using International Classification of Diseases, Ninth Revision (ICD-9) codes. The comorbidities collected were the presence or absence of prediabetes, type 2 diabetes mellitus, hypertension, hyperlipidemia, liver disease, lung disease, myocardial infarction, congestive heart failure, ischemic stroke, hemorrhagic stroke, atrial fibrillation, sleep apnea, depression, and current tobacco use. Medication use was obtained electronically from KPNC pharmacy databases.

Statistical Analysis

Statistical analyses were performed using Stata Version 14 (StataCorp, College Station, TX). Descriptive statistics are presented using means and standard deviation [SD] for normally distributed continuous variables, median, and interquartile range for nonnormally distributed continuous variables, and proportions for dichotomous variables. For model-based estimations, we imputed missing data at baseline and follow-up using multiple imputation methods. We then used a linear mixed-effects model with unstructured covariance and a restricted maximum likelihood test option to assess the changes during the follow-up period. The model included a random intercept for each subject to address within-patient correlation of the repeated measures. Multivariable logistic regression analysis was then used to obtain the predictors of clinically significant weight loss at five years. We undertook several sensitivity analyses to assess whether any substantive variation was noted in effect sizes with and without the use of multiple imputation methods, as well as restricting analysis of five-year outcomes to only those participants who had both baseline and five-year weight data.

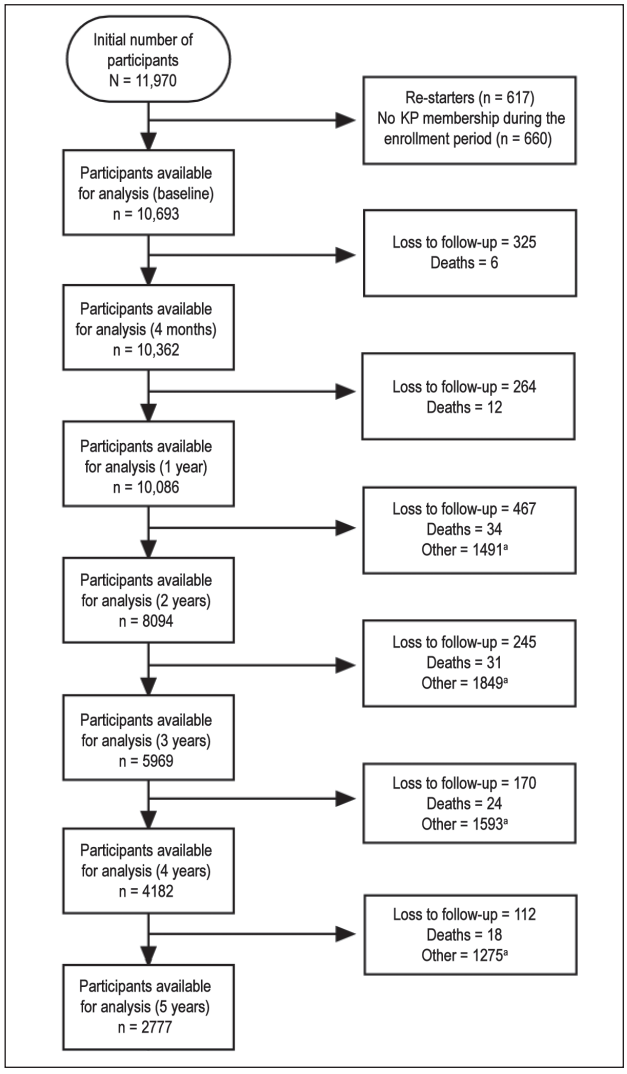

Figure 1. Flow diagram among participants of a weight management program across Kaiser Permanente (KP) Northern California Medical Centers.

[a] Other indicates participants who reached the end of the study before the specified period. For example, among 4182 participants who reached 4 years and who did not die or were not lost to follow-up between Years 4 and 5, the study ended before 1275 participants reached 5 years, and therefore they could not be counted at 5 years.

RESULTS

Patient Characteristics

An overview of patient entry into the study is shown in Figure 1. At baseline, the mean age was 51.1 [SD = 12.4] years, and the mean BMI was 39.7 [SD = 7.2] kg/m^2. White race (72.0%) and women (72.8%) represented most of the cohort. Approximately 42% had either prediabetes or diabetes mellitus, and 49.8% had a history of hypertension. Tobacco use was under 10% in the cohort. The median number of baseline comorbidities was 2, and the median number of baseline medications was 1 (Table 1). Baseline laboratory values of the weight management program participants are shown in Table 2.

Change in Weight

The average baseline weight in the entire cohort was 112.8 kg. The average weight change (in kilograms) at each point was clinically and statistically significant compared with baseline: 4 months (peak weight loss), -17.3 (standard error [SE] = 0.12); 1 year, -14.2 (SE = 0.12); 2 years, -8.6 (SE = 0.14); 3 years, -6.9 (SE = 0.17); 4 years, -6.5 (SE = 0.16); and 5 years, -6.4 (SE = 0.29; $p < 0.0001$]. The accompanying average percentage change from baseline is as shown: 4 months, -15.3%; 1 year, -12.4%; 2 years, -7.6%; 3 years, -6.2%; 4 years, -5.9%; and 5 years, -5.8% (Figure 2). Among participants with 5-year data, weight change between 5.0% weight loss from baseline to weight gain occurred in 48.5% (SE = 0.01, 95% confidence interval [CI] = 46.5% - 50.5%), weight loss 5.0 to 9.9% occurred in 16.3% (SE = 0.004, 95% CI = 15.3 - 17.2%), and weight loss 10.0% and greater occurred in 35.2% (SE = 0.01, 95% CI = 33.6% - 36.7%). The mean number of group behavior sessions attended was 35.1 ± 29.7, with a median of 29 (interquartile range = 29). The magnitude of short-term weight loss, number of group behavior sessions attended, and the number of baseline comorbidities were significantly associated with maintaining 5% or greater weight loss at 5 years (Table 3).

Table 1. Baseline demographics, comorbidities, and medication use among participants of a weight management program across Kaiser Permanente Northern California Medical Centers (N = 10,693)

Baseline variable	Value[a]
Demographics	
Age, mean (SD), years	51.1 (12.4)
Body mass index, mean (SD), kg/m^2	39.7 (7.2)
Average neighborhood income, mean (SD), dollars	66,683 (25,353)
Sex, %	
Women	72.8
Men	27.2
Race and ethnicity, %	
White	72.0
Black/African American	8.3
Latin American (Hispanic)	4.6
Asian/Pacific Islander	6.0
Other	9.1
Comorbidities, %	
Prediabetes	21.4
Diabetes mellitus	21.1
Hypertension	49.8
Hyperlipidemia	41.9
Liver disease	4.6
Lung disease	27.5
Myocardial infarction	1.0
Congestive heart failure	2.2
Ischemic stroke	0.7
Hemorrhagic stroke	0.2
Atrial fibrillation	3.0
Sleep apnea	13.9
Depression	10.7
Number of baseline comorbidities, median (IQR)	2 (2)
Tobacco use (current)	9.2
Medication use, %	
Angiotensin converting enzyme inhibitors	14.1
Angiotensin receptor blockers	9.9
β-blockers	19.8
Calcium channel blockers	10.3
Vasodilators	1.3
Statins	28.6
Diuretics	19.4
Warfarin	3.3
Oral antidiabetic medications	13.0
Insulin	6.1
Number of baseline medications, median (IQR)	1 (2)

[a] Missing values: age (1.0%), neighborhood-level income (15.0%), and baseline comorbidities (2.3%).
IQR = interquartile range; SD = standard deviation.

Sensitivity Analysis for Weight Changes

Sensitivity analyses were undertaken to assess the effect of multiple imputation, as well as limiting analyses to those with available baseline and 5-year weight data. There were no clinically substantive changes between the average weights at baseline and follow-up with or without the use of multiple imputation methods (data furnished on request). Restricting the analysis to only those who were not lost to follow-up, with available weight data at baseline and at 5 years (n = 2092) did not change the summary estimates substantially. The average weight loss at 5 years by this method was -6.7 kg compared with baseline ($p < 0.00001$). Last, we analyzed the differences in baseline characteristics between those with missing 5-year weight data and those without missing 5-year weight data. Participants with missing data were younger; less often white; and had no substantial clinical differences in baseline weight, blood pressure, or income. They represented a slightly healthier population as demonstrated by a lower prevalence of baseline comorbidities and medication use (data furnished on request).

Table 2. Baseline laboratory values among participants of a weight management program across Kaiser Permanente Northern California Medical Centers (N = 10,693)

Laboratory Test	Result[a]
Serum sodium, mg/dL	133.5 ± 28.8
Serum creatinine, mg/dL	0.8 ± 0.3
Glomerular filtration rate, mL/min	57.4 ± 11.7
Hemoglobin, g/dL	13.2 ± 2.8
Alanine transaminase, IU/L	24.5 ± 17.6
Aspartate transaminase, IU/L	20.6 ± 12.0
Total cholesterol, mg/dL	189.3 ± 38.3
Triglycerides, mg/dL	150.8 ± 94.3
HDL-cholesterol, mg/dL	49.6 ± 12.2
LDL-cholesterol, mg/dL	110.1 ± 32.9
Hemoglobin A_{1C}, %	6.3 ± 1.2

[a] Percentage with missing data: sodium, creatinine, glomerular filtration rate, hemoglobin, and alanine and aspartate transaminase (2.3%); total cholesterol (8.1%); triglycerides (8.3%); HDL-cholesterol (8.2%); LDL-cholesterol (8.2%); and hemoglobin A_{1C} (34.8%).
HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Table 3. Predictors of weight loss of 5% or more from baseline at 5 years among participants of a weight management program across Kaiser Permanente Northern California Medical Centers

Variable	Odds ratio (95% CI), 5 years
Percentage difference in weight (baseline to 4 months)	1.04 (1.03-1.05)[a]
Weight management sessions (every 10 sessions)	1.03 (1.01-1.05)[a]
Number of comorbidities at baseline	1.06 (1.01-1.11)[a]
Women	1.02 (0.84-1.22)
Advancing age (every 5 years)	1.02 (0.99-1.05)
Median household income	0.98 (0.97-1.002)

[a] Indicates statistical significance ($p < 0.05$).
CI = confidence interval.

Change in Lipid Concentrations

Figure 3 demonstrates the model-based average percentage changes in lipids (total cholesterol, triglycerides, and LDL-cholesterol) and statin use during five-year follow-up.

DISCUSSION

This observational study of obese adults demonstrated the effectiveness of an 82-week, nonpharmacologic, nonsurgical, weight management program for short-term and long-term weight loss across 21 KPNC Medical Centers. We found that the average weight loss during the follow-up period was statistically and clinically significant. Most importantly, we found an average long-term weight loss of -5.8% from baseline at 5 years. In participants with 5-year data, the average weight loss in approximately half was -5.0% or greater weight loss with a third having, on average, -10% or greater weight loss compared with baseline. We found a significant association between the duration of participation in the program (every 10 weight management sessions attended was associated with a 3% increase in the odds of achieving clinically significant weight loss of -5% or greater at 5 years), along with the magnitude of 4-month weight loss, and the number of baseline comorbidities to long-term clinically significant weight loss of -5% or greater at 5 years. Last, significant lowering in all lipid concentrations was noted at 4 months, with triglyceride lowering seen throughout follow-up ($p < 0.0001$).

To our knowledge, there are no long-term studies of this scale evaluating the effectiveness of a real-world, nonsurgical, nonpharmacologic, behavior-based weight management program that included complete meal replacement at onset conducted either within or outside an integrated health care delivery system. Prior work has concentrated on the overall utility of weight management programs,[8] specific meal replacement programs such as Medifast (Medifast, Owings Mills, MD),[26] Optifast,[5,7] specific outcomes (weight, waist circumference, blood pressure),[26] and specific settings (routine clinical practice).[9] Despite this, our program participants were similar to other weight management cohorts described in the literature, consisting predominantly of middle-aged women with a low prevalence of baseline multimorbidity and medication use.

One meta-analysis of clinical trials performed in the context of usual care found that programs that offered meal replacements had a weight change of -6.8 kg at a follow-up of 1 to 2 years.[9] Another study of participants using liquid shakes and meal bars that replaced 2 meals and 2 snacks found that participants lost 7.1 kg in the first 3 months, and those who continued to replace 1 meal and 1 snack were noted to have a loss of 10.4 kg at 27 months.[20,27] Our program of an initial 16 weeks of complete meal replacement, using predominantly Optifast products, was relatively similar to a program described in 1997.[5] However, the overall sample size in the current study was larger (10,693 vs 621), with longer duration of the program (82 weeks vs 26 weeks), varied statistical analysis (current study using repeated-measure analysis and multiple imputation), and less loss to follow-up (14.8% loss to follow-up and 1.2% death vs 51.6% loss to follow-up). The overall short-term trends in weight outcomes were similar, but low sample sizes and substantial losses to follow-up rendered comparing long-term outcomes unfeasible.

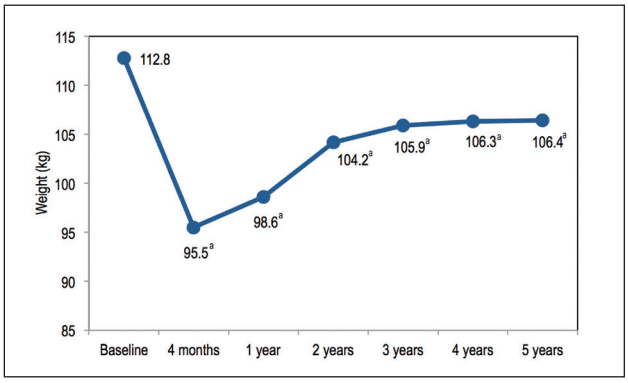

Figure 2. Average baseline and follow-up weights (kg) among participants of a weight management program across Kaiser Permanente Northern California Medical Centers.

[a] Statistically significant compared with baseline ($p < 0.05$). Graph shows the entire cohort after multiple imputation of baseline and follow-up weights and then fitting a linear mixed-effects model with unstructured covariance and a restricted maximum likelihood test option to assess the changes in weight during the follow-up period. The model included a random intercept for each subject to address within-patient correlation of the repeated measures. Standard errors of each estimate are shown and vary from 0.12 to 0.21 kg.

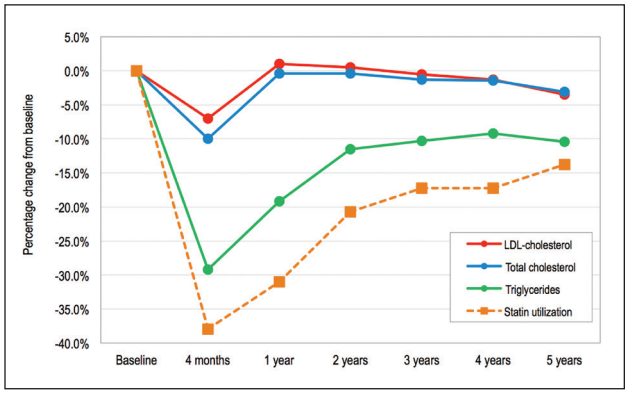

Figure 3. Average baseline and percentage change in lipid fractions and statin utilization during follow-up among participants of a weight management program across Kaiser Permanente Northern California Medical Centers.

LDL = low-density lipoprotein.

We noted in the current study that MSWMP participants lost an average of 17.3 kg at 4 months and 14.2 kg at 1 year. Although weight regain was noted after the initial 4 months, the average weight loss at 5 years continued to be clinically significant at -5.8%. We believe the reported 5-year weight loss was predominantly related to the magnitude of weight loss at 4 months because of initial complete meal replacement therapy, and because of the incremental number of group visits attended. We did not have data on the amount of participant meal replacement used to ascertain the role of long-term partial meal replacement.

The importance of behavior change in weight loss maintenance has been well documented in the literature. Traditionally, behavior modification sessions have been provided on-site and in groups of 10 to 20 participants. Group treatment has been reported to have a higher weight loss,[28] as well as providing social support and being cost-effective.[20,29] These groups are often led by registered dietitians or other health care professionals.[20,30] The length of treatment advocated has also varied, with longer-term support demonstrating a higher long-term weight loss. The results from our study are significant in that we demonstrated the strength of combining a long-term behavior change intervention with an initial meal replacement program in a large, well-developed, integrated health care delivery system. Behavioral interventions have adapted over time from solely in-person classes to the use of electronic media, social networks, and tracking applications. Our approach was in-person sessions provided by trained facilitators during the acute weight loss period and maintenance phases of the program.[1] Last, it is to be noted that our program captured most of the self-management and self-regulatory strategies that have recently been believed necessary for a comprehensive lifestyle modification program to achieve and maintain a -7% to -10% weight loss at 1 year or later.[20]

Prior studies of low calorie diet programs have usually had a comparator group and were often in the setting of a randomized clinical trial. They have described weight changes at 3 to 4 months and noted that the weight loss was between 4.8% and 22.1% favoring weight management programs. These studies were based on a sample size of approximately 300.[8] Our study demonstrated, on average, a 15.3% decrease in weight loss at 4 months. Furthermore, although the -5.8% weight loss at 5 years can be described as modest, this is one of the few studies that had the ability to describe a population of this size. A true nontrial-based control group, if present, we believe would have most likely shown no significant weight loss or perhaps weight gain,[9] because this is the basis of the obesity epidemic. Last, from a population health perspective, the average 5.8% decrease in weight that was achieved in our study is thought to be of sufficient magnitude to be epidemiologically associated with a decrease in mortality[31] and a decrease in the probability of the subsequent development of diabetes mellitus.[32] Future studies are needed to address whether medical weight management programs such as ours, if implemented on even larger scales, will affect population health and decelerate the rise in heart disease mortality attributed to obesity.[33]

The finding of weight loss and weight regain should not be a surprise. Our main analyses, using multiple imputation and repeated-measures regression, were comparable to findings from the intervention arm of the Look AHEAD (Action for Health in Diabetes) study, a large, well-run, randomized clinical trial.[34] Our sensitivity analyses further confirmed the findings, showing no substantive variation in the effect sizes. The rebound in lipid concentrations after acute weight loss also should not come as a surprise. Mehta et al,[35] in their systematic review of 27 trials, described changes in lipid concentrations during a 1-year period. They noted a 6-month change as follows: Total cholesterol, -0.8 to -12.3 mg/dL; LDL-cholesterol, -1.0 to -10.1 mg/dL; and triglycerides, +4.0 to -54.9 mg/dL. They reported a 1-year change of total cholesterol, +9.3 to -16.1 mg/dL; LDL-cholesterol, +13 to -14.9 mg/dL; and triglycerides, +1.0 to -60.0 mg/dL. Our study expanded on this and shows the changes in these 3 lipid concentrations during a 5-year period. We found that the maximum decrease in lipids occurred at 4 months, soon after the complete meal replacement phase. Peak decrease in total cholesterol was -19.0 mg/dL, triglycerides was -44.1 mg/dL:, and LDL-cholesterol was -7.7. mg/dL. The decrease during 5 years in the triglyceride fraction of the lipids was most noticeable. What others have not shown was the accompanying changes in utilization of medications such as statins.

A major strength of the current study is that the cohort is one of the largest followed in a behaviorally based MSWMP. We were able to collect long-term weight data on a reasonable proportion of the cohort. Because the study was carried out in an integrated health care delivery system, measurements of weights were done in a standardized fashion.

An inherent limitation of this study is the observational, retrospective study design. We also did not have access to the exact number of meal replacement products used by program participants during the active phase and beyond, data that could have aided in a further understanding of long-term predictors of clinically significant weight loss. We did not collect data on the incidence of adverse events such as constipation, cholelithiasis, or abnormalities of liver enzyme levels in the current study. Last, the generalizability of this study and this fee-for-service program may be limited to participants with insurance in an integrated health care delivery system.

CONCLUSION

Participation of obese adults in a behaviorally based, nonsurgical, nonpharmacologic, medically supervised weight management program in a large integrated health care delivery system resulted in a maximum weight loss at 4 months of 15.3% from baseline. At 5 years, the average weight change from baseline was -5.8%, with approximately 50% of participants achieving -5% or more, which is clinically significant weight loss. Future analyses will attempt to address the effects of the program on blood pressure and health care utilization. ❖

Disclosure Statement

This study was supported by a grant from Nestlé HealthCare Nutrition Inc, Florham Park, NJ. The sponsor did not have access to the primary data; did not participate in data collection, analysis, or interpretation; and did not have a decision to submit the manuscript for publication.

The author(s) have no conflicts of interest to disclose.

Authors' Contributions

Ashok Krishnaswami, MD, the study supervisor, had full access to the study dataset and takes responsibility for data integrity and analysis accuracy; primary responsibility for study concept and design and statistical analysis and interpretation; wrote the initial draft of the manuscript; and obtained funding. Rohini Ashok, MD; Michael Okimura, MD; Wayne Smith, MD; Sheri Pruitt, PhD; and Beth Kramer, MBA, helped conceptualize and design the study and helped analyze and interpret the data. Stephen Sidney, MD, MPH, and Michael Sorel, MPH, assisted with data acquisition from Kaiser Permanente databases and with analysis and interpretation of data. Lindsey Hogan, MHSA, helped analyze and interpret the data. All authors read and approved the final manuscript.

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References

1. Jensen MD, Ryan DH, Apovian CM, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines; Obesity Society. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. J Am Coll Cardiol 2014 Jul 1;63(25 Pt B):2985-3023. DOI: https://doi.org/10.1016/j.jacc.2013.11.004.
2. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity in the United States, 2009-2010. NCHS Data Brief 2012 Jan;(82):1-8.
3. Finkelstein EA, Trogdon JG, Cohen JW, Dietz W. Annual medical spending attributable to obesity: Payer- and service-specific estimates. Health Aff (Millwood) 2009 Sep-Oct;28(5):w822-31. DOI: https://doi.org/10.1377/hlthaff.28.5.w822.
4. Memorandum from Subcommittee Staff to Congressman Ron Wyden, March 1, 1990. In: News from Congressman Ron Wyden, March 22, 1990. Washington, DC: Cong Ron Wyden; 1990. p 185-94.
5. Wadden TA, Foster GD, Letizia KA, Stunkard AJ. A multicenter evaluation of a proprietary weight reduction program for the treatment of marked obesity. Arch Intern Med 1992 May;152(5):961-6. DOI: https://doi.org/10.1001/archinte.1992.00400170051010.
6. Wadden TA, Sternberg JA, Letizia KA, Stunkard AJ, Foster GD. Treatment of obesity by very low calorie diet, behavior therapy, and their combination: A five-year perspective. Int J Obes 1989;13 Suppl 2:39-46.
7. Kirschner MA, Schneider G, Ertel NH, Gorman J. An eight-year experience with a very-low-calorie formula diet for control of major obesity. Int J Obes 1988;12(1):69-80.
8. Gudzune KA, Doshi RS, Mehta AK, et al. Efficacy of commercial weight-loss programs: An updated systematic review. Ann Intern Med 2015 Apr 7;162(7):501-12. DOI: https://doi.org/10.7326/m14-2238. Erratum in: Ann Intern Med 2015 May 19;162(10):739-40. DOI: https://doi.org/10.7326/l15-5097.
9. Hartmann-Boyce J, Johns DJ, Jebb SA, Summerbell C, Aveyard P; Behavioural Weight Management Review Group. Behavioural weight management programmes for adults assessed by trials conducted in everyday contexts: Systematic review and meta-analysis. Obes Rev 2014 Nov;15(11):920-32. DOI: https://doi.org/10.1111/obr.12220.
10. Caplan W, Histon T, Pettay HS. An overview of the Care Management Institute's weight management and obesity initiative. Perm J 2003 Summer;7(3):41-7. DOI: https://doi.org/10.7812/TPP/03-058.
11. Histon TM, Goeldner JL, Bachman KH, Rothert K. Kaiser Permanente's disease management approach to addressing the obesity epidemic. J Clin Outcomes Manag 2005 Sep;12(9):464-9.
12. Danforth KN, Patnode CD, Kapka TJ, et al. Comparative effectiveness topics from a large, integrated delivery system. Perm J 2013 Fall;17(4):4-13. DOI: https://doi.org/10.7812/TPP/13-036.
13. Perri MG, McAllister DA, Gange JJ, Jordan RC, McAdoo G, Nezu AM. Effects of four maintenance programs on the long-term management of obesity. J Consult Clin Psychol 1988 Aug;56(4):529-34. DOI: https://doi.org/10.1037//0022-006x.56.4.529.
14. Perri MG, Nezu AM, McKelvey WF, Shermer RL, Renjilian DA, Viegener BJ. Relapse prevention training and problem-solving therapy in the long-term management of obesity. J Consult Clin Psychol 2001 Aug;69(4):722-6. DOI: https://doi.org/10.1037//0022-006x.69.4.722.
15. Wadden TA, Stunkard AJ, Brownell KD. Very low calorie diets: Their efficacy, safety, and future. Ann Intern Med 1983 Nov;99(5):675-84. DOI: https://doi.org/10.7326/0003-4819-99-5-675.
16. Kanders BS, Blackburn GL, Lavin P, Norton D. Weight loss outcome and health benefits associated with the Optifast program in the treatment of obesity. Int J Obes 1989;13 Suppl 2:131-4.
17. Fisher JD, Fisher WA. Changing AIDS-risk behavior. Psychol Bull 1992 May;111(3):455-74. DOI: https://doi.org/10.1037//0033-2909.111.3.455.
18. Zarani F, Sarami G, Sadeghian S. Adherence in CABG patients: An empirical test of a health behavior model. Int J Clin Med 2014;5(5):225-33. DOI: https://doi.org/10.4236/ijcm.2014.55036.
19. Klapow JC, Pruitt SD. Living SMART: Five essential skills to change your health habits forever. New York, NY: DiaMedica; 2008.
20. Wadden TA, Webb VL, Moran CH, Bailer BA. Lifestyle modification for obesity: New developments in diet, physical activity, and behavior therapy. Circulation 2012 Mar 6;125(9):1157-70. DOI: https://doi.org/10.1161/circulationaha.111.039453.
21. Bachman KH, Histon TM, Remmers C. Obesity in the Kaiser Permanente patient population and positive outcomes of online weight-management programs. Perm J 2007 Spring;11(2):25-30. DOI: https://doi.org/10.7812/TPP/06-074.
22. Bravata DM, Smith-Spangler C, Sundaram V, et al. Using pedometers to increase physical activity and improve health: A systematic review. JAMA 2007 Nov 21;298(19):2296-304. DOI: https://doi.org/10.1001/jama.298.19.2296.
23. Schutz Y, Nguyen DM, Byrne NM, Hills AP. Effectiveness of three different walking prescription durations on total physical activity in normal- and overweight women. Obes Facts 2014;7(4):264-73. DOI: https://doi.org/10.1159/000365833.
24. Krieger N. Overcoming the absence of socioeconomic data in medical records: Validation and application of a census-based methodology. Am J Public Health 1992 May;82(5):703-10. DOI: https://doi.org/10.2105/ajph.82.5.703.
25. Jaffe MG, Lee GA, Young JD, Sidney S, Go AS. Improved blood pressure control associated with a large-scale hypertension program. JAMA 2013 Aug 21;310(7):699-705. DOI: https://doi.org/10.1001/jama.2013.108769.
26. Coleman CD, Kiel JR, Mitola AH, Langford JS, Davis KN, Arterburn LM. Effectiveness of a Medifast meal replacement program on weight, body composition and cardiometabolic risk factors in overweight and obese adults: A multicenter systematic retrospective chart review study. Nutr J 2015 Aug 6;14:77. DOI: https://doi.org/10.1186/s12937-015-0062-8.
27. Ditschuneit HH, Flechtner-Mors M, Johnson TD, Adler G. Metabolic and weight-loss effects of a long-term dietary intervention in obese patients. Am J Clin Nutr 1999 Feb;69(2):198-204.
28. Renjilian DA, Perri MG, Nezu AM, McKelvey WF, Shermer RL, Anton SD. Individual versus group therapy for obesity: Effects of matching participants to their treatment preferences. J Consult Clin Psychol 2001 Aug;69(4):717-21. DOI: https://doi.org/10.1037//0022-006x.69.4.717.
29. Wadden TA, Foster GD. Behavioral treatment of obesity. Med Clin North Am 2000 Mar;84(2):441-61, vii. DOI: https://doi.org/10.1016/s0025-7125(05)70230-3.
30. Wadden TA, Butryn ML, Wilson C. Lifestyle modification for the management of obesity. Gastroenterology 2007 May;132(6):2226-38. DOI: https://doi.org/10.1053/j.gastro.2007.03.051. Erratum in: Gastroenterology 2007 Jul;133(1):371. DOI: https://doi.org/10.1053/j.gastro.2007.06.003.
31. Prospective Studies Collaboration, Whitlock G, Lewington S, Sherliker P, et al. Body-mass index and cause-specific mortality in 900 000 adults: Collaborative analyses of 57 prospective studies. Lancet 2009 Mar 28;373(9669):1083-96. DOI: https://doi.org/10.1016/s0140-6736(09)60318-4.
32. Resnick HE, Valsania P, Halter JB, Lin X. Relation of weight gain and weight loss on subsequent diabetes risk in overweight adults. J Epidemiol Community Health 2000 Aug;54(8):596-602. DOI: https://doi.org/10.1136/jech.54.8.596.
33. Sidney S, Quesenberry CP Jr, Jaffe MG, et al. Recent trends in cardiovascular mortality in the United States and public health goals. JAMA Cardiol 2016 Aug 1;1(5):594-9. DOI: https://doi.org/10.1001/jamacardio.2016.1326.
34. Look AHEAD Research Group, Wing RR, Bolin P, Brancati FL, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 2013 Jul 11;369(2):145-54. DOI: https://doi.org/10.1056/nejmoa1212914.
35. Mehta AK, Doshi RS, Chaudhry ZW, et al. Benefits of commercial weight-loss programs on blood pressure and lipids: A systematic review. Prev Med 2016 Sep;90:86-99. DOI: https://doi.org/10.1016/j.ypmed.2016.06.028.

Illinois Sunset
photograph

Abdalla Mallouk, MD

This photograph was taken during one of the artist's many trips to rural Illinois, which he finds provides a relaxing break from daily life in Southern CA.

Dr Mallouk is an Internist and Nephrologist for the Southern California Permanente Medical Group. He very much enjoys exploring and photographing the great outdoors.

CME credits available for this article — see page 112

ORIGINAL RESEARCH & CONTRIBUTIONS

Impact of Standardizing Management of Atrial Fibrillation with Rapid Heart Rate in the Emergency Department

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ABSTRACT

Context: There is substantial variation in the emergency treatment of atrial fibrillation with tachycardia. A standardized treatment approach at an academic center decreased admissions without adverse outcomes, but this approach has not been evaluated in a community Emergency Department (ED).

Objective: To evaluate the implementation of a standardized treatment guideline for patients with atrial fibrillation and a rapid heart rate in a community ED.

Design: An observational pre-/postimplementation (August 2013 to July 2014 and August 2014 to July 2015, respectively) study at a community ED. The standardized treatment guideline encouraged early oral treatment with rate control medication, outpatient echocardiogram, and early follow-up. A multiple logistic regression model adjusting for patient characteristics was generated to investigate the association between the intervention and ED discharge rate.

Main Outcome Measures: The primary measure was ED discharge. Secondary measures included stroke or death, ED return visit, hospital readmission, length of stay, and use of oral rate control medications.

Results: A total of 199 (104 pre/95 post) ED encounters were evaluated. The ED discharge rate increased 14% after intervention (57.7% to 71.6%, p = 0.04), and use of rate control medications increased by 19.4% (p < 0.01). Adjusted multivariate results showed a nearly 2-fold likelihood of ED discharge after guideline implementation (odds ratio = 1.97, 95% confidence interval = 1.07-3.63). Length of stay, return visits, and hospital readmissions were similar.

Conclusion: A standardized approach to ED patients with atrial fibrillation and tachycardia is associated with a decrease in hospital admissions without adversely affecting patient safety.

INTRODUCTION

Atrial fibrillation currently affects 2.3 million Americans and is the most common arrhythmia treated in in the Emergency Department (ED).[1,2] Because of the association of atrial fibrillation with increasing age,[2] the number of persons affected by atrial fibrillation is expected to reach 5.6 million by the year 2050.[2] Despite the rising prevalence, there is currently no consensus on the optimal management of atrial fibrillation in the acute care ED setting.[2-6] Multiple reports have shown a great deal of variation in ED treatment strategies for atrial fibrillation with a rapid heart rate above 100/min.[1,6-8]

Of importance to patients, clinicians, and policy makers is the decision whether to admit the patient to the hospital or to refer the patient for outpatient management. Patients prefer outpatient care when possible,[9] and hospitalizing patients without a clear benefit incurs unnecessary costs.[10] A standardized ED guideline emphasizing early oral use of rate control medication and 48-hour follow-up at a dedicated atrial fibrillation clinic in an academic teaching hospital resulted in a significant reduction in hospital admissions without compromising patient outcomes.[11] The translation or implementation of this approach into other EDs has not been reported among different patient populations or different practice settings, most of whom lack routine 48-hour follow-up at a dedicated atrial fibrillation clinic. We lack the understanding of whether this process can be safely translated into a community ED setting, and it will be important to understand if these results are generalizable to an integrated health care system.

The primary objective of our study was to evaluate the impact of a standardized practice guideline on the hospitalization rate of patients presenting to the ED with atrial fibrillation and a rapid heart rate. The secondary objectives were to describe the use of oral medications for these patients, incidence of stroke or death at 30 days, 14-day ED return visit or hospital admission, and length of stay (LOS) before and after initiation of the practice guideline.

METHODS

Study Design and Setting

This observational pre-/postimplementation study evaluated encounters with patients presenting with a rapid heart rate to the ED at Kaiser Permanente (KP) Panorama City Hospital in Panorama City, CA, who received a diagnosis of atrial fibrillation. The cohorts were divided into a preintervention group (August 1, 2013, to July 31, 2014) and an intervention group (August 1, 2014, to July 31, 2015). Retrospective data were collected for the preintervention group using information from our electronic health record, as well as claims data for visits outside our health system. Data after the intervention were prospectively collected from our electronic health record and claims information. Extensive chart review using standard methods

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recommended for emergency medicine research was employed, including a standard chart abstraction form to validate information collected for all encounters included in the study.[12]

The intervention was the implementation of a practice guideline aimed at standardizing the treatment of atrial fibrillation with a rapid heart rate. The practice guideline (Figure 1) was rolled out beginning in August 2014 at KP Panorama City Hospital's ED, a community ED that sees a volume of 60,000 patients per year. The guideline was based on a previously published guideline and is in concordance with current American College of Cardiology/American Heart Association recommendations.[11,13] The essential components of the guideline are early oral use of rate control medication, moderate heart rate control, outpatient echocardiogram, and early follow-up with the primary care physician. The rate control protocol consists of a series of rate control medication administrations (β-blocker or calcium channel blocker), with hourly rechecks (see Sidebar: Protocols for Rate Control Medications). If rate control was achieved, the patient was deemed eligible for discharge from the ED. In the event rate control failed, the patient would be placed on a regimen of continuous intravenous rate control medication and admitted to the hospital.

The protocol was presented to the hospital's emergency physician group in August 2014 as part of a regularly scheduled

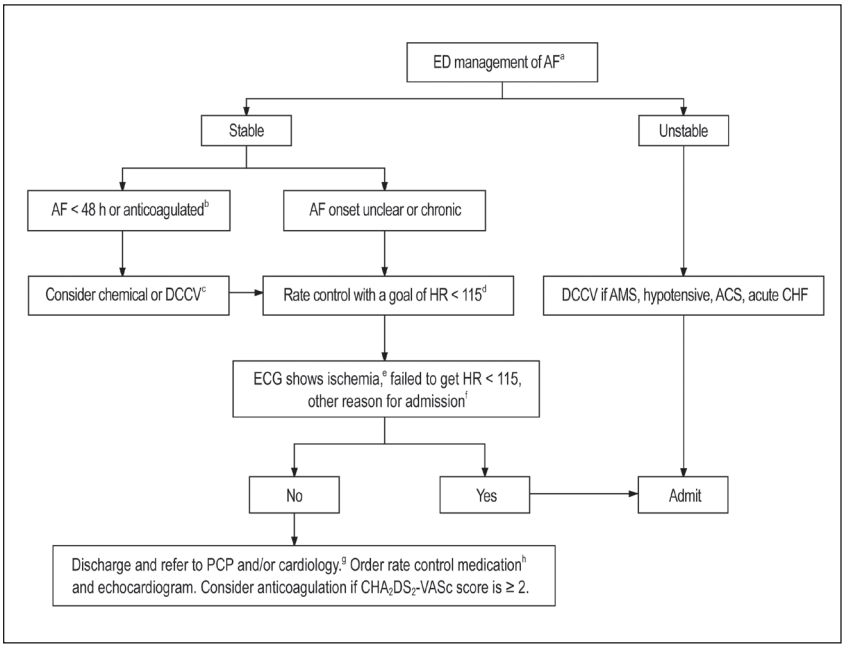

Figure 1. Practice Guideline for Emergency Department Management of Atrial Fibrillation.

[a] This clinical reference is for the care of the patient with a primary diagnosis of atrial fibrillation and no other diagnosis that requires emergency care.
[b] If the patient has an electrocardiogram showing sinus rhythm in the last 48 hours or has had an international normalized ratio > 2.0 for at least 3 weeks, then the patient may be cardioverted. If atrial fibrillation onset is unclear, then rate control only.
[c] Consider consultation with a cardiologist. For electrical cardioversion, consider administering at least 100 J (biphasic) of electricity. Rate control may be attempted before cardioversion, although not required.
[d] Intravenous and oral rate control medications should be ordered at the same time, and the oral medication should be given as soon as possible. See Sidebar: Protocols for Rate Control Medications for recommendations of medication and dosing.
[e] Greater than 2 mm of ST-elevation or depression.
[f] Positive troponin, symptoms consistent with acute coronary syndrome, patient has another reason for admission such as exacerbation of either congestive heart failure or chronic obstructive pulmonary disease.
[g] Referral to primary care physician within 3 days for discussion of anticoagulation, vital signs check, and medication adjustments. Follow-up with cardiologist as per local practice.
[h] See Sidebar: Protocols for Rate Control Medications for recommendations of discharge medication.
ACS = acute coronary syndrome; AF = atrial fibrillation; AMS = altered mental status; CHF = congestive heart failure; DCCV = direct current cardioversion; ECG = electrocardiogram; ED = Emergency Department; HR = heart rate (/min); PCP = primary care physician.

Protocols for Rate Control Medications

Intravenous medications

Diltiazem, 0.25 mg/kg, intravenous bolus over 2 minutes. May repeat diltiazem at 0.35 mg/kg intravenous bolus over 2 minutes, 15 minutes after the prior dose. Caution with doses over 25 mg.

Metoprolol, 2.5 mg to 5.0 mg, slow intravenous bolus. May repeat every 5 minutes for a total of 15 mg.

Oral medications

During initial orders select *either* atenolol, 25 to 50 mg orally, or diltiazem extended release (Diltia XT, Watson Laboratories, Inc, Corona, CA), 120 mg orally, and administer once as soon as it is feasible. Recheck patient 1 hour after oral medication administration.

First heart rate assessment: Heart rate > 115/min at rest: Consider repeating atenolol dose at 25 mg or diltiazem extended release, 120 mg orally once. Recheck patient in 1 hour.

Second heart rate assessment: Heart rate > 115/min at rest: Consider intravenous drip infusion and admission to the hospital.

Maximum atenolol dose is 100 mg/d.

Maximum diltiazem extended release dose is 480 mg/d.

Holding parameters are systolic blood pressure < 100 mmHg and heart rate < 60/min.

On discharge, the patient may be placed on a regimen of atenolol, 25 mg daily, or diltiazem extended release, 120 mg daily, until seen by his/her primary care physician. Start warfarin therapy at your discretion if CHA_2DS_2-VASc score is ≥ 2. Contact pharmacist for bedside education about warfarin and order a 30-day supply. Clerks can direct-book an appointment with the primary physician within 3 days. Refer for urgent echocardiogram as an outpatient. Primary care physician can refer to cardiology if needed, or refer to cardiology if the patient or the cardiologist desires elective cardioversion.

meeting that most physicians attended. A detailed explanation of the protocol, including education regarding the CHA_2DS_2-VASc score[14] (Table 1) and the recommendations for anticoagulation with aspirin or warfarin, was provided and discussed. In addition to reviewing details of the protocol, pharmacologic therapies were discussed, and the expedited direct booking for an echocardiogram and primary care follow-up was explained. Early oral dosing of the rate control medication of the physician's choice was strongly encouraged; however, the guideline is voluntary and patient dependent. Thus, the implementation of the protocol, the type of medication, number of doses of medication, and the decision to discharge the patient were ultimately up to the physician. Follow-up after discharge included a primary care appointment within three days, a cardiology referral as needed, and an outpatient echocardiogram within one week. A physical copy of the protocol was given to each physician, and the protocol was made available for reference on every computer in the ED.

Table 1. CHA_2DS_2-VASc scoring[14]

Risk factor	Points
Age 65-74 y	1
Age ≥ 75 y	2
Women	1
Congestive heart failure	1
Hypertension	1
Stroke/transient ischemic attack/ thromboembolism	2
Vascular disease	1
Diabetes	1

Selection of Participants

To find all potentially eligible encounters, we identified all ED visits with a diagnosis of atrial fibrillation, chronic atrial fibrillation, paroxysmal atrial fibrillation, permanent atrial fibrillation, or atrial fibrillation with rapid ventricular response from the ED or hospital discharge diagnosis (International Classification of Diseases, Ninth Revision, Code 427.31). Next, the investigators manually reviewed all charts to apply the inclusion and exclusion criteria and fill out data sheets. To meet the inclusion criteria, patients had to be at least age 18 years, have presented for treatment/evaluation of stable nonvalvular atrial fibrillation with a rapid heart rate, and be KP Health Plan members. We included only Health Plan members to ensure accurate patient information and because of the recommended early follow-up that could not be coordinated or tracked for nonmembers. Encounters without atrial fibrillation as the primary emergent complaint were excluded (eg, myocardial infarction, congestive heart failure exacerbation), as were patients with known valvular disease or cardiomyopathy. Unstable patients requiring emergency cardioversion because of chest pain, shortness of breath, or altered mental status were also excluded. A single patient was allowed multiple eligible encounters for emergency treatment of atrial fibrillation if 15 or more days had passed between encounters.

We performed chart review for all patients who met the inclusion criteria to determine whether the patient was still alive 30 days after his/her ED encounter. KP members have encounters placed in their medical record when they receive medical care at an outside facility, ensuring accurate follow-up information.

The KP pharmacy data captured all medications dispensed, and that record was compared with the medication administration record to accurately track the type of treatment the patient received while in the ED (oral vs intravenous medication, calcium channel blocker vs β-blocker, etc).

Table 2. Patient characteristics

Variable	Preintervention (n = 104)	Postintervention (n = 95)	p value
Age, mean y (SD)	69.5 (13.43)	70.4 (12.79)	0.5833
Women, no. (%)	61 (58.7)	59 (62.1)	0.6192
Arrival vital signs			
Arrival heart rate, mean beats/min (SD)	133.7 (19.67)	127.5 (18.07)	0.0283
Arrival systolic blood pressure, mean mmHg (SD)	136.8 (20.95)	132.3 (20.22)	0.1982
Arrival oxygen saturation, mean % (SD)	97.6 (2.11)	97.8 (1.68)	0.8324
Comorbidities, no. (%)			
Diabetes	30 (28.8)	33 (34.7)	0.3722
Hypertension	74 (71.2)	69 (72.6)	0.8169
Congestive heart failure	9 (8.7)	11 (11.6)	0.4930
Myocardial infarction	4 (3.8)	10 (10.5)	0.0657
Coronary artery disease	5 (4.8)	16 (16.8)	0.0058
Stroke	6 (5.8)	6 (6.3)	0.8715
Transient ischemic attack	2 (1.9)	3 (3.2)	0.5783
Chronic atrial fibrillation	55 (52.9)	49 (51.6)	0.7839
CHA_2DS_2-VASc score, mean (SD)	3.2 (1.84)	3.7 (1.95)	0.1280
Medication history, no. (%)			
β-blocker	48 (46.2)	40 (42.1)	0.5657
Calcium channel blocker	24 (23.1)	28 (29.5)	0.3049
Digoxin	11 (10.6)	5 (5.3)	0.1685
Warfarin	23 (22.1)	21 (22.1)	0.9986
Presenting symptoms, no. (%)			
Shortness of breath	31 (29.8)	33 (34.7)	0.4571
Chest pain	25 (24)	18 (18.9)	0.3824
Palpitation	68 (65.4)	53 (55.8)	0.1661
Dizziness	28 (26.9)	17 (17.9)	0.1283
Syncope	2 (1.9)	1 (1.1)	0.6147
No symptom or other	17 (16.3)	23 (24.2)	0.1667
Symptom onset < 48 h	59 (56.7)	46 (48.4)	0.3286

SD = standard deviation.

Similar to other atrial fibrillation studies in the ED, we included the following patient variables: Chief complaint, vital signs from triage documentation, chronic atrial fibrillation diagnosis, pharmacy data to assess medication use, disease burden, age, sex, and comorbidities.[1,3,7,11,15] Beyond building on the learning from previous research, these patient characteristics reflect both the risk of stroke in patients with atrial fibrillation and the risk factors for nonvalvular atrial fibrillation.[2,14,16]

Statistical Analysis

A comparison of patient characteristics before and after the intervention was examined by *t*-test for continuous variables and by the χ^2 test for categorical variables. To investigate the association between the intervention and hospital discharge rate, we generated a multiple logistic regression model that adjusted for key patient characteristics. Relevant confounders for this model were selected by their significance in the univariate association test or their clinical relevance as mentioned in Selection of Participants.

All statistical tests were 2-sided. P values less than 0.05 were considered statistically significant. All analyses were performed with SAS EG (Version 9.3, SAS Institute, Cary, NC).

RESULTS

A total of 199 ED encounters were included in the study (104 patients preintervention and 95 postintervention; Table 2). The mean heart rate on arrival to the ED was higher for the preintervention cohort than the intervention cohort: 133.7/min (standard deviation [SD] = 19.67/min) and 127.5/min (SD = 18.07/min), respectively (p = 0.03). Additionally, coronary artery disease was found at a higher rate in the intervention cohort (16.8% vs 4.8%, p < 0.01). Patient characteristics were otherwise similar between groups. Medication use and presenting symptoms were similar in both groups. No statistically significant difference in CHA_2DS_2-VASc score was found between the preintervention (3.2, SD = 1.84) and the postintervention groups (3.7, SD = 1.95).

There was a significant decrease in hospitalization after the intervention was implemented. The discharge rate increased from 57.7% in the preimplementation period to 71.6% after intervention (13.9% change, p = 0.04; Table 3). The increase in the discharge rate was primarily related to a decrease in observation unit admissions demonstrated by a 34.4% reduction (45.5% to 11.1%, p < 0.01), whereas admission to telemetry was the same in both groups. Of note, admission to the intensive care unit increased 29.2% (22.7% to 51.9%, p = 0.01) but the actual numbers show only 4 more admissions to the intensive care unit during the intervention year. Oral rate control increased in the intervention cohort by 19.4% (p < 0.01). The preintervention cohort received calcium channel blockers at a higher rate, 66.3% vs 48.8% (p = 0.01). Cardioversion was the same in both groups (9.6% vs 9.5%, p < 0.99). Adjusted multivariate results showed that patients given the intervention are almost twice as likely to be discharged (OR = 1.97, 95% CI = 1.07-3.63; Table 4).

Return visits to the ED and readmission to the hospital at 14 days were

Table 3. Discharge rate, disposition, and treatment of the cohorts

Variable, no. (%)	Preintervention (n = 104)	Postintervention (n = 95)	p value
Discharged	60 (57.7)	68 (71.6)	0.0411
Hospitalized			
Direct observation unit	10 (22.7)	14 (51.9)	0.0118
Telemetry	11 (25)	10 (37)	0.2807
Observation	20 (45.5)	3 (11.1)	0.0027
Medical-surgical ward	1 (2.3)	0 (0)	0.4302
Treatment[a]			
Oral rate control medication given in the ED	40 (38.5)	55 (57.9)	0.0061
IV rate control medication given in the ED	83 (79.8)	71 (74.7)	0.3930
Received β-blocker	49 (47.1)	40 (42.1)	0.4777
Received calcium channel blocker	69 (66.3)	46 (48.4)	0.0105
Received digoxin	11 (10.6)	5 (5.3)	0.1685
Cardioversion: direct current or chemical	10 (9.6)	9 (9.5)	> 0.99

[a] Patients may have received more than 1 class of medication.
ED = Emergency Department; IV = intravenous.

Table 4. Odds ratio adjusted for vital signs and CHA_2DS_2-VASc score[14]

Effect	Point estimate	95% Wald confidence limits
Intervention, pre vs post	1.967	**(1.067-3.627)**[a]
CHA_2DS_2-VASc	0.965	(0.822-1.133)
Systolic blood pressure	1.013	(0.995-1.031)
Diastolic blood pressure	1	(0.976-1.025)
Heart rate	0.557	(0.254-1.218)

[a] Bold indicates statistical significance

Table 5. Outcomes for preintervention and postintervention cohorts

Outcome	Preintervention (n = 104)	Postintervention (n = 95)	p value
30-d mortality, no. (%)	0 (0)	5 (5.3)	0.0184
30-d ischemic stroke, no. (%)	2 (1.9)	0 (0)	0.1743
14-d return visit to ED, no. (%)	14 (13.5)	11 (11.6)	0.6890
14-d hospital readmission, no. (%)	8 (7.7)	8 (8.4)	0.8502
ED length of stay, mean d (SD)	4.6 (2.55)	4.7 (2.32)	0.6843
Hospital length of stay, mean d (SD)	45.7 (76.43)	45.9 (49.34)	0.6062

ED = Emergency Department; SD = standard deviation.

similar in the pre- and postintervention groups (Table 5). The protocol did not affect LOS in the ED or the hospital (mean ED LOS of 4.6 hours and hospital LOS of 46 hours for both groups). There were 2 strokes in the preintervention group within 30 days of the encounter and none in the intervention group. There were no deaths in the preintervention group and 5 deaths in the intervention group within 30 days. However, on chart review of the deaths, none appeared attributable to the atrial fibrillation protocol. Three deaths were caused by sepsis, 1 was a patient receiving hospice care, and 1 patient died presumably because of a dysrhythmia from propafenone. Further details of the deaths appear in the Sidebar: Details of Patient Deaths.

DISCUSSION

Implementing a recommended guideline to standardize the ED treatment of atrial fibrillation with a rapid heart rate was associated with a 14% decrease in hospitalization. It appears that this effect was specifically related to a 19.4% increase in the use of oral rate control medications, a cardinal component of the guideline. The study ED had a low admission rate to begin with, 42.3% in the preintervention year compared with 64% across the US,[17] which may indicate that EDs with a higher admission rate could experience a greater effect. Additionally, no increase in the LOS in the ED was observed during the intervention year, showing that the practice guideline did not adversely affect the departmental flow. We also found that discharging more patients did not lead to worse outcomes related to atrial fibrillation, nor did it result in higher return visits to the ED or readmissions to the hospital.

The study does have limitations inherent to all retrospective studies, specifically with causation. The Hawthorne effect, which is a change in behavior because the participants in the study know they are being observed, may have influenced the study. That may have led to improved rate control during the intervention year, leading to more patients getting discharged home. Another inherent limitation is that only KP enrollees were used in the study. About 20% of the patients who came into the ED were not included because of nonmembership with the KP Health Plan. The reader should also be aware that the heart rate on arrival showed that there was a statistically significant difference between the preintervention and the intervention groups, 133.7/min and 127.5/min, respectively. This may have led to a greater chance of rate control in the intervention group with a subsequent increase in the discharge rate, but we do not believe that this statistical difference has much clinical meaning to the emergency physician treating someone with rapid atrial fibrillation.

The study from which our guideline was based[11] yielded a 36% decrease in hospital admission rate compared with our modest 14% decrease, but there are several important factors to consider when drawing a comparison between the studies. First, the other authors' preintervention admission rate was 78% compared with the preintervention admission rate of 42% in our study, which shows that our ED was already more aggressive in treating atrial fibrillation at baseline and offered less room for improvement. Second, the patients in the study by Zimetbaum et al[11] were almost exclusively patients with new-onset or paroxysmal atrial fibrillation, whereas only half the population in our study had new-onset or paroxysmal atrial fibrillation. This difference may explain why their cardioversion rate was more than double ours, as their study had more likely candidates for cardioversion. It is known that patients who are cardioverted are much more likely to be discharged from the ED.[15] Last, our study had much higher rates of hypertension and diabetes, a higher heart rate on arrival, and significantly higher rates of calcium channel or β-blocker use at baseline, showing our cohort to be somewhat "sicker." Our study also demonstrates that primary care follow-up may be sufficient for these patients when a dedicated atrial fibrillation cardiology clinic is not available.

Details of Patient Deaths

Patient 1: This patient, who had a history of falling because of a gait problem, fell 4 days after discharge and broke 2 ribs. About 11 days later, sepsis caused by pneumonia developed, and the patient died of sepsis.

Patient 2: The patient was admitted because of rapid atrial fibrillation. After discharge severe *Clostridium difficile* diarrhea developed, and she died of sepsis.

Patient 3: After treatment of rapid atrial fibrillation, a consult was made for admission to the hospital. The admitting team administered propafenone, and the patient died during dialysis several hours later, presumably because of dysrhythmia.

Patient 4: This patient was admitted to control the rate of her atrial fibrillation. Two weeks after discharge sepsis developed because of peritoneal catheter site infection. Shock ensued, and she died of sepsis.

Patient 5: This patient was treated for rapid atrial fibrillation and discharged home. He had a history of refractory chronic lymphoid leukemia. After 3 weeks of continued worsening of the chronic lymphoid leukemia, treatments were stopped, he was placed on hospice care, and he died a week later.

CONCLUSION

Our findings confirm that standardizing acute treatment of primary atrial fibrillation with a rapid heart rate in the ED is associated with a decrease in hospitalization and similar patient outcomes. The paramount element in our treatment guideline was increasing the use of oral medications, but doing rechecks with repeated administration of medications, expedited primary care follow-up, and outpatient echocardiography are also important. As with any clinical guideline, exceptions to the rules can always be found, and decision making should adapt accordingly to treat the individual patient. Because ED physicians will be seeing many more patients with atrial fibrillation in the future, it behooves us to implement proven guidelines to improve care and efficiency. We will also benefit from future research assessing the role of observation units, increased

use of cardioversion, and comparative effectiveness studies evaluating medication regimens for rate control. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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References

1. del Arco C, Martín A, Laguna P, Gargantilla P; Investigators in the Spanish Atrial Fibrillation in Emergency Medicine Study Group (GEFAUR). Analysis of current management of atrial fibrillation in the acute setting: GEFAUR-1 study. Ann Emerg Med 2005 Nov;46(5):424-30. DOI: https://doi.org/10.1016/j.annemergmed.2005.03.002.
2. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: National implications for rhythm management and stroke prevention: The AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001 May 9;285(18):2370-5. DOI: https://doi.org/10.1001/jama.285.18.2370.
3. Scheuermeyer FX, Grafstein E, Stenstrom R, et al. Thirty-day and 1-year outcomes of emergency department patients with atrial fibrillation and no acute underlying medical cause. Ann Emerg Med 2012 Dec;60(6):755-65.e2. DOI: https://doi.org/10.1016/j.annemergmed.2012.05.007.
4. Bontempo LJ, Goralnick E. Atrial fibrillation. Emerg Med Clin North Am 2011 Nov;29(4):747-58, vi. DOI: https://doi.org/10.1016/j.emc.2011.08.008.
5. Raghavan AV, Decker WW, Meloy TD. Management of atrial fibrillation in the emergency department. Emerg Med Clin North Am 2005 Nov;23(4):1127-39. DOI: https://doi.org/10.1016/j.emc.2005.07.013.
6. Rogenstein C, Kelly AM, Mason S, et al. An international view of how recent-onset atrial fibrillation is treated in the emergency department. Acad Emerg Med 2012 Nov;19(11):1255-60. DOI: https://doi.org/10.1111/acem.12016.
7. Stiell IG, Clement CM, Brison RJ, et al. Variation in management of recent-onset atrial fibrillation and flutter among academic hospital emergency departments. Ann Emerg Med 2011 Jan;57(1):13-21. DOI: https://doi.org/10.1016/j.annemergmed.2010.07.005.
8. Taylor DM, Aggarwal A, Carter M, Garewal D, Hunt D. Management of new onset atrial fibrillation in previously well patients less than 60 years of age. Emerg Med Australas 2005 Feb;17(1):4-10. DOI: https://doi.org/10.1111/j.1742-6723.2005.00687.x.
9. Coley CM, Li YH, Medsger AR, et al. Preferences for home vs hospital care among low-risk patients with community-acquired pneumonia. Arch Internal Med 1996 Jul 22;156(14):1565-71. DOI: https://doi.org/10.1001/archinte.1996.00440130115012.
10. Reynolds MR, Essebag V, Zimetbaum P, Cohen DJ. Healthcare resource utilization and costs associated with recurrent episodes of atrial fibrillation: The FRACTAL registry. J Cardiovasc Electrophysiol 2007 Jun;18(6):628-33. DOI: https://doi.org/10.1111/j.1540-8167.2007.00819.x.
11. Zimetbaum P, Reynolds MR, Ho KK, et al. Impact of a practice guideline for patients with atrial fibrillation on medical resource utilization and costs. Am J Cardiol 2003 Sep 15;92(6):677-81. DOI: https://doi.org/10.1016/s0002-9149(03)00821-x.
12. Worster A, Bledsoe RD, Cleve P, Fernandes CM, Upadhye S, Eva K. Reassessing the methods of medical record review studies in emergency medicine research. Ann Emerg Med 2005 Apr;45(4):448-51. DOI: https://doi.org/10.1016/j.annemergmed.2004.11.021.
13. Fuster V, Rydén LE, Cannom DS, et al; American College of Cardiology Foundation/American Heart Association Task Force. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: A report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation 2011 Mar 15;123(10):e269-367. DOI: https://doi.org/10.1161/cir.0b013e318214876d.
14. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: The Euro Heart Survey on Atrial Fibrillation. Chest 2010 Feb;137(2):263-72. DOI: https://doi.org/10.1378/chest.09-1584.
15. Stiell IG, Clement CM, Perry JJ, et al. Association of the Ottawa Aggressive Protocol with rapid discharge of emergency department patients with recent-onset atrial fibrillation or flutter. CJEM 2010 May;12(3):181-91. DOI: https://doi.org/10.1017/s1481803500012227.
16. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. JAMA 1994 Mar 16;271(11):840-4. DOI: https://doi.org/10.1001/jama.1994.03510350050036.
17. McDonald AJ, Pelletier AJ, Ellinor PT, Camargo CA Jr. Increasing US emergency department visit rates and subsequent hospital admissions for atrial fibrillation from 1993 to 2004. Ann Emerg Med 2008 Jan;51(1):58-65. DOI: https://doi.org/10.1016/j.annemergmed.2007.03.007.

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ORIGINAL RESEARCH & CONTRIBUTIONS

Special Report

Lifestyle Medicine: A Brief Review of Its Dramatic Impact on Health and Survival

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ABSTRACT

By ignoring the root causes of disease and neglecting to prioritize lifestyle measures for prevention, the medical community is placing people at harm. Advanced nations, influenced by a Western lifestyle, are in the midst of a health crisis, resulting largely from poor lifestyle choices. Epidemiologic, ecologic, and interventional studies have repeatedly indicated that most chronic illnesses, including cardiovascular disease, cancer, and type 2 diabetes, are the result of lifestyles fueled by poor nutrition and physical inactivity.

In this article, we describe the practice of lifestyle medicine and its powerful effect on these modern instigators of premature disability and death. We address the economic benefits of prevention-based lifestyle medicine and its effect on our health care system: A system on the verge of bankruptcy. We recommend vital changes to a disastrous course. Many deaths and many causes of pain, suffering, and disability could be circumvented if the medical community could effectively implement and share the power of healthy lifestyle choices. We believe that lifestyle medicine should become the primary approach to the management of chronic conditions and, more importantly, their prevention. For future generations, for our own health, and for the Hippocratic Oath we swore to uphold ("First do no harm"), the medical community must take action. It is our hope that the information presented will inspire our colleagues to pursue lifestyle medicine research and incorporate such practices into their daily care of patients. The time to make this change is now.

INTRODUCTION

Many consider lifestyle medicine to be a relatively new subspecialty, although it has been practiced for thousands of years.[1] Unlike conventional medicine, the focus of lifestyle medicine is not on the treatment of chronic diseases but rather on their prevention. Chronic diseases are presently the leading cause of morbidity and mortality and are responsible for most of our health care expenditure.[2] Most of these chronic conditions are preventable and are the result of an unhealthy lifestyle.[3] More than 80% of chronic conditions could be avoided through the adoption of healthy lifestyle recommendations.[3-5] Eighty percent of the population wants to live in a better state of health but do not know how to pursue it.[6] Minimal information is given by health care practitioners on how to implement an effective, long-term plan to achieve health.[3] The ongoing acceptance and adoption of a healthy lifestyle remains our greatest challenge. Implementation of lifestyle recommendations can save lives because lifestyle-related diseases are now the leading cause of mortality in the "modernized" world.[7] An aggressive analysis is needed to review the impact of lifestyle on our health.

So why are we sick and dying prematurely? Cardiovascular disease (CVD) and cancer have come to be known as the two "killer diseases" and account for more than half of all deaths in the US.[8] We are experiencing these diseases in the wealthiest nation in the world, which spends more on health care per capita than any other advanced economy and yet has some of

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the poorest health outcomes.[2] The most important problem is our poor lifestyle choices based on misinformation.[1,4]

There has been a dramatic shift in the leading causes of death in the US in the past 100 years. Whereas infectious diseases were the primary cause of death in the early 20th century, CVD and cancer have now assumed dominance in mortality (Figure 1).[9] Additionally, obesity and diabetes are inflammatory conditions that not only contribute to CVD and cancer but also serve as profound comorbidities; their shared etiologies promote one another. Both are sentinel signals of seriously eroding health, each harboring its own morbidities. This can be changed through a shift in how we take charge of managing our health and the health of our patients—through lifestyle medicine.

In this article, we address the pervasive effects of inflammation, obesity, and type 2 diabetes and their cost on the health care system. We review evidence on how implementation of lifestyle medicine recommendations may lead to a paradigm shift not only in health care delivery but also on its dramatic impact on chronic conditions.

Lifestyle medicine addresses basic recommendations, which may extend lives and may allow patients to live longer, in better health, with fewer disabilities, and with an improved quality of life. The intervention recommendations in lifestyle medicine are healthy eating, active living, healthy weight, and emotional resilience (see Figure 2 and the Sidebar: A Special Note on Emotional Resilience). Also represented in Figure 2 is what we refer to as the "red zone"—the percentage of the Western population that fails to adhere to such recommendations. Lifestyle determines in substantial ways the state of health; a poor lifestyle leads to poor health, and a good lifestyle generally leads to good health.

The quadrants of total health can be affected by the adoption of whole, plant-based foods; a moderate level of exercise; and emotional resilience. Whole, plant-based food maximizes the consumption of nutrient-dense foods and minimizes animal-based products (including dairy) and processed foods with added sugar, salt, and oil. Consuming whole, plant-based foods is synonymous with an anti-inflammatory diet.[10] A whole-foods, plant-based diet promotes the increased consumption of leafy greens, vegetables, fruits, legumes, and whole grains as staple foods.[3,11,12] The benefits of a whole-foods, plant-based diet have been shown to substantially influence the development of CVD as well as many common malignancies.[13-15] In addition, an anti-inflammatory diet has beneficial effects on obesity and diabetes, recognized as risk factors for CVD and numerous cancers.[3,11,16-21] The benefits of adopting a healthy lifestyle have been extensively documented. A less-than-optimal lifestyle is associated with the development of chronic conditions and can have a profound impact on the prognosis of such diseases. We summarize the evidence relevant to CVD and three of the most common malignancies: colorectal, prostate, and breast cancer.

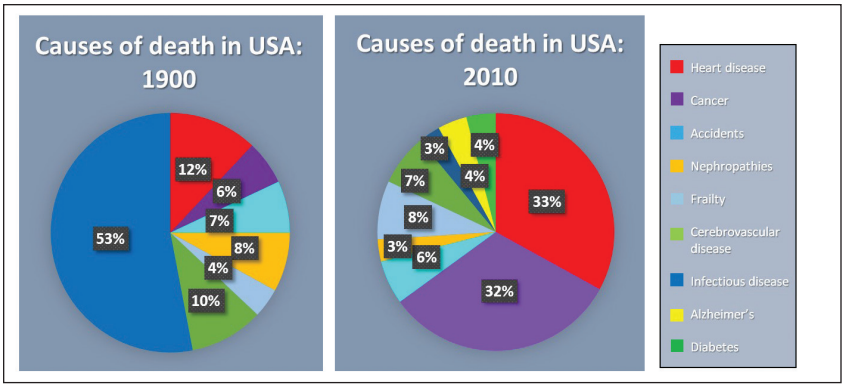

Figure 1. Leading causes of death in the US, 1900 and 2010.[a]

[a] Source: Centers for Disease Control and Infection data from Jones et al.[9]

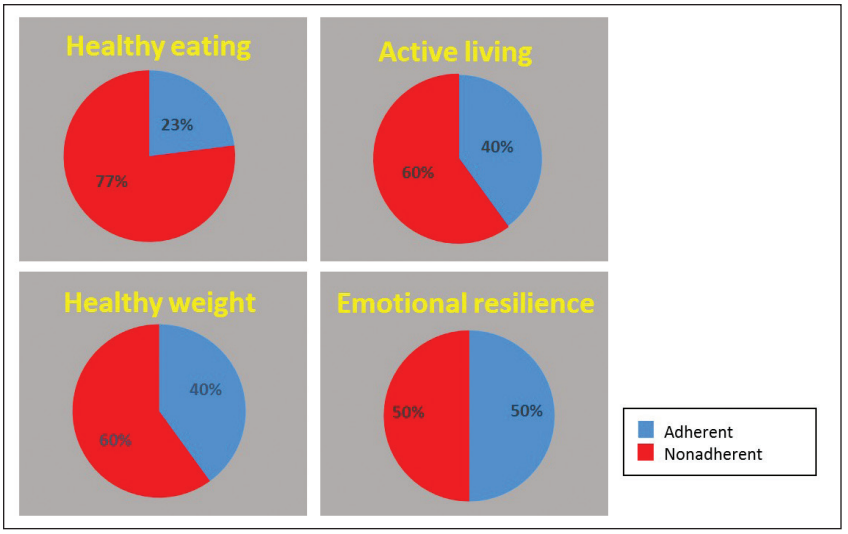

Figure 2. Quadrants of total health.

ENDEMIC CONDITIONS OF THE WESTERN WORLD

In the Western world, we subject ourselves to a poorly recognized, self-inflicted death sentence. We have become victims of three major conditions endemic to the Western World: inflammation, obesity, and type 2 diabetes, which are intricately interrelated and largely result from poor lifestyle choices. Combined, these diseases are lethal. That's the bad news. The good news is that we can now affect these "invaders" of our health through lifestyle changes. Recent reports have addressed the importance of lifestyle interventions (maintaining a healthy body mass index [BMI], a healthy diet, increasing physical activity, and managing stress) on chronic disease management.[3,12,16,18,20,21]

A Special Note on Emotional Resilience

Emotional resilience is defined as one's ability to respond to an adverse situation and, more importantly, a return to the "pre-event" baseline state of health. Factors impairing or affecting emotional resilience include depression, anxiety, stress, insomnia, and the presence of comorbidities, namely, additional chronic conditions. Depression and anxiety are the most common issues that negatively affect emotional resilience in the Western population. Stress is difficult to measure scientifically because of its omnipresence in everyday life. Depression, in particular, is recognized as a leading cause of disability, forecast to be the second-largest contributor to the worldwide burden of disease by 2020.[1] Many of the components of emotional resilience are interrelated, not just among themselves but also with other medical issues, most notably, obesity. The association of obesity and depression has been confirmed by several recent large meta-analysis studies.[2,3]

Depression is a recognized risk factor for the development of cardiovascular disease (CVD, as much as a twofold increase) and serves as a prognostic indicator for poorer outcomes in those already with a diagnosis of CVD.[4,5] Depression in patients after an acute myocardial infarction has been associated with a threefold increase in mortality.[4] The relationship of depression and CVD is reciprocal; each increases the risk of the other. Recent investigations have addressed the interrelationship of depression, stress, and CVD; depression and CVD may result from the cumulative effects of stress on the body.[6] Stress provokes the body's immune system to react by initiating a response to outside irritants, much the same as it does in reaction to bacterial, viral, or chemical intrusions. At the core of the immune response are white blood cells known as macrophages, resulting in the production of cytokines that aid communication in the immune system, promoting the establishment of a chronic inflammatory state and ongoing endothelial cell damage (see Figure 3). Physical activity may decrease such cellular injury.[7]

Depression and anxiety are also seen at higher levels in patients diagnosed with colorectal and prostate cancer.[8,9] Depression remains a major health concern, which is often underdiagnosed and, therefore, undertreated in patients with cancer.[10] Caregivers are increasingly recognizing the importance of screening for and treating depression in patients with breast cancer, but such efforts must be extended to other malignancies.[5] A recent study, the largest to date, addresses the importance of strong social connections; socially integrated women who practiced a healthier lifestyle, perhaps minimizing their stress levels, had decreased recurrence rates and an increase in overall disease-free survival after a diagnosis of breast cancer.[11] Emotional resilience addresses one's potential to return to a "previous normal" and is enhanced by an intense support system. Unfortunately, a substantial number of patients face a cancer diagnosis, treatment, and their outcomes alone and without support from their clinicians in the promotion of a healthier lifestyle.

Interestingly, the gut microbiome is also involved or at least has been implicated, with emotional resilience, affecting anxiety and depression.[12] Processed foods lead to intestinal permeability, which, as previously described, allows toxins to affect distant organs, including the nervous system.[13] It is recognized that lifestyle alterations, including a healthy diet and the pursuit of exercise, can have a positive impact on emotional resilience as well as cardiovascular health.[14] In addition, the influence of exercise in the treatment of depression and anxiety has been well documented and is not limited to the cancer community. Physical activity decreases symptoms of depression and anxiety, and physical inactivity increases the potential for the development of such conditions.[6] The association of psychological distress in the quality of life in patients with cancer has been noted, as well as an increase in the mortality of those with any malignancy.[15,16]

Current technology allows for the analysis of the effect of stress on the body at the molecular level.[17,18] Telomere caplets at the end of each chromosome assist in the regulation of appropriate genetic replication. Each time a cell divides, telomere base pairs shorten, resulting in a lessening of their effective regulation of normal cell replication. Chronic stress and poor health, such as the development of CVD and cancer, are linked. Shortening of telomeres has been associated with the onset of malignancies and the process of aging, which itself is a major risk factor for the development of cancer. Chronic stress has been demonstrated to result in such "shortening damage" of telomeres.[19]

References

1. Lopez AD, Murray CC. The global burden of disease, 1990-2020. Nat Med 1990 Nov;4(11):1241-3. DOI: https://doi.org/10.1038/3218.
2. Luppino FS, de Wit LM, Bouvy PF, et al. Overweight, obesity, and depression: A systematic review and meta-analysis of longitudinal studies. Arch Gen Psychiatry 2010 Mar;67(3):220-9. DOI: https://doi.org/10.1001/archgenpsychiatry.2010.2.
3. Nicholson A, Kuper H, Hemmingway H. Depression as an aetiologic and prognostic factor in coronary heart disease: A meta-analysis of 6362 events among 146 538 participants in 54 observational studies. Eur Heart J 2006 Dec;27(23):2763-74. DOI: https://doi.org/10.1093/eurheartj/ehl338.
4. Hare DL, Toukhsati SR, Johansson P, Jaarsma T. Depression and cardiovascular disease: A clinical review. Eur Heart J 2014 Jun 1;35(21):1365-72. DOI: https://doi.org/10.1093/eurheartj/eht462.
5. Tuso P. Treatment progress indicator: Application of a new assessment tool to objectively monitor the therapeutic progress of patients with depression, anxiety, or behavioral impairment. Perm J 2014 Summer;18(3):55-9. DOI: https://doi.org/10.7812/TPP/13-091.
6. Miller GE, Blackwell E. Turning up the heat: Inflammation as a mechanism linking chronic stress, depression, and heart disease. Curr Dir Psychol Sci 2006;15(6):269-72. DOI: https://doi.org/10.1111/j.1467-8721.2006.00450.x.
7. Carek PJ, Laibstain SE, Carek SM. Exercise for the treatment of depression and anxiety. Int J Psychiatry Med 2011;41(1):15-28. DOI: https://doi.org/10.2190/PM.41.1.c.
8. Medeiros M, Oshima CT, Forones NM. Depression and anxiety in colorectal cancer patients. J Gastrointest Cancer 2010 Sep;41(3):179-84. DOI: https://doi.org/10.1007/s12029-010-9132-5.
9. Korfage IJ, Essink-Bot ML, Janssens AJ, Schröder FH, de Koning HJ. Anxiety and depression after prostate cancer diagnosis and treatment: 5-year follow-up. Br J Cancer 2006 Apr 24;94(8):1093-8. DOI: https://doi.org/10.1038/sj.bjc.6603057.
10. Massie MJ. Prevalence of depression in patients with cancer. J Natl Cancer Inst Monogr 2004;(32):57-71. DOI: https://doi.org/10.1093/jncimonographs/lgh014.
11. Kroenke CH, Michael YL, Poole EM, et al. Postdiagnosis social networks and breast cancer mortality in the After Breast Cancer Pooling Project. Cancer 2017 Apr 1;123(7):1228-37. DOI: https://doi.org/10.1002/cncr.30440.
12. Galland L. The gut microbiome and the brain. J Med Food 2014 Dec;17(12):1261-72. DOI: https://doi.org/10.1089/jmf.2014.7000.
13. Kelly JR, Kennedy PJ, Cryan JF, Dinan TG, Clarke G, Hyland NP. Breaking down the barriers: The gut microbiome, intestinal permeability and stress-related psychiatric disorders. Front Cell Neurosci 2015 Oct 14;9:392. DOI: https://doi.org/10.3389/fncl.2015.00392.
14. Mosovich SA, Boone RT, Reichenberg A, et al. New insights into the link between cardiovascular disease and depression. Int J Clin Pract 2008 Mar;62(3):423-32. DOI: https://doi.org/10.1111/j.1742-1241.2007.01640.x.
15. Brown LF, Kroenke K, Theobald DE, Wu J, Tu W. The association of depression and anxiety with health-related quality of life in cancer patients with depression and/or pain. Psychooncology 2010 Jun;19(7):734-41. DOI: https://doi.org/10.1002/pon.1627.
16. Russ TC, Stamatakis E, Hamer M, Starr JM, Kivimäki M, Batty GD. Association between psychological distress and mortality: Individual participant pooled analysis of 10 prospective cohort studies. BMJ 2012 Jul 31;345:e4933. DOI: https://doi.org/10.1136/bmj.e4933.
17. Hofker MH, Fu J, Wijmenga C. The genome revolution and its role in understanding complex diseases. Biochim Biophys Acta 2014 Oct;1842(10);1889-95. DOI: https://doi.org/10.1016/j.bbadis.2014.05.002.
18. Wilson BJ, Nicholls SG. The Human Genome Project, and recent advances in personalized genomics. Risk Manage Healthc Policy 2015 Feb 16;8:9-20. DOI: https://doi.org/10.2147/rmhp.s58728.
19. Epel ES, Blackburn EH, Lin J, et al. Accelerated telomere shortening in response to life stress. Proc Natl Acad Sci U S A 2004 Dec 7;101(49):17312-5. DOI: https://doi.org/10.1073/pnas.0407162101

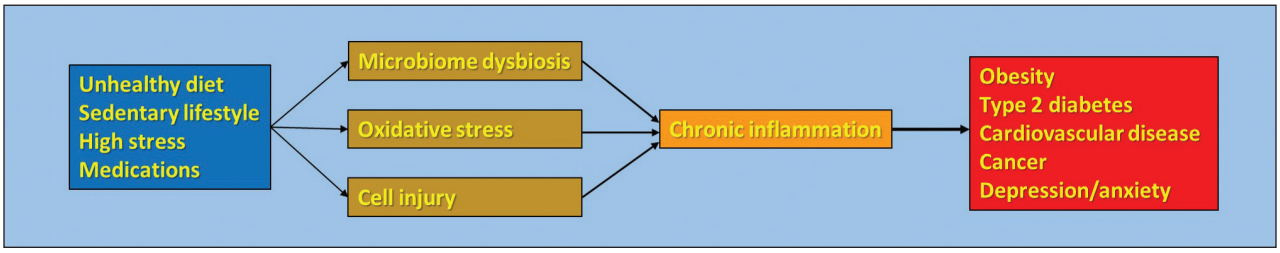

Figure 3. Steps in the pathogenesis of inflammation leading to progression of chronic diseases.

Such interventions are based on large-scale, prospective studies, which provide evidence-based conclusions.[6,13,18-21]

Inflammation

We live in a world that initiates, promotes, and accelerates chronic inflammation. Inflammation has been implicated as a causative factor in nearly all chronic diseases.[22] From an evolutionary perspective, the body's inflammatory response was vital for survival before modern sanitation processes (water purification, sewage systems, and the recognition of hygiene issues such as hand washing). Today, we live longer, and thus inflammatory responses are more likely to confuse and overwhelm the body's defense systems. Many attributes of our Western lifestyle incite an inflammatory response, and such continued lifestyle exposures perpetuate unmitigated inflammation.

Obesity

Obesity is the second endemic condition we face. Two of three Westerners are either overweight or obese (Figure 2). Furthermore, obesity is an inflammatory disease.[23] Adequate physical activity and normalizing weight decreases the inflammatory reaction of the body and may help mitigate the massive immune response to infectious agents that serve as a stimulus for carcinogenesis. Inflammatory proteins (Interleukin-6, tumor necrosis factor, and C-reactive protein, among others) are elevated in obese patients because of excess adipose tissue.

The current focus of obesity is centered on CVD, yet cancer is far more feared and less frequently addressed. A 2008 Surveillance, Epidemiology, and End Results (SEER) Program Study[21] estimated that nearly 90,000 cases of cancer were caused by obesity. Estimates are that the continuing trend in obesity will lead to an additional 500,000 deaths by the year 2030.[21] Additionally, obese individuals are more likely to live in a state of chronic inflammation.[23]

The common link between inflammation and obesity may well reside in the gastrointestinal (gut) microbiome. The physiology of the gut remains poorly defined. However, recent advances in molecular tools, such as gene sequencing, have allowed a more intricate understanding of the role of the gut microbiome as an endocrine organ that manufactures hundreds, if not thousands, of chemicals that influence the regulation of multiple distant organs.[24] Such compounds play a substantial role in the development of a "leaky" gut, which allows toxins to enter the bloodstream and results in inflammation and promotion of CVD, obesity, Type 2 diabetes, and chronic diseases.[25-30] The gut microbial complex appears to be a major factor responsible for metabolic and inflammatory diseases, linking inflammation and obesity to additional factors such as alterations in lipid metabolism and insulin signaling. The accumulation of fat promotes a chronic inflammatory state that results in the activation and recruitment of immune cells, which leads to an ongoing, self-perpetuating process.[31] A major hallmark of obesity is documentation of the occurrence of inflammation.[32] The result is a state of chronic inflammation promoting the disease states of our modern civilization. The steps in the pathogenesis of inflammation are depicted in Figure 3 in their most simplified form to help readers understand chronic disease progression.

Diabetes

The rate of diabetes has steadily risen in the past decade.[33] It is recognized as the leading cause of target organ complications (limb amputations, end-stage renal failure, and adult-onset blindness). Diabetes is also a major risk factor for CVD. With its increasing prevalence and long-term complications, diabetes has become one of the costliest medical conditions in the US. Between 2007 and 2012, costs associated with diabetes increased an alarming 48%.[2] Obesity, as described earlier, has been associated with chronic inflammation, insulin resistance, and the development of type 2 diabetes.[34] Diabetes has been identified to be far beyond a metabolic disease and is now acknowledged to be an inflammatory condition.[35,36]

The increasing prevalence and costs associated with diabetes have resulted in the need for improved efforts directed at prevention. Exercise and weight reduction are well established as important priorities in prevention, with strong supportive evidence.[37-40] Recent attention to diet quality as it pertains to diabetes prevention has focused on the reduction of refined sugar consumption, and rightfully so; each serving per day of sugar-sweetened beverages (eg, soft drinks) has been associated with a 25% increased risk of diabetes.[41]

Refined sugar consumption is an important focus, but currently lacking in the conversation on diabetes prevention is the importance of animal product consumption. A large study of more than 60,000 North Americans showed a stepwise increase in the prevalence of diabetes with increasing animal product consumption. Those eating no animal products at all (vegans) had the lowest diabetes prevalence overall, at 2.9%, with omnivores having the highest prevalence at 7.6%. Even when risk factors such as age, BMI, and physical activity were adjusted for, there persisted a statistically significant reduction of 49% in the risk of later

development of diabetes.[21] Data from the Nurses and Physicians' Health Studies (more than 4 million person-years combined) demonstrated that the substitution of just 5% of calories from animal to plant protein reduced the risk of diabetes by 23%.[42] Data looking at processed meats (bacon, sausage, hot dogs, and deli meat) and egg consumption in relation to diabetes risk have been impressive. A meta-analysis of processed meat consumption revealed that each serving of processed meat daily was associated with a 51% increased risk of diabetes.[43] A separate meta-analysis looking at egg consumption demonstrated that high egg consumption was associated with a 68% increase in the risk of diabetes development.[44]

Prevention is ideal, but the reality is that more than 29 million Americans already have diabetes, making prevention management the priority. The past decades have focused on glycemic management with medications. However, recent studies question this approach, including a meta-analysis of 13 randomized controlled trials, which found that intensive glycemic management with medications resulted in a doubling of the risk of severe hypoglycemia, with no overall mortality or cardiovascular mortality benefit.[45] A separate review of 328 articles, 11 meta-analyses, and 5 randomized controlled trials all published in the last decade cast doubt on the supposed benefits of fewer microvascular complications with intensive glycemic management; specifically, no significant benefit was found with respect to the risk of dialysis/transplantation/renal death, blindness, or neuropathy.[46] Medications used in the treatment of diabetes also carry a wide range of side effects, which include the following: diarrhea, vitamin B12 deficiency, lactic acidosis (caused by metformin), hypoglycemia, weight gain (sulfonylureas and insulin), heart failure, an increase in fractures (thiazolidinediones), pancreatitis, yeast infections, urinary tract infections, and acute kidney injury.[47]

With legitimate concerns about the utility and safety of the intensive management of diabetes with medications, it is essential and timely to note that lifestyle changes are as effective as, and perhaps more so than, medications, with no side effects. The most effective lifestyle changes have been exercise and diets based on whole, plant foods (fruits, vegetables, whole grains, beans, nuts, and seeds). Regarding exercise, a meta-analysis of 27 studies found that regular exercise, regardless of type (aerobic, resistance, or combined), resulted in the improvement of hemoglobin A_{1C} control by an average of 0.8%,[48] a benefit comparable to current diabetes medications.[47]

Dietary studies focused on diabetes have demonstrated consistent results when based on whole, plant foods. A randomized controlled trial of 99 patients compared a whole-foods, plant-based diet with the American Diabetes Association diet and found that although both diets improved glycemic control, the plant-based diet group had superior results.[49] In the plant-based diet group, hemoglobin A_{1C} control improved by 1.23 points,[49] an effect comparable to, if not superior to, that of the most currently prescribed medications.[47] A larger study analyzed 232 patients with diabetes who were placed on a plant-based diet as part of a residential dietary intervention program. More than 90% of patients were able to decrease or discontinue their diabetes medications in just 7 days while improving or maintaining control of their diabetes.[50] A review of 14 randomized diet trials concluded that the best results occurred with plant-based diets.[51]

The annual health care costs attributable to obesity alone exceed $100 billion.[2] Add to this the rapid rise in the costs of treating type 2 diabetes, which total approximately $101 billion annually.[2,52] Escalation of health care costs from other complications of obesity and type 2 diabetes are inevitable as these conditions continue to result in substantial future complications that will require further expensive medical care. Inflammation, obesity, and diabetes are intricately related, fuel one another, and will drive health care expenses beyond affordability.

Cardiovascular Disease

Despite major advances in the treatment of cardiac events, CVD remains the leading cause of death and disability in the US.[53-55] More than 600,000 deaths (1 in 4) are attributable to heart disease each year, and CVD accounts for more than $70 billion annually (approximately 17% of the total health care expenditure).[56-58] By the year 2030, 40% of the US population is projected to have some form of CVD, and care will exceed $800 billion, making it our most costly disease.[56]

The understanding of the pathogenesis of atherosclerosis has recently undergone a dramatic update. The role of chronic inflammation in its development, particularly in the setting of obesity, serves as the foundation for the most current theory.[59,60] Atherosclerosis appears to be the result of oxidative damage to the endothelial cells that line the vascular system, including, of course, the coronary arterial anatomy.[61] The damage to the endothelial layer of the coronary arteries is a progressive process beginning with inflammation secondary to oxidative stresses that result from the oxidation of low-density lipoproteins, energizing the low-density lipoproteins to penetrate the endothelial layer; this process leads to the subsequent development of plaques, the rupture of which may result in a myocardial infarction or often sudden death.[61,62]

Dietary components consumed by the Western population promote CVD by directly affecting the gut microbiota.[63] In particular, consumption of red meats, which are high in L-carnitine, elevate serum levels of trimethylamine oxide (TMAO) because of the hepatic conversion of its microbially derived precursor, trimethylamine.[63] Reducing red meat consumption results in decreased TMAO production, which downregulates the macrophagic uptake of oxidation of low-density lipoproteins. Levels of TMAO are reduced in patients who are following an anti-inflammatory diet. Although measurement of TMAO levels is not readily available, future technology may soon develop a test measuring TMAO and allow for the early intervention of individuals at risk of atherogenic threats before they progress to the point of sudden death.[61] Some authors offer an in-depth discussion of the biochemical basis and pathogenesis of oxidative stress and vascular injury.[59-62]

A lifestyle program that incorporates a whole, plant-based diet has been shown to reverse CVD, a feat largely elusive to medications and technologic advances. Numerous studies have demonstrated that lifestyle interventions can have a major

impact on the development of, and even the reversal of, CVD.[1,13,62,64] Evidence has accumulated associating a healthy dietary pattern with lower rates of cardiac events, and an extensive review has been presented endorsing the cardioprotective effects of a diet that endorses the increased consumption of plant-based foods.[65] Lifestyle management offers support for the adoption of a diet consisting of mostly plants to prevent CVD.[11] A whole-foods, plant-based diet offers additional protection against CVD because of the beneficial effect that polyphenols have on the endothelial layer of the vasculature, including the negation of oxidation of low-density lipoproteins and its impact on inflammation.[11,61,66-68] Large epidemiologic studies support the fact that those following an anti-inflammatory, plant-based diet may decrease the risk of CVD development by nearly 25%.[69,70] The promotion of a diet contrary to the standard American diet—embracing the increased consumption of plant-based foods and the avoidance of red meat, highly processed foods, added sugars, salt, and fat—appears to be beneficial in the improvement of cardiovascular health.[71]

Recent scientific advances have allowed us to characterize the human genome, opening the door to the genetic expression of disease in its earliest development.[72,73] Regarding CVD, a recently published study demonstrated the effect of lifestyle modification on pro-inflammatory gene expression.[74] The impact of our understanding of disease at the epigenomic level presents an opportunity to intervene in the development of chronic diseases and increase the odds for cure. Lifestyle interventions (tobacco cessation; adoption of a whole-foods, plant-based diet; and exercise) focusing on CVD have been documented as remarkably effective.[75] Even in patients with a high genetic risk profile, a favorable lifestyle has been associated with a 50% decreased risk of CVD development.[76]

Physical activity in individuals at increased risk of CVD has been noted to significantly decrease mortality.[61,75,77] Those who are least fit may, in fact, gain the most benefit from exercise and thus realize a more statistically significant impact on their survival.[78] Interestingly, many common malignancies share similar pathologic characteristics that are akin to CVD—notably, inflammation and obesity.

CANCER

Despite enormous research efforts and funds expended, cancer continues to be a major cause of death. Each year, 17.5 million cancers are diagnosed and 8.7 million deaths caused by cancer occur worldwide.[79] In the US, 1.6 million Americans receive a diagnosis of cancer, and more than 600,000 deaths are attributable to this disease.[80] In the next few years, the world population will exceed 7.5 billion, which is expected to drive these figures even higher.[81] The current belief is that most cancers are the result of inherited genetic abnormalities, yet 90% of malignancies are rooted in our lifestyle and environmental exposures. Many of these exposures are modifiable; we can avoid tobacco and alcohol, decrease our exposure to ultraviolet light, increase our level of physical activity, and, perhaps most importantly, alter our diets.

In the US, October is National Breast Cancer Awareness Month; September is set aside for prostate cancer awareness; and March is dedicated to colorectal cancer awareness. These awareness campaigns are laudable; however, their emphasis on early detection, treatment, and survivorship does not address the more crucial issue that many such cancers can actually be prevented by lifestyle changes. For instance, obesity is a well-recognized risk factor for the development of a large number of malignancies, as well as for cancer recurrence and mortality.[82,83] In 2016, the US will have more than 14 million persons alive as survivors of cancer. In comparison, in 1971, there were 3 million cancer survivors. By 2020, there will be 20 million people in whom some form of cancer has been diagnosed who are alive and well. More than 75% of all cancer patients currently live beyond 5 years.[84] As such, there is ample time for patients to implement lifestyle changes that may further contribute to their overall disease-free, long-term survival.

Colorectal Cancer

In 2015, there were 1.7 million cases of colorectal carcinoma with 832,000 deaths worldwide.[79] More than 140,000 people in the US will receive a diagnosis of colorectal carcinoma in 2016, and more than 50,000 will die.[80] Colorectal cancer is the third most commonly diagnosed non-sex-specific cancer. Less than 20% of colorectal carcinomas have a genetic basis[85]; therefore, most colorectal cancer cases have been linked to environmental exposures (eg, food-borne mutagens) and chronic intestinal inflammation.[86] Perhaps no malignancy other than colorectal carcinoma demonstrates so dramatically the connection between inflammation and the development of neoplasms. Patients with chronic inflammatory bowel disease (ulcerative colitis and Crohn disease) are at an increased risk of breast cancer development,[87] adding to the ever-growing body of evidence linking chronic inflammation to the progression of cancer. The risk of colorectal cancer developing increases with the duration and extent of inflammatory bowel disease.[87] The microbiome of the gut has also been implicated in the development of sporadic colorectal carcinoma.[25,88]

Risk factors for the development of colorectal cancer include a sedentary lifestyle, obesity, and the dietary components that form the basis of the standard American diet (large consumption of red meats and highly processed foods and low amounts of fruit, vegetables, legumes, and fiber intake).[89] Low-fiber diets, such as the standard American or "Westernized" diet that promotes inflammation, have been linked to the increased risk and development of colorectal cancer.[90] In addition, patients with colorectal cancers appear to have more comorbidities at the time of diagnosis than patients with other malignancies.[91] For example, patients with diabetes have a 26% increased risk of developing colon cancer and a 30% increased risk of dying because of it compared with patients without diabetes.[92] Data exist that modifiable lifestyle issues (diet and activity) are increasingly associated with the risk of colorectal cancer development, perhaps more so than any other malignancy.[93,94]

Prostate Cancer

Prostate cancer is the most commonly diagnosed malignancy in men, affecting 1.6 million worldwide and resulting in the death of nearly 370,000 in 2015.[79] In the US, nearly 150,000 men received a diagnosis of prostate cancer in 2016, and close to 40,000 will die of this cancer.[80] Somewhat alarming is a recent report that

the incidence of metastatic prostate cancer has increased by 72% since 2004.[95] Of particular concern is that the largest increase in new cases was in the age range of 55 to 69 years, ironically the same group most likely to benefit from early treatment.[96] If this increase is, as some postulate, caused by a more aggressive presentation of the disease, then the importance of lifestyle changes may further increase in relevancy. As with many other malignancies, diet and obesity contribute to chronic inflammatory processes that lead to disease aggressiveness.[81,97] Furthermore, obesity has been implicated in not only the development but also the progression of prostate cancer.[81,97]

Prostate cancer patients are often advised to make lifestyle changes. Such changes could be beneficial but need further verification. In one study,[98] changes in prostate-specific antigen levels were monitored in a small group of patients. The experimental group was subjected to an intensive lifestyle intervention program, which included a vegan diet, soy protein, supplemental vitamins (E and C), selenium, exercise (30 minutes of walking 6 d/wk), and a support group/stress management program for 1 hour per week. Prostate-specific antigen levels decreased 4% in the experimental group and increased 6% in the control group.[99] In addition, blood taken from both groups demonstrated that the serum of the experimental group inhibited growth of prostate cancer cells nearly 8-fold more intensively than the serum of the control group. Furthermore, these comprehensive nutrition and lifestyle changes have been shown to downregulate prostate gene expression in men after a diagnosis of early-stage prostate cancer.[99]

The incidence and mortality of prostate cancer appear to be associated with a Western lifestyle, and a strong corollary relationship has been noted with the intake of animal foods.[97,100] Men in developing countries who drift toward a Western-oriented lifestyle experience an increased incidence of prostate cancer. Furthermore, migration studies have demonstrated that those populations that live in low-cancer-risk geographic areas assume Western rates of cancer within 1 to 2 decades of immigration to the West. This observation is not limited to prostate cancer but involves the development of other malignancies as well.[81]

Breast Cancer

The most common malignancy among women in 2016 was breast cancer, affecting 2.4 million women worldwide and taking the lives of more than 520,000.[79] In 2017, nearly 250,000 women will receive a diagnosis of breast cancer and more than 40,000 will die in the US.[80] Breast cancer is the most feared disease by many women, yet heart disease is the leading cause of death in women in the US.[3] Interestingly, less than 50% of women are aware that heart disease is the leading cause of death.[3]

As with previously addressed malignancies, breast cancer can be attributed in part to a lifestyle fueled by a poor diet that often results in obesity.[101] Sinicrope and Dannenberg[101] addressed this topic in a recent publication. Obesity leads to insulin resistance, resulting in elevated blood levels of insulin and insulin-like growth factor (IGF) and a decrease in sex hormone-binding globulin. Consequently, the availability of estradiol increases, which may fuel the development and aggressiveness of breast cancers. Fatty tissues (adipocytes) have been demonstrated to be an independent endocrinogenic organ capable of manufacturing and storing estrogenic compounds that contribute to multiple malignancies. Importantly, fatty

Table 1. Daily dietary recommendations[1]

Decrease substantially or eliminate	Increase or consume heavily
Inflammatory effects	Anti-Inflammatory effects
Low nutrient and/or high calorie	**High nutrient/low calorie**
Meat: beef, pork, lamb, chicken, turkey, seafood	Leafy greens
Processed meats: salami, bologna, ham, turkey, chicken	Vegetables: cruciferous, squash, garlic
Animal dairy: milk, cheese, yogurt, kefir, sour cream, cottage cheese, butter	Mushrooms
Sugar substitutes and refined sugars: aspartame, high-fructose corn syrup	Fruits: berries, bananas, pomegranates
Processed foods: refined grains (white bread, cookies, fried potato chips)	Legumes: green beans, lentils, soybeans, sugar snap peas
Soft drinks, alcohol	Whole grains: quinoa, wheat, oat, rice, pasta, barley, corn
	Seeds: flax, chia, pumpkin, sesame
	Plant-based "dairy": soy, almond, rice milk
	High nutrient/high fat: Limited consumption
	Nuts: walnuts, pecans, almonds, etc

[1] Bodai BI, Tuso P. Breast cancer survivorship: A comprehensive review of long-term medical issues and lifestyle recommendations. Perm J 2015 Spring;19(2):48-79. DOI: https://doi.org/10.7812/TPP/14-241.

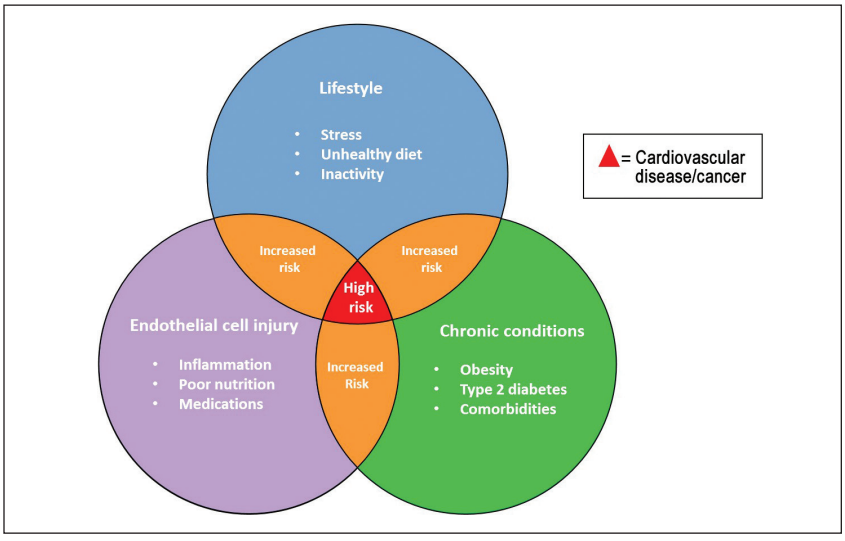

Figure 4. Effects of cellular damage, chronic conditions, and lifestyle practices appear to raise the risk of cardiovascular disease and cancer.

tissues also store a dozen or more inflammatory proteins that promote carcinogenesis.[101] In a recent study, low-dose aspirin was shown to reduce inflammation, resulting in a lower incidence of breast cancer.[102]

Not only is obesity a risk factor for breast cancer development, it is an independent prognostic factor for distant metastases and an increased risk of death.[103] Comorbidities also have a role in oncogenesis. Patients with diabetes have a 23% increased risk of breast cancer developing and a 38% increased risk of dying of the disease compared with patients without diabetes.[92] A substantial proportion of breast cancer patients are both obese and sedentary, emphasizing the need for lifestyle interventions that may improve prognosis and ultimate outcomes.[3]

Understanding of breast cancer and the influence of dietary consumption patterns has recently advanced. Dietary recommendations, including an increase in fiber intake, have been made to aid in the prevention of this cancer.[104,105] Recently the human "estrobolome" has been discovered as the set of gut bacterial genes that metabolize estrogen.[106] Dysbiosis of the gastrointestinal tract is involved in the re-cycling of estrogen through the enterohepatic circulation, increasing its potency, which may further fuel the development of breast cancer.[107,108] Estrogen levels are further decreased by the increased consumption of fiber intake because fiber inhibits the absorption of estrogen in the gastrointestinal tract.[104,109] The American Institute for Cancer Research reported in 2014, from worldwide data, that diet, physical activity, and weight control are major contributors to long-term survival after a diagnosis of breast cancer.[110] Furthermore, a 2011 meta-analysis of postdiagnosis exercise in patients with breast cancer involving more than 12,000 patients demonstrated a 34% decrease in risk of death caused by breast cancer, a 24% decrease in recurrence, and a 41% decrease in the risk of all-cause mortality.[111] This conclusion is the result of the review of 67 published articles addressing lifestyle changes as they relate to the reduction of breast cancer recurrence.[112]

Additional studies have documented that physical activity not only increases survival and decreases recurrence but also improves overall quality of life in patients with breast cancer and in patients with colon cancer.[113-115] Another study followed nearly 1500 women diagnosed with early-stage breast cancer. These patients were followed for up to 9 years and demonstrated a 50% decreased death rate in those who adhered to a high fruit and vegetable intake (5 servings/d) and a regular physical activity regimen (30 minutes, 5 times weekly) compared with those who did not.[116] Although the exact mechanism of the action of exercise and its impact on cancer recurrence remains elusive, some have pointed to the possibility that exercise may affect the inflammatory response of the body, resulting in a decreased rate of recurrence.[117] Regular exercise may also have a protective role in the initial development of breast cancer.[118]

DISCUSSION

For far too long, patients have experienced chronic illnesses because our health care system has not taken a proactive role in promoting healthy eating, active living, and the promotion of emotional resilience (see Sidebar: A Special Note on Emotional Resilience). The medical community has been proud to announce major achievements in health care and their impact, yet a recent analysis on cardiovascular mortality brings into question such advances; the decreasing rate of CVD that has been noted since the 1970s appears to be declining at a slower pace.[119] Advances in CVD survival no longer approach the prior rate of decline despite improvements in treatment. Perhaps the management of CVD should focus more on lifestyle recommendations and prevention than on treatment once the disease has become symptomatic. In addition, it has been suggested that the recently noted decline in cancer incidence may be related to the recession of 2008, which may have decreased screening accessibility for many.[120] It is increasingly recognized that the real issue in health care—lifestyle—should become the primary prescription for the leading causes of disease that result in the highest rates of mortality.[4-7,9,22] The slow progress in decreasing mortality rates from CVD incriminates an unhealthy diet and a sedentary lifestyle as major contributing factors.[121]

Ample evidence exists to support the avocation of a diet on the basis of the recommendations outlined in Table 1.[3,7,116,122-127]

Lifestyle medicine addresses principles that are the cornerstone of health and well-being. The current practice of prescribing medications or performing surgery for nearly every illness must be revisited. A paradigm shift to lifestyle medicine needs urgent implementation. Dramatic effects using lifestyle interventions have been demonstrated in patients with chronic conditions. Several large studies have conclusively shown that diet and exercise modifications not only substantially improve long-term survival but also result in a portrait more nearly approaching total health.[5,105,116,122,128,129] As an example, a prospective study of 23,000 participants evaluated adherence to 4 simple recommendations[5]: No tobacco use, 30 minutes of exercise 5 times per week, maintaining a BMI of less than 30 kg/m^2, and eating a healthy diet as previously described. Participants who adhered to these 4 recommendations had an overall 78% decreased risk of development of a chronic condition during an 8-year timeframe. Furthermore, in participants adhering to these recommendations, there was a 93% reduced risk of diabetes mellitus, an 81% reduced risk of myocardial infarction, and a 36% reduction in the risk of the development of cancer.[5]

The additive effects of cellular damage, chronic conditions, and lifestyle practices appear to place us at an ever-increasing risk of CVD and cancer (Figure 4). Risk factors are interactive and should be recognized as such. Those who fall into the high-risk category in Figure 4 need urgent attention and lifestyle interventions.

Medications, particularly in chronic or repeated sequences, may also play an important role in the development of malignancies. The overprescription of antibiotics has received recent attention in the promotion of "super strain" bacteria that are resistant to most currently available antibiotics. Prostate cancer risk increased with the use of penicillin, quinolones, sulfonamides, and tetracycline; breast cancer risk was demonstrated to modestly increase with exposure to sulfonamides.[130] This increased risk may well be caused by the drugs' influence and/or the depletion of the natural microbiome resulting in a state of dysbiosis.

The potential carcinogenicity of red and processed meats has drawn extensive attention since the Interventional Agency for

Research on Cancer evaluated these products.[131] Consuming a whole, plant-based food (anti-inflammatory) diet promotes high-nutrient foods with fewer calories per pound compared with low-nutrient foods.[3] This will result in a healthy BMI, potential weight loss, and a lower risk of development of CVD and some of the most common malignancies. Vegetables, fruits, legumes, whole grains, and healthy fats should become our staple foods and have been recommended as key components of a healthy lifestyle to avert the three chronic conditions that are responsible for the majority of deaths in the US (Figure 1). Recently, the association of animal vs plant protein intake with all-cause mortality has been documented. Specifically, high consumption of animal protein was associated with an increased risk of cardiovascular mortality and all-cause mortality.[132] In this same study, high consumption of plant-based protein demonstrated an overall decrease in all-cause mortality.[132]

Genetic variants have been associated with susceptibilities to the development of chronic disease. However, evidence is available that the hereditability of such variants may, in fact, be only modest.[31] Thus, credibility is added to the fact that most chronic conditions are, in reality, the result of lifestyle. An invitation to the development of chronic conditions is related to shifts in the human microbiome as represented by Western influence. Evidence for a strong correlation between the gut microflora and disease is exponentially expanding, particularly relevant to the development of CVD and cancer.[133-135] Along with our growth of knowledge comes an opportunity to intervene in the prevention of disease. An incredible shift in cancer care has recently become recognized because of technologic advances, and priming of the immune system has now been shown to be effective in treating patients with a wide variety of malignancies. Epigenomics may play a major role in our immunogenetic capabilities, and, as such, lifestyle modifications, demonstrated to have an influence on the modulation of genetic expression profiles, are worthy of further investigation. Dietary and lifestyle changes can and should be pursued to avert poor outcomes.[136]

Profit motives play a large role in the food industry as well as "Big Pharma" and health care; therefore, the delivery of information and the care of patients may themselves become the victims of politics. Most chronic conditions are influenced by lifestyle and account for 75% or more of health care costs.[4,137] Since 2010, nearly 18% of the US gross national product has been spent on health care, which exceeded $3.0 trillion in 2015.[138,139] Few of these dollars have been spent on identifying the true underlying causes of patients' chronic conditions. Lifestyle recommendations, as the primary treatment of disease, fail to be recognized as a priority. If we continue our current path of treating risk factors and advanced diseases, costs for care will continue to escalate and the health care system will approach bankruptcy in the near future.[4] As a consequence, lives will be lost. The enormous cost of health care directed toward CVD and cancer account for up to one-third of the health care fiscal burden in the US. If 1 in 10 of the US population would adopt a healthy lifestyle, the amount of money saved could well fund others more in need. A 10% reduction in such costs may results in billions of dollars saved.

Given the benefits of lifestyle medicine interventions, it would seem that our health care system would rush to embrace this movement; however, nothing could be further from the truth. Through the decades, leading proponents of lifestyle interventions have faced resistance or marginalization. Such resistance to change has to do with barriers on multiple levels affecting patients, clinicians, administrators, government, and society in general. Most patients typically gather their food and nutrition information from popular media rather than from clinicians, many of whom may have limited knowledge of lifestyle interventions. In addition, much of this may reflect the limited time available in a typical office visit. Perhaps a more important issue stems from the formal education in medical school, residency, or fellowship programs, which lack a focus on scientific evidence supporting the importance of nutrition related to a healthy lifestyle.[140,141] Health care practitioners as well as administrators are often focused on the bottom line and find it challenging to direct resources toward new and innovative practices given low reimbursement rates for counseling on lifestyle changes. Adding to this, they may fear that patients will find such changes difficult and not sustainable. We are long overdue for a "rethink" about health care to achieve a more directive role in the lifestyle intervention of patients.

Currently, multiple forces maintaining the status quo exist at the systemic level. Special interest groups, including certain lobbyists, maintain barriers by spending monies to influence governmental and professional targets. For example, national dietary guidelines are watered down out of a concern over the economic interests of certain industries instead of reflecting on the evidence-based recommendations regarding the consumption of meat and dairy products. On the societal level, the hedonistic aspects of food are promoted over their health and nutritional aspects.

Despite the status quo, there is a groundswell of interest in lifestyle medicine and a hunger for change. There exists reason for optimism. The growing interest in wellness programs and the mainstreaming of yoga, tai chi, and mindfulness practices are examples of such changing attitudes. Integrating lifestyle medicine into clinical practice in the areas of food, nutrition, exercise, and stress reduction is becoming more commonplace. Multiple organizations, including health care systems and large successful corporations, have come to realize the enormous benefits of a healthy lifestyle not only to wellness but also positively influencing enhanced productivity.

The establishment of lifestyle medicine as an effective therapy will ultimately depend on a strategic plan to embrace the basic concepts addressed. We propose and advocate for a series of multiple approaches with a focus on potential future ventures. In an ideal setting, establishing a lifestyle medicine clinic within a health care organization would be a major step toward the promotion of patient wellness. Establishing a trained, interested team of dedicated professionals would be key to a successful patient experience. Although many different lifestyle medicine approaches have been implemented, they all share some common characteristics: A physician trained in lifestyle techniques, supportive staff, patient educators who are strong in plant-based diets, and access to behavioral health. Such a team approach can be used to encourage, educate, and

support patients for motivation to achieve their goals.

It will take time to break down the barriers that exist. We recommend the allocation of resources dedicated to the expansion and further development of such programs. More research documenting the efficacy and cost-saving benefits of innovative lifestyle clinics is needed. True preventive care must include tools and information on lifestyle recommendations. It is time for the medical community to intervene and provide the proper treatment when confronting preventable conditions. Many conditions are reversible with education and ongoing support to patients regarding lifestyle changes. Addressing the root cause of diseases and taking immediate corrective action may avert the health care crisis and restore a solid foundation for patients and the medical community. The practice of medicine is ever evolving, and the medical community must keep pace of new information as it becomes available to implement best practices. Creating change takes courage and a willingness to think creatively as we begin to shift our medical system from one characterized by sick care to one deserving of the label of health care.

In conjunction with building specific clinic workflows, we would recommend and endorse activities so that all practitioners possess at least an awareness and a basic understanding of what lifestyle modifications can do to prevent, treat, and even reverse chronic diseases. Large health care organizations must obligate themselves to such programs. Numerous health care practitioners may not have the essential information available to share with patients. Some, particularly in a solo-practice environment, may not have time to address lifestyle issues or have access to support such a program, despite their best intentions to do so. Many of our colleagues are uncomfortable in addressing lifestyle issues as they feel they are not qualified in such concerns, despite the fact that many of their patients seek such information. Multiple courses are available, at numerous conferences and through programs online, where practitioners can easily gain the knowledge they need to promote a healthy lifestyle.

Healthy lifestyle interventions need not be limited to the clinic environment. Numerous opportunities to share information with a direct impact on overall health are readily available. Community events, such as religious celebrations and festivals, present a major forum for valuable information dissemination. Most large and influential companies have come to realize the importance of a healthy lifestyle for their employees and now understand the increased effectiveness and productivity associated with good health. Social media, perhaps the most powerful contemporary means of connectivity, provides incredible opportunities to disseminate information promoting a healthy lifestyle. Although not all practitioners may be able to incorporate lifestyle goals into their practice, at least having the information easily available and knowing how to access such tools is a major step forward (see Sidebar: Moving Forward: Healthy Lifestyle Recommendations and Resources for Daily Practice).

Moving Forward: Healthy Lifestyle Recommendations and Resources for Daily Practice

Practitioner education regarding benefits of healthy lifestyle recommendations
- Plant-based nutrition certification, Cornell University
- American College of Lifestyle Medicine certification
- Lifestyle conference attendance (eg, The Plantrician Project: www.plantricianproject.org)
- Endorsement by providers to adopt such practices
- Online resources: T Colin Campbell Center for Nutrition Studies (http://nutritionstudies.org); Physicians Committee for Responsible Medicine (www.pcrm.org)

Identification of team members engaged in promotion of a healthy lifestyle
- Physician colleagues
- Dietitians trained in whole-foods, plant-based nutrition
- Social workers
- Behavioral therapists
- Lifestyle coaches

Promotion of exercise programs
- Walk to Thrive (https://kpwalktothrive.org/)
- Exercise coaches

Endorsement of alternative approaches to health and well-being
- Yoga
- Meditation
- Dance
- Aromatherapy

Establishment of and participation in cooking demonstrations and classes in the clinic and community—patient provision of resources
- Health education handouts and pamphlets addressing health and wellness
- Community-provided educational materials
- Reputable Web site resources
- Vigorous endorsement by providers to adopt such practices

CONCLUSION

Escalating health care costs and the impact on care delivery are enormous and underestimated. Projections of chronic diseases lack an accurate forecast because of our ongoing endorsement of a poor Western lifestyle. We have become a society that has embraced a lifestyle of convenience and availability, fueled by technology and misinformation. We are no longer forced to search for foods and nutrients; computers and electronics have replaced physical activity.

A potential decline in life expectancy in the US in the current century was forecast 12 years ago.[142] That prediction has now come to fruition, verified by the latest statistics, which demonstrate a decrease in life expectancy by 0.1% years in 2015.[143] This is the first decline noted since the 1990s. The evidence is irrefutable, and the message is clear. We must prevent disease in all aspects of our lives and in the lives of the people we love. It is time to change our health destiny by shifting our attitude toward a healthy lifestyle. It is time to move from a state of disease to a state of health. It is time to eat healthy, be active, and decrease stress.

We must address the impact of lifestyle changes on our future generations. Numerous studies have shown that the positive impact of a healthy lifestyle carries forward as children mature. The youngest of our population must be exposed to a healthy lifestyle from their earliest ages because CVD risk factors begin in childhood.[144] Such recommendations have been demonstrated to lead to a significant decrease in annual mortality owing to not only CVD but also type 2 diabetes.[145]

We are charged with providing patients the information they need to live a long, healthy life, which can be readily accomplished through the practice of lifestyle medicine. It has been stated that we, as caregivers, owe our patients this information to stay well and healthy.[3] Changing medicine to a culture that teaches lifestyle empowers patients to take control of their own health. Nutritional education is key to the implementation of a healthy lifestyle. Authors of several recent articles address this and have come forth with solid recommendations, educational resources, and guidelines to aid physicians in achieving these objectives.[11,146] Positive recommendations are presented as how physicians can educate themselves and present an effective treatment plan to patients, which include multiple options.[146]

As an aging population, we are faced with confronting inflammation, obesity, and diabetes, resulting in a dysbiotic microbiome, which contributes to our contemporary chronic conditions. Most deaths from chronic illness in the US are preventable and related to how we live. The system has failed to implement well-documented strategies and has fallen short of addressing risk factors that continue to contribute to long-term disabilities that greatly influence the potential to extend our lifespan—in an enjoyable manner.

We have addressed current concerns regarding a healthy lifestyle; such factors are being increasingly recognized as prognostic indicators of health. Weight loss, a major concern in the US, is a priority of most people yet is often a goal unachieved. Adherence to a healthy lifestyle, including a whole-foods, plant-based diet regimen and moderate exercise, has been shown to result in long-term weight loss comparable to that with conventional "reduced"-calorie diets, but with better results in overall health. A focus on lifestyle includes understanding the quadrants of health: Healthy eating, active living, healthy weight, and emotional resilience. This can be achieved by adopting a healthy lifestyle, and our goal is to deliver this message.

We should all be concerned about the wellness of each other. It's time to save our patients as well as ourselves. Medicine, as currently practiced, is approaching a strategic inflection point; a need for change must be recognized and instituted. Practitioners, insurance providers, and governmental agencies must inform the population that we have identified the root causes of many of our diseases and must implement a plan to halt and reverse these conditions. The misconception that many chronic illnesses are simply the result of aging must be corrected. Maladies such as hypertension, heart disease, diabetes, and osteoarthritis are not inevitable outcomes of aging, but are an end product of poor lifestyles. To those of us looking for solutions to our health care crisis, the gaping need for lifestyle medicine in daily practice is evident. Initiatives must be identified and put in place that focus on wellness promotion. We are running out of time to reverse a destructive trend. Our survival and the survival of the next generation are at risk. The modernization of our civilization has led to the birth of many current diseases, largely because of the adoption of a 21st-century lifestyle. Our health problems are manmade and, therefore, solvable. We must multiply our wisdom regarding the future of health, our health care, and our survival. We constantly strive to protect endangered species from extinction, while, in fact, it may well be that we ourselves are far closer to extinction.

It is our hope and anticipation that this article will motivate and inspire our colleagues to share their stories and successes with implementing lifestyle medicine programs in their Regions, service areas, clinics, and practices. We are aware of faculty at numerous campuses, many of whom are coauthors of this paper, who have implemented successful projects that have incorporated lifestyle practices with excellent clinical results. Sharing "best practice" models will result in the most effective care of our patients. Because many of our colleagues are educated in the science of lifestyle medicine, this should serve as a call to action. The impact of such projects, when adequately publicized, may result in a dramatic impact on the future of health care delivery, and more importantly the long-term well-being of our patients. ❖

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Dedication

We dedicate this article to T Collin Campbell, PhD, whom many consider the patriarch of the whole-foods, plant-based diet and author of The China Study, *a landmark work on health, and who has stated that "everything in food works together to create health or disease."*

References

1. Minich DM, Bland JS. Personalized lifestyle medicine: Relevance for nutrition and lifestyle recommendations. Scientific World Journal 2013 Jun 26;2013:129841. DOI: https://doi.org/10.1155/2013/129841.
2. Dieleman JL, Baral R, Birger M, et al. US spending on personal health care and public health, 1993-2013. JAMA 2016 Dec 27;316(24):2627-46. DOI: https://doi.org/10.1001/jama.2016.16885.
3. Bodai BI, Tuso P. Breast cancer survivorship: A comprehensive review of long-term medical issues and lifestyle recommendations. Perm J 2015 Spring;19(2):48-79. DOI: https://doi.org/10.7812/TPP/14-241.
4. Hyman MA, Ornish D, Roizen M. Lifestyle medicine: Treating the causes of diseases. Altern Ther Health Med 2009 Nov-Dec;15(6):12-4.
5. Ford ES, Bergmann MM, Kröger J, Schienkiewitz A, Weikert C, Boeing H. Healthy living is the best revenge: Findings from the European Prospective Investigation Into Cancer and Nutrition-Potsdam study. Arch Intern Med 2009 Aug 10;169(15):1355-62. DOI: https://doi.org/10.1001/archinternmed.2009.237.
6. Alpert JS. Failing grades in the adoption of healthy lifestyle choices. Am J Med 2009 Jun;122(6):493-4. DOI: https://doi.org/10.1016/j.amjmed.2009.01.010.
7. Murray CJ, Atkinson C, Bhalla K, et al; US Burden of Disease Collaborators. The state of US health, 1990-2010: Burden of diseases, injuries, and risk factors. JAMA 2013 Aug 14;310(6):591-608. DOI: https://doi.org/10.1001/jama.2013.13805.
8. Twombly R. Cancer surpasses heart disease as leading cause of death for all but the very elderly. J Natl Cancer Inst 2005 Mar 2;97(5):330-1. DOI: https://doi.org/10.1093/jnci/97.5.330.
9. Jones DS, Podolsky SH, Greene JA. The burden of disease and the changing task of medicine. N Engl

J Med 2012 Jun 21;366(25):2333-8. DOI: https://doi.org/10.1056/NEJMp1113569.

10. Watzl B. Anti-inflammatory effects of plant-based foods and of their constituents. Int J Vitam Nutr Res 2008 Dec;78(6):293-8. DOI: https://doi.org/10.1024/0300-9831.78.6.293.
11. Tuso PJ, Ismael MH, Ha BP, Bartolotto C. Nutritional update for physicians: Plant-based diets. Perm J 2013 Spring;17(2):61-6. DOI: https://doi.org/10.7812/TPP/12-085.
12. Blaney D, Diehl H. The optimal diet: The official CHIP cookbook. Hagerstown, MD: Autumn House Publishing; 2009 Jan 1.
13. Ornish D, Scherwitz LW, Billings JH, et.al. Intensive lifestyle changes for reversal of coronary heart disease. JAMA 1998 Dec 16;280(23):2001-7. DOI: https://doi.org/10.1001/jama.280.23.2001.
14. Esselstyn CB Jr. Resolving the coronary artery disease epidemic through plant-based nutrition. Prev Cardiol 2001 Autumn;4(4):171-7. DOI: https://doi.org/10.1111/j.1520-037x.2001.00538.x.
15. Esselstyn CB Jr, Gendy G, Doyle J, Golubic M, Roizen MF. A way to reverse CAD? J Fam Pract 2014 Jun;63(7):356-364b.
16. Wang Y, Beydoun MA. Meat consumption is associated with obesity and central obesity among US adults. Int J Obes (Lond) 2009 Jun;33(6):621-8. DOI: https://doi.org/10.1038/ijo.2009.45.
17. Berkow SE, Barnard N. Vegetarian diets and weight status. Nutr Rev 2006 Apr;64(4):175-88. DOI: https://doi.org/10.1111/j.1753-4887.2006.tb00200.x.
18. Farmer B, Larson BT, Fulgoni VL 3rd, Rainville AJ, Liepa GU. A vegetarian dietary pattern as a nutrient-dense approach to weight management: An analysis of the national health and nutrition examination survey 1999-2004. J Am Diet Assoc 2011 Jun;111(6):819-27. DOI: https://doi.org/10.1016/j.jada.2011.03.012.
19. Ornish D, Brown SE, Scherwitz LW, et al. Can lifestyle changes reverse coronary heart disease? The Lifestyle Heart Trial. Lancet 1990 Jul 21;336(8708):129-33. DOI: https://doi.org/10.1016/0140-6736(90)91656-U.
20. Tonstad S, Butler T, Yan R, Fraser GE. Type of vegetarian diet, body weight, and prevalence of type 2 diabetes. Diabetes Care 2009 May;32(5):791-6. DOI: https://doi.org/10.2337/dc08-1886.
21. Polednak AP. Estimating the number of US incident causes attributable to obesity and the impact on temporal trends in incident rates for obesity-related cancers. Cancer Detect Prev 2008;32(3):190-9. DOI: https://doi.org/10.1016/j.cdp.2008.08.004.
22. Hunter P. The inflammation theory of disease EMBO reports 2012. 13;11:968-70.doi:10.1038/embor.2012.142
23. Cancello R, Clément K. Review article: Is obesity an inflammatory illness? Role of low-grade inflammation and macrophage infiltration in human white adipose tissue. BJOG 2006 Oct:1141-7. DOI: https://doi.org/10.1111/j.1471-0528.2006.01004.x.
24. Clarke G, Stilling RM, Kennedy PJ, Stanton C, Cryan JF, Dinan TG. Minireview: Gut microbiota: The neglected endocrine organ. Mol Endocrinol 2014 Aug;28(8):1221-38. DOI: https://doi.org/10.1210/me.2014-1108.
25. Marchesi JR, Adams DH, Fava F, et al. The gut microbiota and host health: A new clinical frontier. Gut 2016 Feb;65(2):330-9. DOI: https://doi.org/10.1136/gutjnl-2015-309990.
26. Tang WH, Wang Z, Levison BS, et al. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. N Engl J Med 2013 Apr 25;368(17):1575-84. DOI: https://doi.org/10.1056/nejmoa1109400.
27. Rajendhran J, Shanker M, Dinakaren V, Rathinavel A, Gunasekaran P. Contrasting circulating microbiome in cardiovascular disease patients and healthy individuals. Int J Cardiol 2013 Oct 12;168(5):5118-20. DOI: https://doi.org/10.1016/j.ijcard.2013.07.232.
28. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature 2006 Dec 21;444(7122):1027-31. DOI: https://doi.org/10.1038/nature05414.
29. Larsen N, Vogensen FK, van den Berg FW, et al. Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. PLoS One 2010 Feb 5;5(2):e9085. DOI: https://doi.org/10.1371/journal.pone.0009085.
30. Windey K, De Preter V, Verbeke K. Relevance of protein fermentation to gut health. Mol Nutr Food Res 2012 Jan;56(1):184-96. DOI: https://doi.org/10.1002/mnfr.201100542.
31. Boulangé CL, Neves AL, Chilloux J, Nicholson JK, Dumas ME. Impact of the gut microbiota on inflammation, obesity, and metabolic disease. Genome Med 2016 Apr 20;8(1):42. DOI: https://doi.org/10.1186/s13073-016-0303-2.
32. Gregor MF, Hotamisligil GS. Inflammatory mechanisms in obesity. Ann Rev Immunol 2011;29:415-45. DOI: https://doi.org/10.1146/annurev-immunol-031210-101322.
33. Klonoff DC. The increasing incidence of diabetes in the 21st century. J Diabetes Sci Technol 2009 Jan;3(1):1-2. DOI: https://doi.org/10.1177/193229680900300101
34. Goldfine AB, Shoelson SE. Therapeutic approaches targeting inflammation for diabetes and associated cardiovascular risk. J Clin Invest 2017 Jan 3;127(1):83-93. DOI: https://doi.org/10.1172/JCI88884.
35. Navarro JF, Mora C. Role of inflammation in diabetic complications. Nephrol Dial Transplant 2005 Dec;20(12):2601-4. DOI: https://doi.org/10.1093/ndt/gfi155.
36. Wellen KE, Hotamisligil GS. Inflammation, stress, and diabetes. J Clin Invest 2005 May;115(5):1111-9. DOI: https://doi.org/10.1172/jci25102.
37. Tuomilehto J, Lindström J, Eriksson JG, et al; Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001 May 3;344(18):1343-50. DOI: https://doi.org/10.1056/nejm200105033441801.
38. Knowler WC, Barrett-Connor E, Fowler SE, et al; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002 Feb 7;346(6):393-403. DOI: https://doi.org/10.1056/nejmoa012512.
39. Pan XR, Li GW, Hu YH, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. Diabetes Care 1997 Apr;20(4):537-44. DOI: https://doi.org/10.2337/diacare.20.4.537.
40. Saito T, Watanabe M, Nishida J, et al; Zensharen Study for Prevention of Lifestyle Diseases Group. Lifestyle modification and prevention of type 2 diabetes in overweight Japanese with impaired fasting glucose levels: A randomized controlled trial. Arch Intern Med 2011 Aug 8;171(15):1352-60. DOI: https://doi.org/10.1001/archinternmed.2011.275.
41. Imamura F, O'Connor L, Ye Z, et al. Consumption of sugar sweetened beverages, artificially sweetened beverages, and fruit juice and incidence of type 2 diabetes: Systematic review, meta-analysis, and estimation of population attributable fraction. BMJ 2015 Jul 21;351:h3576. DOI: https://doi.org/10.1136/bmj.h3576.
42. Malik VS, Li Y, Tobias DK, Pan A, Hu FB. Dietary protein intake and risk of type 2 diabetes in US men and women. Am J Epidemiol 2016 Apr 16;183(8):715-28. DOI: https://doi.org/10.1093/aje/kwv268.
43. Micha R, Michas G, Mozaffarian D. Unprocessed red and processed meats and risk of coronary artery disease and type 2 diabetes—An updated review of the evidence. Curr Atheroscler Rep 2012 Dec;14(6):515-24. DOI: https://doi.org/10.1007/s11883-012-0282-8.
44. Djoussé L. Relation of eggs with incident cardiovascular disease and diabetes: Friends or foes? Atherosclerosis 2013 Aug;229(2):507-8. DOI: https://doi.org/10.1016/j.atherosclerosis.2013.05.003.
45. Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M, et al. Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: Meta-analysis of randomised controlled trials. BMJ 2011 Jul 26;343:d4169. DOI: https://doi.org/10.1136/bmj.d4169.
46. Rodríguez-Gutiérrez R, Montori V. Glycemic control for patients with type 2 diabetes mellitus: Our evolving faith in the face of evidence. Circ Cardiovasc Qual Outcomes 2016 Sep;9(5):504-12. DOI: https://doi.org/10.1161/circoutcomes.116.002901.
47. American Diabetes Association. 8. Pharmacologic approaches to glycemic treatment. Diabetes Care 2017 Jan;40(Suppl 1):S64-S74. DOI: https://doi.org/10.2337/dc17-S011. Erratum in: Diabetes Care 2017 Jul;40(7):985. DOI: https://doi.org/10.2337/dc17-er07b.
48. Snowling NJ, Hopkins WG. Effects of different modes of exercise training on glucose control and risk factors for complications in type 2 diabetic patients: A meta-analysis. Diabetes Care 2006 Nov;29(11):2518-27. DOI: https://doi.org/10.2337/dc06-1317.
49. Barnard ND, Cohen J, Jenkins DJ, et al. A low-fat vegan diet improves glycemic control and cardiovascular risk factors in a randomized clinical trial in individuals with type 2 diabetes. Diabetes Care 2006 Aug;29(8):1777-83. DOI: https://doi.org/10.2337/dc06-0606.
50. McDougall J, Thomas LE, McDougall C, et al. Effects of 7 days on an ad libitum low-fat vegan diet: The McDougall Program cohort. Nutr J 2014 Oct 14;13:99. DOI: https://doi.org/10.1186/1475-2891-13-99. Erratum in: Nutr J 2017 Feb 10;16(1):12. DOI: https://doi.org/10.1186/s12937-017-0234-9.
51. Wolfram T, Ismail-Beigi F. Efficacy of high-fiber diets in the management of type 2 diabetes mellitus. Endocr Pract 2011 Jan-Feb;17(1):132-42. DOI: https://doi.org/10.4158/ep10204.ra.
52. Rowley WR, Bezold C, Arikan Y, Byrne E, Krohe S. Diabetes 2030: Insights from yesterday, today, and future trends. Popul Health Manag 2017 Feb;20(1):6-12. DOI: https://doi.org/10.1089/pop.2015.0181.
53. Roberston RM. Women and cardiovascular disease: The risks of misperception and the need for action. Circulation 2001 May 15;103(19):2318-20. DOI: https://doi.org/10.1161/01.cir.103.19.2318.
54. Mensah GA, Brown DW. An overview of cardiovascular disease burden in the United States. Health Aff (Millwood) 2007 Jan-Feb;26(1):38-48. DOI: https://doi.org/10.1377/hlthaff.26.1.38.
55. Thom T, Haase N, Rosamond W, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2006 update: A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2006 Feb 14;113(6):e85-151. DOI: https://doi.org/10.1161/circulationaha.105.171600. Erratum in: Circulation 2006 Apr 11;113(14):e696. DOI: https://doi.org/10.1161/circulationaha.106.174501. Erratum in: Circulation 2006 Dec 5;114(23):e630. DOI: https://doi.org/10.1161/circulationaha.106.180110.
56. Heidenreich PA, Trogdon JG, Khavjou OA, et al; American Heart Association Advocacy Coordinating Committee; Stroke Council; Council on Cardiovascular Radiology and Intervention; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Arteriosclerosis; Thrombosis

and Vascular Biology; Council on Cardiopulmonary; Critical Care; Perioperative and Resuscitation; Council on Cardiovascular Nursing; Council on the Kidney in Cardiovascular Disease; Council on Cardiovascular Surgery and Anesthesia, and Interdisciplinary Council on Quality of Care and Outcomes Research. Forecasting the future of cardiovascular disease in the United States: A policy statement from the American Heart Association. Circulation 2011 Mar 1;123(8):933-44. DOI: https://doi.org/10.1161/hhf.0b013e318291329a.

57. Writing Group Members, Mozaffarian D, Benjamin EJ, Go AS, et al; American Heart Association Statistics Committee; Stroke Statistics Subcommittee. Heart disease and stroke statistics—2016 update: A report from the American Heart Association. Circulation 2016 Jan 26;133(4):e38-360. DOI: 10.1161/CIR.0000000000000350. Erratum in: Circulation 2016 Apr 12;133(15):e599. DOI: https://doi.org/10.1161/CIR.0000000000000409.
58. Song Z, Blumenthal DM. Expanding payment reform in Medicare: The cardiology episode-based payment model. JAMA 2016 Nov 15;316(19):1973-4. DOI: https://doi.org/10.1001/jama.2016.16146.
59. Mathieu P, Lemieux I, Deprés JP. Obesity, inflammation, and cardiovascular risk. Clin Pharmacol Ther 2010 Apr;87(4):407-16. DOI: https://doi.org/10.1038/clpt.2009.311.
60. Libby P, Ridker PM, Hansson GK; Leducq Transatlantic Network on Atherothrombosis. Inflammation in atherosclerosis: From pathophysiology to practice. J Am Coll Cardiol 2009 Dec 1;54(23):2129-38. DOI: https://doi.org/10.1016/j.jacc.2009.09.009.
61. Tuso P, Stoll SR, Li WW. A plant-based diet, atherogenesis, and coronary artery disease prevention. Perm J 2015 Winter;19(1):62-7. DOI: https://doi.org/10.7812/TPP/14-036.
62. Esselstyn CB Jr. Is the present therapy for coronary artery disease the radical mastectomy of the twenty-first century? Am J Cardiol 2010 Sep 15;106(6):902-4. DOI: https://doi.org/10.1016/j.amjcard.2010.05.016.
63. Koeth RA, Wang Z, Levison BS, et al. Intestinal microbiota of L-carnitine, a nutrient in red meat, promotes atherosclerosis. Nat Med 2013 May;19(5):576-85. DOI: https://doi.org/10.1038/nm.3145.
64. Ornish D. Avoiding revascularization with lifestyle changes: The Multicenter Lifestyle Demonstration Project. Am J Cardiol 1998 Nov 26;280(10B):72T-76T. DOI: https://doi.org/10.1016/s0002-9149(98)00744-9.
65. Franklin BA, Cushman M. Recent advances in preventive cardiology and lifestyle medicine: A themed series. Circulation 2011 May 24;123(20):2274-83. DOI: https://doi.org/10.1161/circulationaha.110.981613.
66. Eichelmann F, Schwingshackl L, Fedirko V, Aleksandrova K. Effect of plant-based diets on obesity-related inflammatory profiles: A systematic review and meta-analysis of intervention trials. Obes Rev 2016 Nov;17(11):1067-79. DOI: https://doi.org/10.1111/obr.12349.
67. Mink PJ, Scrafford CG, Barraj LM, et al. Flavonoid intake and cardiovascular disease mortality: A prospective study in postmenopausal women. Am J Clin Nutr 2007 Mar;85(3):895-909.
68. Mente A, de Koning L, Shannon HS, Anand SS. A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease. Arch Intern Med 2009 Apr 13;169(7):659-69. DOI: https://doi.org/10.1001/archinternmed.2009.38.
69. Schwingshackl L, Hoffmann G. Diet quality as assessed by the healthy eating index, the alternate healthy eating index, the dietary approaches to stop hypertension score, and health outcomes: A systematic review and meta-analysis of cohort studies. J Acad Nutr Diet 2015 May;115(5):780-800.e5. DOI: https://doi.org/10.1016/j.jand.2014.12.009.
70. Dinu M, Abbate R, Gensini GF, Casini A, Sofi F. Vegetarian, vegan diets and multiple health outcomes: A systematic review with meta-analysis of observational studies. Crit Rev Food Sci Nutr 2017 Nov 22;57(17):3640-3649. DOI: https://doi.org/10.1080/10408398.2016.1138447.
71. Harland J, Garton L. An update of the evidence relating to plant-based diets and cardiovascular disease, type 2 diabetes and overweight. Nutr Bull 2016 Dec;41(4):323-38. DOI: https://doi.org/10.1111/nbu.12235.
72. Hofker MH, Fu J, Wijmenga C. The genome revolution and its role in understanding complex diseases. Biochim Biophys Acta 2014 Oct;1842(10):1889-95. DOI: https://doi.org/10.1016/j.bbadis.2014.05.002.
73. Wilson BJ, Nicholls SG. The Human Genome Project, and recent advances in personalized genomics. Risk Manag Healthc Policy 2015 Feb 16;8:9-20. DOI: https://doi.org/10.2147/rmhp.s58728.
74. Ellsworth DL, Croft DT, Weyandt J, et al. Intensive cardiovascular risk reduction induces sustainable changes in expression of genes and pathways important to vascular function. Circulation: Cardiovascular Genetics 2014 Apr;7(2):151-60. DOI: https://doi.org/10.1161/circgenetics.113.000121.
75. Chow CK, Jolly S, Rao-Melacini P, Fox KA, Anand SS, Yusuf S. Association of diet, exercise, and smoking modification with risk of early cardiovascular events after acute coronary syndrome. Circulation 2010 Feb 16;121(6):750-8. DOI: https://doi.org/10.1161/circulationaha.109.891523.
76. Khera AV, Emdin CA, Drake I, et al. Genetic risk, adherence to a healthy lifestyle, and coronary disease. N Engl J Med 2016 Dec 15;375(24):2349-58. DOI: https://doi.org/10.1056/nejmoa1605086.
77. Nocon M, Heimann T, Müller-Riemenschneider F, Thalau F, Roll S, Willich SN. Association of physical activity with all-cause and cardiovascular mortality: A systematic review and meta-analysis. Eur J Cardiovasc Prev Rehabil 2008 Jun;15(3):239-46. DOI: https://doi.org/10.1097/hjr.0b013e3282f55e09.
78. Franklin BA, McCullough PA. Cardiorespiratory fitness: An independent and additive marker of risk stratification and health outcomes. Mayo Clin Proc 2009 Sep;84(9):776-9. DOI: https://doi.org/10.4065/84.9.776.
79. Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Allen C, Barber RM, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990-2015. A systematic analysis for the Global Burden of Disease Study. JAMA Oncol 2017 Apr 1;3(4):524-48. DOI: https://doi.org/10.1001/jamaoncol.2016.5688.
80. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017 Jan;67(1):7-30. DOI: https://doi.org/10.3322/caac.21387.
81. Anand P, Kunnumakkara AB, Sundaram C, et al. Cancer is a preventable disease that requires major lifestyle changes. Pharm Res 2008 Sep;25(9):2097-116. DOI: https://doi.org/10.1007/s11095-008-9690-4.
82. Ligibel J. Lifestyle factors in cancer survivorship. J Clin Oncol 2012 Oct 20;30(30):3697-704. DOI: https://doi.org/10.1200/jco.2012.42.0638.
83. Kyrgiou M, Kalliala I, Markozannes G, et al. Adiposity and cancer at major anatomical sites: Umbrella review of the literature. BMJ 2017 Feb 28;356:j477. DOI: https://doi.org/10.1136/bmj.j477.
84. Miller KD, Siegel RL, Lin CC, et al. Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin 2016 Jul;66(4):271-89. DOI: https://doi.org/10.3322/caac.21349.
85. Rustgi AK. The genetics of hereditary colon cancer. Genes Dev 2007 Oct 15;21(20):2525-38. DOI: https://doi.org/10.1101/gad.1593107.
86. Terzić J, Grivennikov S, Karin E, Karin M. Inflammation and colon cancer. Gastroenterology 2010 Jun;138(6):2101-14.e5. DOI: https://doi.org/10.1053/j.gastro.2010.01.058.
87. Tsai MS, Chen HP, Hung CM, Lee PH, Lin CL, Kao CH. Hospitalization for inflammatory bowel disease is associated with increased risk of breast cancer: A nationwide cohort study of an Asian population. Ann Surg Oncol 2015;22(6):1996-2002. DOI: https://doi.org/10.1245/s10434-014-4198-0.
88. Ou J, Carbonero F, Zoetendal EG, et al. Diet, microbiota, and microbial metabolites in colon cancer risk in rural Africans and African Americans. Am J Clin Nutr 2013 Jul;98(1):111-20. DOI: https://doi.org/10.3945/ajcn.112.056689.
89. Platz EA, Willet WC, Colditz GA, Rimm EB, Spiegelman D, Giovannucci E. Proportion of colon cancer risk that might be preventable in cohort of middle-aged US men. Cancer Causes Control 2000 Aug;11(7):579-88. DOI: https://doi.org/10.1023/A:1008999232442.
90. Bultman SJ. Emerging roles of the microbiome in cancer. Carcinogenesis 2014 Feb;35(2):249-55. DOI: https://doi.org/10.1093/carcin/bgt392.
91. Edwards BK, Noone AM, Mariotto AB, et al. Annual report to the nation on the status of cancer, 1975-2010, featuring prevalence of comorbidity and impact on survival among persons with lung, colorectal, breast, or prostate cancer. Cancer 2014 May 1;120(9):1290-314. DOI: https://doi.org/10.1002/cncr.28509.
92. De Bruijn KM, Arends LR, Hansen BE, Leeflang S, Ruiter R, van Eijck CH. Systematic review and meta-analysis of the association between diabetes mellitus and the incidence and mortality in breast and colorectal cancer. Br J Surg 2013 Oct;100(11):1421-9. DOI: https://doi.org/10.1002/bjs.9229.
93. Van Blarigan EL, Meyerhardt JA. Role of physical activity and diet after colorectal cancer diagnosis. J Clin Oncol 2015 Jun 1;33(16):1825-34. DOI: https://doi.org/10.1200/jco.2014.59.7799.
94. Campbell PT, Patel AV, Newton CC, Jacobs EJ, Gapstur SM. Associations of recreational physical activity and leisure time spent sitting with colorectal cancer survival. J Clin Oncol 2013 Mar 1;31(7):876-85. DOI: https://doi.org/10.1200/jco.2012.45.9735.
95. Weiner AB, Matulewicz RS, Eggener SE, Schaeffer EM. Increasing incidence of metastatic prostate cancer in the United States (2004-2013). Prostate Cancer Prostatic Dis 2016 Dec;19(4):395-7. DOI: https://doi.org/10.1038/pcan.2016.30.
96. Carter HB, Albertsen PC, Barry MJ, et al. Early detection of prostate cancer: AUA guideline. J Urol 2013 Aug;190(2):419-26. DOI: https://doi.org/10.1016/j.juro.2013.04.119.
97. Freedland SJ, Aronson WJ. Examining the relationship between obesity and prostate cancer. Rev Urol 2004 Spring;6(2):73-81.
98. Ornish D, Weidner G, Fair WR, et al. Intensive lifestyle changes may affect the progression of prostate cancer. J Urol 2005 Sep;174(3):1065-70. DOI: https://doi.org/10.1097/01.ju.0000169487.49018.73.
99. Ornish D, Magbanua MJ, Weidner G, et al. Changes in prostate gene expression in men undergoing an intensive nutrition and lifestyle intervention. Proc Natl Acad Sci U S A 2008 Jun 17;105(24):8369-74. DOI: https://doi.org/10.1073/pnas.0803080105.
100. Yang M, Kenfield SA, Van Blarigan EL, et al. Dietary patterns after prostate cancer diagnosis in relation to disease-specific and total mortality. Cancer Prev Res (Phila) 2015 Jun;8(6):545-51. DOI: https://doi.org/10.1158/1940-6207.capr-14-0442.
101. Sinicrope FA, Dannenberg AJ. Obesity and breast cancer prognosis: Weight of the evidence. J Clin Oncol 2011 Jan 1;29(1):4-7. DOI: https://doi.org/10.1200/JCO.2010.32.1752.

102. Clarke CA, Canchola AJ, Moy LM, et al. Regular and low-dose aspirin, other non-steroidal anti-inflammatory medications and prospective risk of HER2-defined breast cancer: The California Teachers Study. Breast Cancer Res 2017 May 1;19(1):52. DOI: https://doi.org/10.1186/s13058-017-0840-7.
103. Ewertz M, Jensen MD, Gunnarsdóttir KÁ, et al. Effect of obesity on prognosis after early-stage breast cancer. J Clin Oncol 2011 Jan 1;29(1):25-31. DOI: https://doi.org/10.1200/jco.2010.29.7614.
104. Kotepui M. Diet and risk of breast cancer. Contemp Oncol (Pozn) 2016;20(1):13-9. DOI: https://doi.org/10.5114/wo.2014.40560.
105. Kushi LH, Doyle C, McCullough M, et al; American Cancer Society 2010 Nutrition and Physical Activity Guidelines Advisory Committee. American Cancer Society Guidelines on nutrition and physical activity for cancer prevention: Reducing the risk of cancer with healthy food choices and physical activity. CA Cancer J Clin 2012 Jan-Feb;62(1):30-67. DOI: https://doi.org/10.3322/caac.20140.
106. Adams S. Estrobolome disparities may lead to developing biomarkers that could mitigate cancer risk. J Natl Cancer Inst 2016;108(8):djw130. DOI: https://doi.org/10.1093/jnci/djw130.
107. Shapira I, Sultan K, Lee A, Taioli E. Evolving concepts: How diet and the intestinal microbiome act as modulators of breast malignancy. ISRN Oncol 2013 Sep 25;2013:693920. DOI: https://doi.org/10.1155/2013/693920.
108. Goedert JJ, Jones G, Hua X, et al. Investigation of the association between the fecal microbiota and breast cancer in postmenopausal women: A population-based case-control pilot study. J Natl Cancer Inst 2015 Jun 1;107(8):dvj147. DOI: https://doi.org/10.1093/jnci/djv147.
109. Kwa M, Plottel CS, Blaser MJ, Adams S. The intestinal microbiome and estrogen receptor-positive female breast cancer. J Natl Cancer Inst 2016 Apr 22;108(8):djw029. DOI: https://doi.org/10.1093/jnci/djw029.
110. What breast cancer survivors can do [Internet]. Washington, DC: American Institute for Cancer Research (AICR); 2014 Oct [cited 2017 Jul 27]. Available from: www.aicr.org.
111. Ibrahim EM, Al-Homaidh A. Physical activity and survival after breast cancer diagnosis: Meta-analysis of published studies. Med Oncol 2011 Sep;28(3):753-65. DOI: https://doi.org/10.1007/s12032-010-9536-x.
112. Hamer J, Warner E. Lifestyle modifications for patients with breast cancer to improve prognosis and optimize overall health. CMAJ 2017 Feb 1;189(7):E268-74. DOI: https://doi.org/10.1503/cmaj.160464.
113. Irwin ML, McTiernan A, Manson JE, et al. Physical activity and survival in postmenopausal women with breast cancer: Results from the women's health initiative. Cancer Prev Res (Phila) 2011 Apr;4(4):522-9. DOI: https://doi.org/10.1158/1940-6207.capr-10-0295.
114. Chlebowski RT. Nutrition and physical activity influence on breast cancer incidence and outcome. Breast 2013 Aug;22 Suppl 2:S30-7. DOI: https://doi.org/10.1016/j.breast.2013.07.006.
115. Meyerhardt JA, Heseltine D, Niedzwiecki D, et al. Impact of physical activity on cancer recurrence and survival in patients with stage III colon cancer: Findings from CALGB 89803. J Clin Oncol 2006 Aug 1;24(22):3535-41. DOI: https://doi.org/10.1200/jco.2008.26.15_suppl.4039.
116. Pierce JP, Stefanick ML, Flatt SW, et al. Greater survival after breast cancer in physically active women with high vegetable-fruit intake regardless of obesity. J Clin Oncol 2007 Jun 10;25(17):2345-51. DOI: https://doi.org/10.1200/jco.2006.08.6819.
117. Morgan RJ Jr. Underserved topics in oncology: The role of physical activity in improving quality of life and decreasing recurrence risk in patients with cancer. J Natl Compr Canc Netw 2014 May;12(5):735-7. DOI: https://doi.org/10.6004/jnccn.2014.0075.
118. Fournier A, Dos Santos G, Guillas G, et al. Recent recreational physical activity and breast cancer risk in postmenopausal women in the E3N cohort. Cancer Epidemiol Biomarkers Prev 2014 Sep;23(9):1893-902. DOI: https://doi.org/10.1158/1055-9965.epi-14-0150.
119. Sidney S, Quesenberry CP Jr, Jaffe MG, et al. Recent trends in cardiovascular mortality in the United States and public health goals. JAMA Cardiol 2016 Aug 1;1(5):594-9. DOI: https://doi.org/10.1001/jamacardio.2016.1326.
120. Gomez SL, Canchola AJ, Nelson DO, et al. Recent declines in cancer incidence: Related to the Great Recession? Cancer Causes Control 2017 Feb;28(2):145-54. DOI: https://doi.org/10.1007/s10552-016-0846-y.
121. Lloyd-Jones DM. Slowing progress in cardiovascular mortality rates: You reap what you sow. JAMA Cardiol 2016 Aug 1;1(5):599-600. DOI: https://doi.org/10.1001/jamacardio.2016.1348.
122. Gonzales JF, Barnard ND, Jenkins DJ, et al. Applying the precautionary principle to nutrition and cancer. J Am Coll Nutr 2014;33(3):239-46. DOI: https://doi.org/10.1080/07315724.2013.866527.
123. Pan A, Sun Q, Bernstein AM, et al. Red meat consumption and mortality: Results from 2 prospective cohort studies. Arch Intern Med 2012 Apr 9;172(7):555-63. DOI: https://doi.org/10.1001/archinternmed.2011.2287.
124. Wang X, Ouyang Y, Liu J, et al. Fruit and vegetable consumption and mortality from all causes, cardiovascular disease, and cancer: Systematic review and dose-response meta-analysis of prospective cohort studies. BMJ 2014 Jul 29;349:g4490. DOI: https://doi.org/10.1136/bmj.g4490.
125. Allen NE, Appleby PN, Davey GK, Kaaks R, Rinaldi S, Key TJ. The associations of diet with serum insulin-like growth factor I and its main binding proteins in 292 women meat-eaters, vegetarians, and vegans. Cancer Epidemiol Biomarkers Prev 2002 Nov;11(11):1441-8.
126. Westley RL, May FE. A twenty-first century cancer epidemic caused by obesity: The involvement of insulin, diabetes, and insulin-like growth factors. Int J Endocrinol 2013;2013:632461. DOI: https://doi.org/10.1155/2013/63246.
127. Bellavia A, Larsson SC, Bottai M, Wolk A, Orsini N. Fruit and vegetable consumption and all-cause mortality: A dose-response analysis. Am J Clin Nutr 2013 Aug;98(2):454-9. DOI: https://doi.org/10.3945/ajcn.112.056119.
128. Demark-Wahnefried W, Campbell KL, Hayes SC. Weight management and its role in breast cancer rehabilitation. Cancer 2012 Apr 15;118(8 Suppl):2277-87. DOI: https://doi.org/10.1002/cncr.27466.
129. Ford ES, Bergmann MM, Boeing H, Li C, Capewell S. Healthy lifestyle behaviors and all-cause mortality among adults in the United States. Prev Med 2012 Jul;55(1):23-7. DOI: https://doi.org/10.1016/j.ypmed.2012.04.016.
130. Boursi B, Mamtani R, Haynes K, Yang YX. Recurrent antibiotic exposure may promote cancer formation—Another step in understanding the role of human microbiota? Eur J Cancer 2015 Nov;51(17):2655-64. DOI: https://doi.org/10.1016/j.ejca.2015.08.015.
131. Bouvard V, Loomis D, Guyton KZ, et al; International Agency for Research on Cancer Monograph Working Group. Carcinogenicity of consumption of red and processed meat. Lancet Oncol 2015 Dec; 16(16):1599-600. DOI: https://doi.org/10.1016/s1470-2045(15)00444-1.
132. Song M, Fund TT, Hu FB, et al. Association of animal and plant protein intake with all-cause and cause-specific mortality. JAMA Intern Med 2016 Oct 1;176(10):1453-63. DOI: https://doi.org/10.1001/jamainternmed.2016.4182.
133. Tang WH, Hazen SL. The contributory role of gut microbiota in cardiovascular disease. J Clin Invest 2014 Oct;124(10):4204-11. DOI: https://doi.org/10.1172/jci72331.
134. Brown JM, Hazen SL. The gut microbial endocrine organ: Bacterially derived signals driving cardiometabolic diseases. Ann Rev Med 2015;66:343-59. DOI: https://doi.org/10.1146/annurev-med-060513-093205.
135. Plottel CS, Blaser MJ. Microbiome and malignancy. Cell Host Microbe 2011 Oct 20;10(4):324-35. DOI: https://doi.org/10.1016/j.chom.2011.10.003.
136. Deukota S, Chang EB. Nutrition, microbiomes, and intestinal inflammation. Curr Opin Gastroenterol 2013 Nov;29(6):603-7. DOI: https://doi.org/10.1097/mog.0b013e328365d38f.
137. Ornish D. Intensive lifestyle changes and health reform. Lancet Oncol 2009 Jul;10(7):638-9. DOI: https://doi.org/10.1016/s1470-2045(09)70175-5.
138. Iuga AO, McGuire MJ. Adherence and health care costs. Risk Manag Healthc Policy 2014 Feb 20;7:35-44. DOI: https://doi.org/10.2147/rmhp.s19801.
139. National Center for Health Statistics. Fast Stats [Internet]. Atlanta, GA: Centers for Disease Control and Prevention; 2016 [cited 2017 Jul 28]. Available from: www.cdc.gov/nchs/products/series.htm.
140. Adams KM, Butsch WS, Kohlmeier M. The state of nutrition education at US medical schools. J Biomed Educ 2015;2015:357627. DOI: https://doi.org/10.1155/2015/357627.
141. Lenders CM, Deen DD, Bistrian B, et al. Residency and specialties training in nutrition: A call for action. Am J Clin Nutr 2014 May;99(5 Suppl):1174S-83S. DOI: https://doi.org/10.3945/ajcn.113.073528.
142. Olshansky SJ, Passaro DJ, Hershow RC, et al. A potential decline in life expectancy in the United States in the 21st century. N Engl J Med 2005 Mar 17;352(11):1138-45. DOI: https://doi.org/10.1056/nejmsr043743.
143. Xu J, Murphy SL, Kochanek KD, Arias E. Mortality in the United States, 2015. NCHS data brief no. 267 [Internet]. Hyattsville, MD: National Center for Health Statistics; 2016 Dec 8 [cited 2017 Jul 27]. Available from: www.cdc.gov/nchs/data/databriefs/db267.pdf.
144. Macknin M, Kong T, Weier A, et al. Plant-based, no-added-fat or American Heart Association diets: Impact on cardiovascular risk in obese children with hypercholesterolemia and their parents. J Pediatr 2015 Apr;166(4):953-9.e1-3. DOI: https://doi.org/10.1016/j.jpeds.2014.12.058.
145. Micha R, Peñalvo JL, Cudhea F, Imamura F, Rehm CD, Mozaffarian D. Association between dietary factors and mortality from heart disease, stroke, and type 2 diabetes in the United States. JAMA 2017 Mar 7;317(9):912-24. DOI: https://doi.org/10.1001/jama.2017.0947.
146. Hever J. Plant-based diets: A physician's guide. Perm J 2016 Summer;20(3):93-101. DOI: https://doi.org/10.7812/TPP/15-082.

The Muse
photograph

Sapna Reddy, MD

This lone willow tree, standing in Lake Wanaka on New Zealand's South Island and set against the backdrop of the majestic southern alps of Mount Aspiring National Park, is the most photographed tree in New Zealand. The azure water, the delicate nature of the tree's foliage, and the incredible backdrop draws photographers from all over the world.

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Special Report

Psychiatric Aspects of Extreme Sports: Three Case Studies

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ABSTRACT

Extreme sports, defined as sporting or adventure activities involving a high degree of risk, have boomed since the 1990s. These types of sports attract men and women who can experience a life-affirming transcendence or "flow" as they participate in dangerous activities. Extreme sports also may attract people with a genetic predisposition for risk, risk-seeking personality traits, or underlying psychiatric disorders in which impulsivity and risk taking are integral to the underlying problem. In this report, we attempt to illustrate through case histories the motivations that lead people to repeatedly risk their lives and explore psychiatry's role in extreme sports. A sports psychiatrist can help with therapeutic management, neuromodulation of any comorbid psychiatric diagnosis, and performance enhancement (eg, risk minimization) to cultivate improved judgment which could include identifying alternative safer recreational options. Because flirting with death is critical to the extreme sports ethos, practitioners must gain further understanding of this field and its at-risk participants.

INTRODUCTION

Extreme sports are leisure activities that involve major risk to life and limb. The lay perception that extreme sports participants are primarily thrill-seeking, adrenaline-addicted youths may be oversimplified. Investigators have narrowed the definition to refer only to sporting activities during which "a mismanaged mistake or accident would most likely result in serious injury or death."[1,2]

Participation in extreme sports may suggest a powerful, life-affirming, and enhancing transcendent primal drive akin to attainment of a "flow experience."[3] Conquering the "death wish" (Thanatos drive), overcoming paralyzing fear, and searching for a transformative or "life wish" (Eros drive) are considered integral motivators for the extreme sportsperson.[1,2,4] Available leisure time; abundant finances; and sophisticated yet affordable equipment attract upper and middle class participants, enabling them to temporarily escape constrained socially acceptable and defined roles and to explore nature and challenge themselves to transcend fear.[5,6] Gender factors likely play a role in extreme sports. Women have overlapping, but different, motivators for extreme sports involvement, although we are not aware of any strong evidence that addresses this issue.[7] Some extreme sports activities have been codified and fall under the umbrella of the X Games,[8] whereas others such as wingsuit flying and ice climbing are too challenging and life-endangering to fully integrate into a field that proudly defines itself by bravado.

BASE jumping (jumping from Buildings, Antennas, Spans, and Earth), for example, involves often-illegal risk-taking extreme sport jumping activities and is associated with a fearfully high mortality rate (see Table 1). The term was coined by "the two Phils," Phil Smith and Phil Mayfield, after their initial parachute-assisted jump in January 1981 from a Houston building.[9,10] It is worth noting that many sports, including those integrated into the Winter and Summer Olympic Games, share risk factors with extreme sports that place participants at risk for major injury (luge and downhill skiing are two examples). The 2010 death of third-generation Georgian luge competitor Nodar Kumaritashvili during practice at the Vancouver Winter Olympic Games is testament to this fact.[11]

Geneticists have explored possible links between a propensity for high-risk activities and genetic markers. The putative connection of polymorphisms of the D4 subtype of the dopamine 2 receptor, a G protein-coupled receptor that inhibits adenylyl cyclase, with risk-taking, novelty-seeking behavior in humans and other living organisms is a link from a teleologic perspective.[12-15] The work of Thomson and associates[14] with skiers and snowboarders is especially intriguing. Dopamine is the neurotransmitter most associated with "action," addiction, and substance abuse. There is a clear link between risk taking and the adrenaline/dopamine/endorphin surge experienced by extreme sports participants. This surge is like the phenomenon seen in gambling and risk-heavy professions such as financial trading, which continually entice participants back to their chosen "edge work."[16]

For participants with severe hyperactive/impulsive attention-deficit/hyperactivity disorder (ADHD), extreme sports can be fairly calming and can even provide therapeutic neuromodulation with "positive" reinforcement potential elicited by dopamine, serotonin, epinephrine, endorphins, and stress hormone hypothalamic-pituitary-adrenal axis activation, which produces a state of optimal arousal.[17,18] The dopamine and norepinephrine neurotransmitter surge may help to modulate behavior, reversing under-activation in the dorsolateral prefrontal cortex and dysregulation of multiple brain pathways

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involved in the attentional and impulse control processes.[19,20] Cloninger's work on personalities[21] regarding four dimensions of human behavior (harm avoidance, reward dependence, novelty seeking, and perseverance) serves as a helpful template with which to evaluate the personality structures of those who actively participate in extreme sports. Similarly, Zuckerman's Sensation Seeking Scale, now in its fifth iteration,[22] which evaluates four different subscales of thrill and adventure seeking, disinhibition, experience seeking, and boredom susceptibility, provides an excellent framework with which to assess the behavioral traits and functioning of extreme sports participants.

A suicidal level of risk taking may be present in extreme athletes. Dean Potter, a pioneering free climber, slackline walker, and "free BASER," frequently referred to death. He stated, "You are playing with death then and it feels so good." About wingsuit flying he said, "[It] turns the impossible into the possible," and "Instead of dying, I'm flying." He earned the grudging admiration of rangers and throngs of climbing visitors at Yosemite National Park, where he completed many of his most audacious feats.[23,24]

Likelihood of affective disturbance or diathesis is much higher in this risk-taking population. Extreme sports participation may serve as a temporary antidepressant, lifting mood at least on a short-term basis, perhaps not dissimilar to the way the anesthetic agent ketamine can potentially help in the setting of resistant depression.[25] The combination of an endogenous "rush" of multiple neurotransmitters and physical activity greatly amplifies the protective and healthy effect that people involved in "safe" sporting exercise also experience.[26]

Bike motocross (BMX) participants describe the degree to which an athlete's desire to pull a never-before-seen trick or stunt outweighs conventional calculations of risk.[27] Participants in this sport, an X Games favorite, tend to idealize, romanticize, and mythologize extravagant risk taking as "highly motivational passion." Descriptions include:

"'We are not normal people. … In the best sense of the word, we are childlike.'"[27]

"His mind was 'so trigger.'"[27]

There is a naïve explorer's curiosity vis-à-vis the severe pain response as exemplified by ex-BMX racer TJ Lavin, who said, "I didn't know we could slam like that," after breaking both legs.[27]

When champion BMX biker Dave Mirra retired from BMX in 2011, he said of his younger competitors, "They'll die. Just like I would when I was younger. I would have died to win."[27] In February 2016, Mirra committed suicide by gunshot wound in his car after an argument with friends. A postmortem examination identified chronic traumatic encephalopathy attributable to innumerable concussions sustained during his freestyle BMX career.[28]

More than 300 BASE jumping-related deaths were recorded between 1981 and 2016; interest in the sport accelerated after 2000 with increased coverage and financial rewards associated with the sport.[29] The number of wingsuit deaths is unknown, but many of the most prominent proponents and pioneers of this field have died, including Dean Potter and Mark Sutton, who was famous for parachuting as James Bond into the stadium at the opening ceremony for the 2012 London Summer Olympic Games.[30]

Table 1. Extreme sports and morbidity/mortality risk

Type of extreme sport or study	Years	Morbidity/mortality rate
BASE jumping	1981-2015	More than 300 deaths worldwide[1] Wingsuit mortality as high as 1/50 participants[1-5]
Swedish BASE Jumping Study[1]	2002	1 fatality/60 participants; 1 death/2317 jumps[1]
Mei-Dan et al[2] (Israel)	2013	72% witnessed death or serious injury, 43% of jumpers sustained a serious BASE jumping injury, 76% witnessed a "near miss" or narrowly avoided fatality Injury rate estimates of 0.2% to 0.4% per jump and fatality rates of 0.04% per jump or 1.7% per participant and year
Sky diving	2000-2016	1 death/100,000 jumps[6]
Scuba diving, Divers Alert Network[7]	1970-2017	16.7 deaths/100,000 divers per year
Rock climbing	1998-2011	1 death/320,000 climbs[8,9]
Skiing	2011-2012	1 death/1,351,000 trips (5.5 deaths/million participants)[10]
Free diving	2006-2011	417 free diving accidents: 308 fatal, 109 nonfatal[7]
Hang gliding, paragliding	1993-2017	In the US, 1 death/560 flights[11]

1. Cooper J. BASE jumping: The life-or-death appeal of the world's most dangerous sport [Internet]. London, UK: The Telegraph; 2015 May 18 [cited 2017 Nov 15]. Available from: www.telegraph.co.uk/men/active/11612292/BASE-jumping-the-life-or-death-appeal-of-the-worlds-most-dangerous-sport.html.
2. Mei-Dan O, Monasterio E, Carmont M, Westman A. Fatalities in wingsuit BASE jumping. Wilderness Environ Med 2013 Dec;24(4):321-7. DOI: https://doi.org/10.1016/j.wem.2013.06.010.
3. Soreide K, Ellingsen CL, Knutson V. How dangerous is BASE jumping? An analysis of adverse events in 20,850 jumps from the Kjerag Massif, Norway. J Trauma 2007 May;62(5):1113-7. DOI: https://doi.org/10.1097/01.ta.0000239815.73858.88.
4. Westman A, Rosén M, Berggren P, Björnstig U. Parachuting from fixed objects: Descriptive study of 106 fatal events in BASE jumping 1981-2006. Br J Sports Med 2008;42:431-6. DOI: https://doi.org/10.1136/bjsm.2008.046565.
5. Fatality statistics [Internet]. BLiNC Magazine; c2017 [cited 2017 Nov 21]. Available from: www.blincmagazine.com/forum/wiki_index.php?title=Fatality_Statistics.
6. Spiegelhalter D. Extreme sports: What are the risks? [Internet]. London, UK: BBC; 2014 Nov 18 [cited 2017 Nov 15]. Available from: www.bbc.com/future/story/20120302-extreme-sports-a-risky-business.
7. Denoble PJ, Marroni A, Vann RD. Annual fatality rates and associated risk factors for recreational scuba diving [Internet]. Durham, NC: The Rubicon Foundation, Inc; 2011 [cited 2017 Nov 23]. Available from: http://archive.rubicon-foundation.org/xmlui/bitstream/handle/123456789/9329/DAN_Fatalities_8.pdf.
8. Green S. Statistics for climbing accidents, injuries, and fatalities [Internet]. Columbus, OH: ThoughtCo, LLC; 2017 Feb 19 [cited 2017 Nov 15]. Available from: www.thoughtco.com/climbing-accidents-statistics-756064.
9. Lack DA, Sheets AL, Entin JM, Christenson DC. Rock climbing rescues: Causes, injuries and trends in Boulder County, Colorado. Wilderness Environ Med 2012 Sep;23(3):223-30. DOI: https://doi.org/10.1016/j.wem.2012.04.002.
10. NSSA fact sheet: Facts about skiing/snowboarding safety [Internet]. Lakewood, CO: National Ski Areas Association; updated 2012 Oct 1 [cited 2017 Nov 23]. Available from: www.nsaa.org/media/68045/NSAA-Facts-About-Skiing-Snowboarding-Safety-10-1-12.pdf.
11. Fatalities: Fatality reports [Internet]. Colorado Springs, CO: US Hang Gliding and Paragliding Association, Inc; c2017 [cited 2017 Nov 23]. Available from: www.ushpa.org/page/fatalities.

CASE PRESENTATIONS

Here we present three cases. To our knowledge, none of the three extreme sport participants described here sought mental health treatment, but we were familiar with each of them. We describe them posthumously, to illustrate the complex constellation of social and psychological factors that probably influenced and motivated each extreme sports participant. In Table 2 we compare these three cases.

Case 1: "Allan"

"Allan," a 48-year-old married father of 3 teenagers, was a successful businessman and a "pillar of society." He had a multitude of business and family responsibilities, and he may have felt trapped in his societal roles. Perhaps in an effort to escape these psychological shackles, Allan became a regular "weekend warrior" at a local hang-gliding site. He was extremely careful with his equipment, meticulously prepared, and had a strong awareness about local wind patterns. He died of severe injuries sustained after being buffeted by a strong, unexpected gust of wind that threw him against a cliff face and caused a crash. His death was perceived as a major tragedy by his family and community.

The crash location was associated with well-known risk; at least three serious injury events occurred each year at the site, and yet Allan, like many other thrill seekers, was willing to take this risk.[31] People at his funeral emphasized that he loved the excitement and sense of freedom the flights provided. Grief management, counseling, and individual and family support cannot replace the ongoing role that Allan would have had as a father, husband, and community leader.

Case 2: Dean Potter

Dean Potter, the youngest of three sons, was born in the Midwest to a military father and a free-spirited mother, an RN and a yoga teacher who had embraced an alternative lifestyle.[32]

His father was described as a deeply caring, family-oriented man. His mother was described as flighty. When he was seven years old, Dean's parents separated and had shared custody of the children. His first climbing experience was as a four-year-old in the West Bank while his father was a peace keeper in the Middle East.[33]

Dean described his childhood as difficult. In school, he was often in trouble, largely because of his challenges with attention and impulsivity. His family did not seek therapy or psychiatry to address his behaviors, which were consistent with combined-type ADHD. Dean was also painfully shy, withdrawn, and socially isolated from peers. He described himself as having resentment toward others as a youth because he felt excluded and shunned, although his feelings may have been only partially based in reality. Dean finally established his first friendship when he and another boy snuck into a restricted area on his father's Air Force base in New Boston, NH, by climbing a 200-foot cliff.[34] Dean easily and fearlessly climbed the cliff without a rope and established his life's path. He described rock climbing and free soloing (climbing without safety gear or ropes—a fall causes serious injury or death) as "perfect," spiritual experiences.[32] Dean went to college in NH and continued to struggle to find a peer group with which he could mesh.[32]

Despite not feeling at ease, Dean forced himself to participate in team sports. He summarized his attitude toward his crew team as "destroy everybody and establish my dominance."[35] Shortly after Dean left school and started rock climbing full time at age 20, he found himself drifting around the western US, finally settling down in the Yosemite National Park area. He described several vivid spiritual dreams and hallucinations, which began in early childhood, that involved flight and ravens. He had vivid hallucinations, or visions, of being a shamanistic raven in an area of Hueco Tanks State Park

Table 2. Case presentation comparisons

Categories	Case 1: "Allan"	Case 2: Dean Potter	Case 3: Dan Osman
Baseline social functioning	Excellent	Fair to limited	Variable/poor
Risk for extreme sports	Medium	Very high	Very high
Level of skill attained at chosen extreme sport	"Weekend warrior"	Elite professional	Elite professional
Relationships, family stability	Fairly good	Relatively unstable	Moderately unstable
Genetic predisposition for risk taking	Unknown	High	High
Treatment history	No known treatment	No known treatment	No known treatment
Presumptive psychiatric diagnosis	Dysthymia (persistent depression); rule out ADHD; rule out SUDs, partner/relational problems, and generalized anxiety disorder	Impulse control disorder, ADHD, generalized anxiety disorder, conduct disorder, parent-child problems, narcissism; rule out bipolar disorder 1 (manic with psychotic features); rule out SUDs	ADHD, severe conduct disorder, cluster B personality traits; rule out SUDs
Expressed suicidality	Unknown	Extremely cavalier	Very cavalier
Conscious awareness of likelihood of death	Risk taker aware of life-endangering nature of sport, embraced the thrill-seeking component of his sport	Fatalistic, intimately aware, and embracing closeness to death as part of the excitement and challenge of his sport	Enjoyed the ability to "cheat" death and felt "bulletproof"

ADHD = attention-deficit/hyperactivity disorder; SUDs= substance use disorders.

near El Paso, TX, that is sacred to Native Americans and to climbers. Many of his peers thought these visions were brought on by substance use, but, although he did "dabble," Dean denied these claims. Over time, despite his proficiency and ability to climb at high skill levels, his ability to gain prominence in traditional climbing circles was limited, causing him to become somewhat disillusioned.

But Dean did have a competitive drive to be famous, well recognized, and unique; consequently, he cultivated a passion for riskier, more life-endangering activities such as free soloing, high-lining, BASE jumping, and wingsuiting. Worldwide attention, accolades, and sponsorships were finally available to him. In public, Dean presented a spiritual and charismatic persona. However, accomplishing these feats necessitated access to a primal motivation that led to his nickname, "The Dark Wizard."[36,37] Fiercely competitive and proud, he was prepared to go to extreme lengths to protect and extend his records and accomplishments. Impulsively climbing in illegal national park sites cost him and his then-wife several sponsors including Patagonia, loyal supporters, and alienation of potential backers.[38]

Potter died in 2015 while attempting a risky, illegal, and never-before-performed wingsuit flight through a notch on a granite face at Yosemite National Park; an acolyte, 29-year-old Graham Hunt, also was killed.[23,24,39] Potter was 43 years old and had inspired generations of young climbers and extreme sports enthusiasts.

Case 3: Dan Osman

Dan Osman was born in Orange County, CA, in 1963. He had a strong genetic and environmentally supportive background in risk-taking. His father was a former SWAT team officer and detective. His mother was a former world-champion rodeo barrel racer and a horse trainer. A paternal descendant of Samurai families in the Takeuchi Clan, Dan was trained in the Samurai Bushido code of ethics by his father and studied aikido and kung fu, but he did not feel worthy of the katana sword he received in 1994. Dan probably had untreated, fairly severe combined ADHD and as a child was nicknamed, "Danny I forgot."[40]

When Dan discovered rock climbing at the age of 12, he considered himself a slow learner, taking 8 years to achieve the elite Yosemite grade of 5.12.[40,41] Dan became known for his bold (some would say senseless), reckless climbing, ice climbing, free soloing, and speed climbing (to which his many YouTube videos attest).[42] Because some ascending routes he pioneered were subsequently downgraded in terms of difficulty, Dan increased the challenge by working on speed free soloing, once racing up a 400-foot rock face, ropeless, in 4 minutes, 25 seconds. While bolting a new route in Lake Tahoe, he discovered his love of falling and began to engage in large roped falls. As time progressed, he became bolder and enjoyed mastering falling and associated fears and other emotions.[40] Dan often encouraged others to attempt his feats, and when his 25-year-old friend Bobby Tarver died during a jump, Dan quickly dismissed the event as "pilot error."[43] Although Dan was often credited with being meticulous and extremely focused when it came to his rope jumps and solo climbs, the rest of his life was marked by impulsivity, disorganization, forgetfulness, illegal jumps, brushes with the law, and episodes of brief jail time.

Friends began to refer to him as being on "DANO time," as he often arrived hours or even days later than expected. His father eventually told Dan that he would no longer bail him out for his continued minor legal infractions such as unpaid parking and traffic tickets. Friends picked up the slack, but Dan's Bohemian lifestyle did not make it easy for him to maintain relationships or care for his daughter. Part-time carpentry and climbing were not lucrative occupations.[40]

Dan was excited to be included in the *Guinness World Records* for speed free climbing, and for rope jumping 1000 feet. Aware of the danger, after the record jump he stated on video, "I'll give my guardian angels some time off because they've been doing a heck of a job."[42]

After being released from a brief incarceration, Dan returned to Yosemite and the site of a jump he had performed several months earlier to take down the rigging and ropes. He must have noticed that winter snows and intermittent freezes had substantially damaged his rope system. Dan could not resist his impulses despite warnings from friends and attempted an 1100-foot fall. This time, the rope broke at the 900-foot mark, the spot at which the safety knot had been tied from his autumn jump. Dan died in 1998 at age 35, leaving a young daughter.[43]

MANAGING RISK IN EXTREME SPORTS

Overlearning and practicing skills safely until they become automatic is critical when people participate in high-risk, high-skill activities such as mountain or boulder climbing, alpinism, and other extreme sports. The only way to succeed is to keep practicing toward the goal of reaching the top. It often takes a long time to unlock the sequence of movements to complete the combination required for a particular climb.

The process of practicing in grueling, risky conditions often is just as rewarding for a dedicated climber as the goal of reaching the top or succeeding at any highly challenging task. An essential part of this process is mindfulness, the quieting of the mind. As a free climber pointed out, "It puts me into a position where I can concentrate and be more mindful than any other thing I do. … The act of climbing without a rope has been very valuable, in that it's been one of the things I can go do that truly forces me to quiet my mind."[44] Another participant points out, "… it's such a hyper-focused and, at the same time, calming experience."[44]

Extreme sports are generally performed outdoors in natural settings. Conditions must be close to perfect to complete an activity or a climb. However, small variabilities in temperature, humidity, sweat response, and light are always factors. For this reason, many successful climbs are completed at night in colder but more predictable and consistent conditions. When conditions are less than ideal, failure; conscious, prudent withdrawal from a climbing attempt; or severe injury or death are much more likely.

In our opinion there is a notable difference between impulsive high-risk takers and cutting-edge, expert, pioneering extreme sport proponents. Both types of participants risk injury and death while exploring their outer skill limits. Highly

trained extreme sport expert proponents have developed the skill set to manage the frustration associated with deferred gratification and have learned to channel rather than be driven by their impulsivity. Climbers such as those who may die on Mount Everest or while free soloing spend years and thousands of hours developing their skills to the point at which they feel ready to attempt a task that is at the peak of their perceived difficulty scale. They believe their level of preparation lowers risk despite the many variables that heighten risk.

Expert proponents probably turn away from an activity if conditions are not perfect. They use ropes to climb the most difficult sections numerous times before gaining the expertise and confidence to even attempt a climb without ropes. Peter Croft and Alex Honnold, who was the first person to free solo climb the most difficult central route up the El Capitan vertical rock formation in Yosemite National Park in June 2017, are both proponents of this approach.

Two examples of successful, very high-risk athletes/stuntmen who enthralled the world were Felix Baumgartner, who free fell and parachuted from Earth's stratosphere in October 2012 at speeds upwards of 800 miles per hour (Mach 1.2), and Luke Aikens, a third-generation skydiver who free fell from 25,000 feet into a net in July 2016. Sport and adventure psychologist Michael Gervais, PhD, a consultant on free fall attempts, perhaps put it best when he said, "Those that are pushing into territories that are yet to be conquered, we need them to tell us what is possible and truly explore what is not yet known."[45] Baumgartner's humble comment before he left the safety of his parachute capsule exemplified the extreme sports mindset when he said, "Sometimes you have to be up really high to understand just how small you are."[46]

THE ROLES FOR PRIMARY CARE AND SPORT PSYCHIATRY IN EXTREME SPORTS

Primary care physicians must become knowledgeable about extreme sports and the associated signs that warrant referral to therapists and psychiatrists. While taking patient histories, physicians should solicit descriptions of all leisure activities, not just "regular" sporting activities. Physicians who develop an alliance with physically healthy patients with incipient psychiatric illness can help to foster their long-term mental health.

The current role of the psychiatrist in extreme sports is probably underutilized and is evolving. Sports psychologists can help participants with motivation and mindfulness skills to prepare for highly risky situations. Participants in extreme sports are aware of their risks and most likely are somewhat contemptuous or dismissive of the role that mental health professionals may play other than in performance enhancement. Consequently, extreme sports enthusiasts may avoid accessing psychiatric services. There also is high risk for ego-syntonic polysubstance use, abuse, and dependence in this population. Substance use and abuse may play a part in the ability to overcome the fear of performing some of these activities. Extreme sports participants need to know that psychiatric services are available and that expressing their concurrent challenges, concerns, or traumas may prove helpful.

The ability to harness and even normalize a quasisuicidal "death wish" to perform these activities suggests that friends and family can encourage consultations with sport psychiatrists. At the very least, therapy may help participants articulate and understand the motivations at work and identify ways to minimize risk. Supportive involvement does not always denote agreement with the extreme project at hand. Support may lead to an intervention whereby an actively suicidal and perhaps manic or psychotic person can be hospitalized and stabilized or successfully treated as an outpatient. Identifying alternative yet high-action safer activities that extend survival may be considered in a therapeutic environment. Patients with associated Axis II disorders may benefit from interventions such as Dialectical Behavior Therapy.

Dean Potter's articulation of this Icarus-like statement is telling: "I know it's insane to think I could fly, but to make it possible, you truly have to believe in it—to go to a place that's not accepted."[47] Despite their life-endangering behaviors, most of these athletes do not intend to die, at least from an overt cognitive standpoint. Using medications to manage any underlying Axis I psychiatric disorder such as severe bipolar disorder with psychotic features, major depression, uncontrolled substance abuse or dependence, or severe hyperactive/impulsive ADHD may enable safer execution and fine-tuning of the choices these athletes make while participating in extraordinary activities. Psychiatry and sports psychiatrists, in particular, must acquire a deeper understanding of this fascinating field. ❖

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References

1. Brymer GE. Extreme dude! A phenomenological perspective on the extreme sport experience [thesis] [Internet]. Wollongong, New South Wales, Australia: University of Wollongong; 2005 [cited 2017 Nov 15]. Available from: http://ro.uow.edu.au/cgi/viewcontent.cgi?article=1379&context=theses.
2. Brymer E, Schweitzer R. Phenomenology and the extreme sport experience. Abingdon, UK: Routledge Press; 2017.
3. Csikszentmihalyi M. Flow: The psychology of optimal experience. New York, NY: Harper & Row; 1990.
4. Timms E. Wilhelm Stekel's dialogue with Sigmund Freud: The case for brief therapy and the symbolism of dreams. Psychoanalysis and History 2013 Jul;15(2):207-20. DOI: http://doi.org/10.3366/pah.2013.0133.
5. Lewis N. Sustainable adventure: Embodied experiences and ecological practices within British climbing. In: Wheaton B, editor. Understanding lifestyle sports: Consumption, identity and difference. Abingdon, UK: Routledge; 2004. p 70-93.
6. Fletcher R. Living on the edge: The appeal of risk sports for the professional middle class. Sociology of Sport Journal 2008 Sep;25(3):310-30. DOI: https://doi.org/10.1123/ssj.25.3.310.
7. Gieseler CM. Performance of gender and sexuality in extreme sports culture [thesis] [Internet]. Tampa, FL: University of South Florida; 2012 Jan [cited 2017 Nov 15]. Available from: http://scholarcommons.usf.edu/cgi/viewcontent.cgi?article=5245&context=etd.
8. X games [Internet]. Los Angeles, CA: ESPN Internet Ventures; c2017 [cited 2017 Nov 15]. Available from: http://xgames.espn.com/xgames/.

9. Hurt H III. The ground's the limit. Texas Monthly 1981 Dec;1981:178-83.
10. BASENumbers.org [Internet]. Hitchcock, TX: BASENumbers.org; c2107 [cited 2017 Nov 15]. Available from: www.basenumbers.org.
11. Death of Georgian athlete highlights dangers of luge [Internet]. San Bruno, CA: YouTube; 2010 Feb 16 [cited 2017 Nov 15]. Available from: www.youtube.com/watch?v=VPr8AXF-sVc.
12. Norbury A, Manohar S, Rogers RD, Husain M. Dopamine modulates risk-taking as a function of baseline sensation-seeking trait. J Neurosci 2013 Aug 7;33(32):12982-6. DOI: https://doi.org/10.1523/JNEUROSCI.5587-12.2013.
13. Kluger AN, Siegfried Z, Ebstein RP. A meta-analysis of the association between DRD4 polymorphism and novelty seeking. Mol Psychiatry 2002;7(7):712-7. DOI: https://doi.org/10.1038/sj.mp.4001082.
14. Thomson CJ, Hanna CW, Carlson SR, Rupert JL. The - 521 C/T variant in the dopamine-4-receptor gene (DRD4) is associated with skiing and snowboarding behavior. Scand J Med Sci Sports 2013 Mar;23(2):e108-13. DOI: https://doi.org/10.1111/sms.12031.
15. Reynolds G. The genetics of being a daredevil [Internet]. New York, NY: The New York Times; 2014 Feb 19 [cited 2017 Nov 15]. Available from: https://well.blogs.nytimes.com/2014/02/19/the-genetics-of-being-a-daredevil/.
16. Lyng S. Edgework: A social psychological analysis of voluntary risk taking. AJS 1990 Jan;95(4):851-86. DOI: https://doi.org/10.1086/229379.
17. Monasterio E, Mei-Dan O, Hackney AC, et al. Stress reactivity and personality in extreme sport athletes: The psychobiology of BASE jumpers. Physiol Behav 2016 Dec 1;167:289-97. DOI: https://doi.org/10.1016/j.physbeh.2016.09.025.
18. Hackney AC. Endocrine stress reactivity associated with extreme sports [Internet]. Proceedings from the 1st International Extreme Sports Medicine Congress; 2004 Jun 13-14; Boulder, CO. Denver, CO: University of Colorado Denver; 2014 [cited 2017 Nov 15]. Available from: www.ucdenver.edu/academics/colleges/medicine/sportsmed/cusm_events/2014-Extreme-Sports-Medicine-Congress/Documents/Presentations/Endocrine%20Stress%20Reactivity.pdf.
19. Seidman LJ, Valera EM, Makris N. Structural brain imaging of attention deficit/hyperactivity disorder. Biol Psychiatry 2005 Jun;57(11):1263-72. DOI: https://doi.org/10.1016/j.biopsych.2004.11.019.
20. Arnsten AF, Scahill L, Findling RL. alpha2-adrenergic receptor agonists for the treatment of attention-deficit/hyperactivity disorder: Emerging concepts from new data. J Child Adolesc Psychopharmacol 2007 Aug;17(4):393-406. DOI: https://doi.org/10.1089/cap.2006.0098.
21. Cloninger CR, Svrakic DM, Przybeck TR. A psychobiological model of temperament and character. Arch Gen Psychiatry 1993 Dec;50(12):975-90. DOI: https://doi.org/10.1001/archpsyc.1993.01820240059008.
22. Zuckerman M. The sensation seeking scale V (SSS-V): Still reliable and valid. Pers Individ Dif 2007 Oct;43(5):1303-5. DOI: https://doi.org/10.1016/j.paid.2007.03.021.
23. Outside TV. Dean Potter: A premonition of death [Internet]. San Bruno, CA: YouTube; 2015 May 20 [cited 2017 Nov 15]. Available from: www.youtube.com/watch?v=UGzuTpdD-sM.
24. Branch J. Dean Potter, extreme climber, dies in BASE-jumping accident at Yosemite [Internet]. New York, NY: The New York Times; 2015 May 17 [cited 2017 Nov 15]. Available from: www.nytimes.com/2015/05/18/sports/dean-potter-extreme-climber-dies-in-jumping-accident-at-yosemite.html.
25. Ketamine lifts depression via a byproduct of its metabolism [Internet]. Bethesda, MD: National Institutes of Health; 2016 May 4 [cited 2017 Nov 15]. Available from: www.nih.gov/news-events/news-releases/ketamine-lifts-depression-byproduct-its-metabolism.
26. Maddock RJ, Casazza GA, Fernandez DH, Maddock MI. Acute modulation of cortical glutamate and GABA content by physical activity. J Neurosci 2016 Feb 24;36(8):2449-57. DOI: https://doi.org/10.1523/jneurosci.3455-15.2016.
27. Miller L. The last days of extreme-sports superstar Dave Mirra [Internet]. New York, NY: New York Media LLC; 2016 Apr 6 [2017 Nov 15]. Available from: http://nymag.com/daily/intelligencer/2016/04/bmx-dave-mirra-last-days.html.
28. Roenigk A. Dave Mirra: A hero's death and CTE's arrival [Internet]. Los Angeles, CA: ESPN Internet Ventures; 2016 May 24 [cited 2017 Nov 15]. Available from: www.espn.com/action/story/_/id/15613973/dave-mirra-hero-death-cte-arrival-lauren-mirra.
29. Bisharat A. Why are so many BASE jumpers dying? [Internet]. Tampa, FL: National Geographic Partners, LLC; 2016 Aug 30 [cited 2017 Nov 15]. Available from: www.nationalgeographic.com/adventure/features/why-are-so-many-base-jumpers-dying/.
30. Williams A. A thumbs-up before he leapt to his death: Video footage captures the last moments of James Bond stuntman before he died in fall 20 seconds later [Internet]. London, UK: DailyMail.com; 2013 Oct 2 [cited 2017 Nov 15]. Available from: www.dailymail.co.uk/news/article-2441593/Mark-Sutton-death-Video-footage captures-moments-James-Bond-stuntman.html.
31. Fatalities: Fatality reports [Internet]. Colorado Springs, CO: US Hang Gliding and Paragliding Association, Inc; c2017 [cited 2017 Nov 28]. Available from: www.ushpa.org/page/fatalities.
32. Buchanan R. Climbing at the speed of soul [Internet]. Santa Fe, NM: Outside; 2002 Dec 1 [cited 2017 Nov 28]. Available from: www.outsideonline.com/1821221/climbing-speed-soul.
33. Forum: Dean Potter interview Outside magazine 2002 [Internet]. Cheyenne, WY: SuperTopo; 2012 Mar 27 [cited 2017 Nov 28]. Available from: www.supertopo.com/climbers-forum/1785758/Dean-Potter-Interview-Outside-Magazine-2002.
34. Samet M. How Dean Potter became everyone's favorite wingsuited slacklining speed climber [Internet]. Sante Fe, NM: Outside; 2011 Jun 15 [cited 2017 Nov 28]. Available from: www.outsideonline.com/1898131/aerialist.
35. Potter D. Dean Potter: What I've learned [Internet]. Carbondale, CO: Rock and Ice, Bigstone Publishing; 2016 May 16 [cited 2017 Nov 28]. Available from: http://rockandice.com/lates-news/dean-potter-what-ive-learned/.
36. Duane D. Dean Potter: Yosemite's elder madman speaks [Internet]. New York, NY: Men's Journal; 2015 Apr 22 [cited 2017 Nov 28]. Available from: www.mensjournal.com/adventure/outdoor/dean-potter-yosemite-s-elder-madman-speaks-20150422.
37. Soldinger M. Daredevils: The sky walker [documentary]. London, UK: Firecracker Films; 2009 Oct 5.
38. Heil N. Dean Potter, extreme risk and the allure of the 'dangerous arts' [Internet]. New York, NY: Time; 2015 May 28 [cited 2017 Nov 28]. Available from: http://time.com/3898978/dean-potter-extreme-risk-and-the-allure-of-the-dangerous-arts/.
39. Bisharat A. Remembering pioneering climber Dean Potter [Internet]. Washington, DC: Beyond the Edge, National Geographic; 2015 May 17 [cited 2017 Nov 27]. Available from: http://adventureblog.nationalgeographic.com/2015/05/17/pioneering-climber-dean-potter-died-in-base-jumping-accident/.
40. Todhunter A. The precipitous world of Dan Osman [Internet]. New York, NY: The Atlantic; 1996 Feb [cited 2017 Nov 27]. Available from: www.the atlantic.com/magazine/archive/1996/02/the–precipitous-world-of-dan-osman/304382/.
41. Todhunter A. Fall of the phantom lord: Climbing and the face of fear. New York, NY: Doubleday; 1998.
42. Guinness looks back at Dan Osman [video]. San Bruno, CA: YouTube; 2017 Apr 24 [cited 2017 Nov 28]. Available from: www.youtube.com/watch?v=Iy9CP58Ee30.
43. Vetter C. Terminal velocity: The death of the master of gravity [Internet]. Santa Fe, NM: Outside Magazine; 2013 Mar 29 [cited 2017 Nov 15]. Available from: www.outsideonline.com/1914776/terminal-velocity-death-master-gravity.
44. Sparks JR. Extreme sports: A study of free-solo rock climbers [thesis] [Internet]. Provo, UT: Brigham Young University; 2016 Dec 1 [cited 2017 Nov 15]. p 21. Available from: https://scholarsarchive.byu.edu/cgi/viewcontent.cgi?article=7136&context=etd.
45. Bold skydiver jumps off 7.6 km above sea level without a parachute [Internet]. Brooklyn, NY: Health Units Inc; 2016 Aug 1 [cited 2017 Nov 28]. Available from: https://healthunits.com/trending/bold-skydiver-jumps-off-7-6-km-above-sea-level-without-a-parachute/.
46. Felix Baumgartner space jump world record 2012 [Internet]. San Bruno, CA: YouTube; 2012 Oct 14 [cited 2017 Nov 15]. Available from: www.youtube.com/watch?v=vvbN-cWe0A0.
47. Kaplan S. Dean Potter, extreme climber, dies in Yosemite base jumping accident [Internet]. Washington, DC: The Washington Post; 2015 May 18 [cited 2017 Nov 21]. Available from: www.washingtonpost.com/news/morning-mix/wp/2015/05/18/dean-potter-extreme-climber-who-risked-falling-in-order-to-fly-dies-in-base-jumping-accident/?utm_term=.021863d7450a.

This is a story and illustration from the upcoming book *100 Little Stories of Big Moments* published by The Permanente Press.

The stories were written by physicians in 15 minutes in writing workshops about meaningful moments in their work and life of practicing medicine. Professional artists were asked to create a visual representation of the story.

To Die at Home

Russ David Granich, MD

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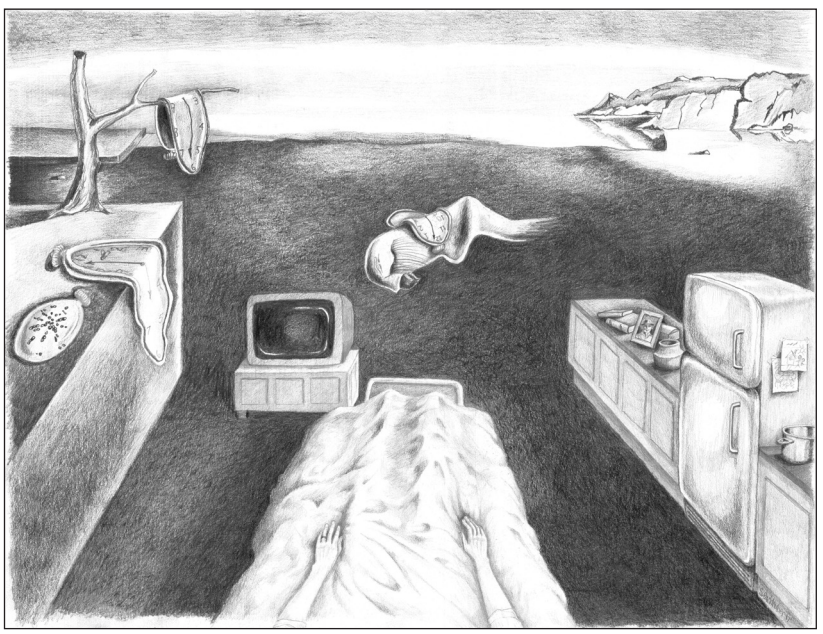
She was an elderly lady who came to the Emergency Department septic. I was on call for palliative care the 22nd day of her hospitalization. The intensivist said she had become ventilator dependent. One of her sons visited every day—we arranged a meeting to coincide with his presence.

She was alert and understood her predicament. We talked as best we could, her writing things, the son filling in info, answering yes and no questions. Her husband of 57 years had died about 10 years ago. She lived in her own house, but it was divided up so her other son could live there. He paid rent, enabling her to keep her home. She had no desire to live on a ventilator. She had a full and meaningful life. Her son agreed and was willing to honor her wishes for terminal extubation. However, she had one wish: To die at home. Usually patients who want their ventilator turned off do so in the hospital. However, I felt I needed to make that wish come true. The intensivist did not think she would make it home if we extubated her in the ICU. There was only one solution—send her home on the ventilator and remove her endotrachial tube there. I had never done that before but I couldn't see why not. The hospice manager listed many objections and concerns. I worked with my colleague, a skilled palliative care nurse specialist, as well as the nurse manager of the ICU, and we dealt with each objection.

Three days later we were ready. The patient was picked up by critical care transport (CCT) at 9 am while I waited at her house. She arrived, on a portable ventilator, but her medicine had not arrived. There were issues with pharmacy about dispensing IV morphine (MS) that we had already addressed, but apparently our arrangements fell through. I quickly called my team, and the ICU manager showed up with the MS 30 minutes later. While we waited, we got her settled in her bed. The CCT nurse stayed and helped. We put her favorite movie on her TV. Her son held her hand. The hospice nurse arrived and started doing her evaluation. I looked around her home. Why was it important for her to be there? It was obvious. Her home was filled with love and memories. All her shelves were filled with knick-knacks. She had very old appliances, all well maintained. You could tell that everything had some meaning. When her medicine arrived, I removed her tube and gave her IV medication. We made her comfortable. She was awake and could talk a little. She enjoyed her movie. I stayed for a couple of hours to make sure she was stable. While I sat and waited, I was looking around and observing everything I saw. One item was a Salvador Dali-style melting clock. I never learned what that meant to her.

She died later that night, comfortable, at home with her family. The next day I bought the same clock online. It sits over my desk and every day I look at it and think of her. ❖



Accompanying artwork: **The Persistence of Memory of Home by Stephen Bachhuber, MD**

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CME credits available for this article — see page 112

REVIEW ARTICLE

Current Epidemiology and Management of Radiocontrast-Associated Acute- and Delayed-Onset Hypersensitivity: A Review of the Literature

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ABSTRACT

Radiocontrast-associated acute-onset hypersensitivity reactions now occur less frequently than before 1990, when high-osmolar, ionic, radiocontrast agents were widely used. Premedication with corticosteroids and antihistamines does not reliably prevent recurrent low-osmolar radiocontrast-associated acute hypersensitivity reactions. Corticosteroid prophylaxis for acute hypersensitivity currently causes more morbidity than benefit. The specific radiocontrast agent that is associated with a patient's adverse reaction must be displayed in the drug intolerance or drug "allergy" field of their electronic health record to enable effective management and prevention of future reactions. The term *iodine allergy* should never be used in the context of radiocontrast-associated adverse reactions because it leads to poorer clinical outcomes. The time to onset of the reaction and the nature of the reaction must be noted in enough detail in the drug intolerance comment fields in the electronic health record to determine the potential mechanism for the reaction and to enable selection of the appropriate radiocontrast material for future exposures. Most individuals with a history of radiocontrast agent hypersensitivity can be effectively managed by selecting an alternative radiocontrast agent, without any premedication. Radiology Departments, catheterization laboratories, and all physicians who use parenteral radiocontrast media must have management plans in place to treat severe acute reactions when they occur. Patients should be informed that delayed-onset reactions, mostly benign rashes within one week of exposure, are as common or more common than acute reactions. Future radiocontrast-associated acute and delayed-onset reactions can be minimized, but never completely avoided, by using an appropriate alternative agent.

INTRODUCTION

The epidemiology and optimal management of radiocontrast-associated adverse reactions have changed dramatically since 1985, with the almost exclusive current use of low-osmolality nonionic radiocontrast agents and very low rates of use of high-osmolality ionic radiocontrast agents.[1] This review will concentrate on reports published since 2010. The goal of this review is to add clarity and specificity to the general suggestions given in the American College of Radiology's *ACR Manual on Contrast Media, Version 10.3*, last updated on May 31, 2017.[2]

REVIEW OF THE LITERATURE

Radiocontrast Agent Hypersensitivity Mechanisms

There are four general categories of radiocontrast-associated hypersensitivity reactions: benign acute-onset, anaphylaxis, benign delayed-onset, and severe delayed-onset. *Acute onset*, which occurs less than one hour after exposure, is typically caused by mast cell activation, either directly or, rarely, is immunoglobulin E (IgE) mediated.[3] *Delayed onset* is defined as starting more than one hour but typically starting more than three hours and up to two to five days after exposure; these reactions are thought to be T-cell-mediated, delayed-type hypersensitivity.[4] These reactions rarely rise to the level of a serious cutaneous adverse reaction, such as toxic epidermal necrolysis or Stevens-Johnson syndrome.[5]

Epidemiology

Li and coworkers[6] in 2016 reported on 120,822 individuals receiving iopromide, iodixanol, iopamidol, ioversol, iobitridol, or iohexol between January 2014 and March 2016 at a single institution in Chongqing, China. They prospectively collected data on all cases. They identified 506 (0.4%) hypersensitivity reactions, of which 90.0% were mild, 7.7% were moderate, and 1.4% were considered severe. Hypersensitivity reactions were more common with iso-osmolar agents than with hypo-osmolar radiocontrast media. Risk factors for acute reactions included previous acute reactions, asthma, doses higher than 100 mL, and injection rates higher than 5 mL/s. The authors were unable to reliably collect delayed-onset reaction data because many patients were in the facility only for the procedure.

We reported in 2012 that of 2,375,424 Kaiser Permanente Southern California (KPSC) Health Plan members who had a health care visit and at least 11 months of health care coverage during 2009, a total of 0.5% of females and 0.3% of males had a radiocontrast agent "allergy."[7] During 2009 a new radiocontrast "allergy" was reported in 0.1% of females who had at least 1 other drug "allergy," in 0.1% of males who had at least 1 other drug "allergy," 0.04% of females who had no other drug "allergy," and in 0.02% of males who had no other drug "allergy." Individuals with any drug "allergies" were more likely to use more health care services and thus might be more likely to be exposed to radiocontrast media. Between January 1, 2014, and April 30, 2017, there were 372 serious, acute-onset, radiocontrast-associated reactions reported by KPSC Radiology Departments, 335 (90.1%) associated with iohexol, 19 (5.1%) associated with iodixanol, 1 (0.3%) associated with diatrizoate, and 17 (4.6%) with the associated radiocontrast agent not reported. It is currently not possible to accurately identify all exposures to radiocontrast agents throughout the entire KPSC health care

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system or to capture all new acute and delayed-onset reactions because of the poor quality of the adverse drug reaction reporting in the electronic health record (EHR). Even when reported, the specific radiocontrast agent implicated is virtually never noted in the EHR, nor are the symptoms described in enough detail to confidently determine a mechanism. It was, however, possible to identify how much radiocontrast medium was purchased each year for KPSC and then estimate annual exposures. The amount of iohexol and iodixanol used annually in KPSC in 2014 through 2016 is displayed in Table 1. In KPSC we annually used about 11.5 to 16 times as much iohexol as iodixanol. We had approximately 1 reported severe acute reaction for every 183,697 mL (about 3674 exposures [range, 1837-18,370]) of iohexol and 1 reported severe acute reaction for every 229,684 mL (about 4594 exposures [range 1199-22,968]) of iodixanol.

Scheinfeld and colleagues[8] at Albert Einstein College of Medicine in New York, NY, reported in 2014 that of 927,000 total "allergies" documented during a 10-year period in their EHR, virtually none of the more than 7000 patients with "allergies" reported to "contrasts" or "iodine" had a specific radiocontrast agent listed.

Dean et al[9] reported in 2015 that adverse reactions after radiocontrast-enhanced computed tomography (CT) scans were reported at a lower overall rate in inpatients compared with outpatients, but the reactions reported were more severe. Less than 10% of the reported reactions were delayed onset. Most patients were exposed to iohexol; only a small minority were exposed to iodixanol. There were 86 (0.23%) of 34,508 reactions reported after outpatient CT scans vs 10 (0.03%) of 38,066 reactions reported after inpatient CT scans. The overall use of adrenaline was the same in both groups—4 uses in inpatients (1 in 9516 exposures), and 4 uses in outpatients (1 in 8627 exposures).

Palmiere and Reggiani Bonetti[10] reviewed radiocontrast-associated anaphylaxis fatalities in 2014. They identified 24 cases, initially reported between 1972 and 2012. Only a minority of the cases had any previous exposure to radiocontrast agents. The authors concluded that "risk" factors for fatal anaphylaxis included any history of asthma, allergic rhinitis, atopic dermatitis, multiple allergies, drug allergy, food allergy, previous radiocontrast exposure, β-blocker or nonsteroidal anti-inflammatory drug use, and any preexisting condition including any cardiovascular, renal, hematologic, autoimmune, or metabolic disease. This list is of questionable utility, with almost as many "risk" factors as reported cases.

Table 1. Radiocontrast agent use in Kaiser Permanente Southern California, 2014 through 2016

Agent	2014	2015	2016	Total
Iohexol[a] (mL)	19,088,565	20,385,128	22,064,825	61,538,518
Iodixanol[b] (mL)	1,650,500	1,361,000	1,352,500	4,364,000
Total (mL)	20,739,065	21,746,128	23,417,325	65,902,518
Approximate exposures at 50 mL per exposure	414,782	434,922	468,346	1,318,050

[a] Typically used at 10 mL to 100 mL per exposure.
[b] Typically used at 10 mL to 250 mL per exposure.

There have been only rare reported cases of radiocontrast-associated serious cutaneous adverse reactions, specifically Stevens-Johnson syndrome or toxic epidermal necrolysis.[5] There has been one case of recurrent iopromide-associated Stevens-Johnson syndrome reported, with three distinct episodes.[11]

Prevention of Recurrent Radiocontrast-Associated Reactions

Kolbe and coworkers[12] at the Mayo Clinic in Rochester, MN, reported in 2014 data from 245 individuals with reactions (0.08%, or 1 in 1222), of 299,413 total individuals exposed to low-osmolality contrast media between 2002 and 2008. All affected individuals noted only acute-onset hives associated with their radiocontrast agent exposure. Seventy-three of these 245 individuals then had at least 1 additional radiocontrast exposure through 2009. The authors excluded 8 patients who were receiving long-term corticosteroid therapy and 15 additional patients who had their index radiocontrast-associated reaction before 2002, to avoid individuals with their index reaction occurring after high-osmolar ionic radiocontrast agent exposure. The remaining 50 study subjects had 133 subsequent radiocontrast exposures, with a median of 2 exposures and a range of 1 to 11. There were 19 individuals (38.0%) who had at least 1 additional episode of radiocontrast-associated hives, for a total of 26 events (19.5%) in the 133 imaging studies. Paradoxically, individuals who were premedicated were more likely to have hives with subsequent exposures. The was no premedication given before 89 (66.9%) of the scans. Those premedicated with diphenhydramine had an adjusted odds ratio of 1.2 (95% confidence interval = 0.2-7.3, p = 0.85). Those premedicated with corticosteroids had an adjusted odds ratio of 14.3 (95% confidence interval = 4.1-50.4, p < 0.0001). Those premedicated with corticosteroids and diphenhydramine had an adjusted odds ratio of 8.3 (95% confidence interval = 1.8-37.9, p = 0.006). The authors concluded that premedication may not be necessary, but radiology personnel need to be aware of prior reaction history and be knowledgeable in recognition and treatment of these reactions.

Mervak and coworkers[13] in 2015 reported on 626 inpatients with a history of acute-onset radiocontrast-associated hypersensitivity who received a 13-hour corticosteroid and diphenhydramine premedication regimen before reexposure to low-osmolar radiocontrast materials between January 2010 and December 2013. Breakthrough reactions occurred in 13 (1.2%). This is about 3 or 4 times the ordinary reaction rate in the general population.[13]

Jung et al[14] in 2016 retrospectively reported on 322 patients with a history of acute-onset radiocontrast agent reactions, seen between June 2010 through May 2012, who were reexposed to low-osmolar contrast media after premedication with

antihistamines, corticosteroids, or both. Breakthrough reactions occurred in 3.4% of all patients and in 14.3% of patients with severe index reactions.

Abe and coworkers[15] from Japan reported in 2016 data from 771 individuals seen between January 2006 and September 2014 with a history of a previous radiocontrast-associated adverse reaction who were reexposed to a nonionic radiocontrast agent. The same radiocontrast medium was used in 220 individuals (28.5%) without premedication (Group 1) and in 271 (35.1%) with premedication (Group 2). A different radiocontrast agent was used in 58 (7.5%) without any premedication (Group 3) and in 222 (28.8%) with premedication (Group 4). Group 1 had 61 (27.7%) repeated reactions. Group 2 had 47 repeated reactions (17.3%, $p < 0.01$). Group 3 had only 3 repeated reactions (5.2%, $p < 0.001$). Group 4 had 6 repeated reactions (2.7%, $p < 0.001$). The authors concluded that changing the radiocontrast agent was more effective than premedication for subsequent exposures. Premedication was also not helpful in preventing reactions to nonionic radiocontrast agents in individuals with a history of an ionic radiocontrast-associated reaction.[15]

Mammarappallil and coworkers[16] from Wake Forest University and Duke University in NC reported in 2016 on the first 500 patients newly labeled as "allergic" to iodinated contrast agents between 1999 and 2009 at a single academic tertiary care hospital. They found that only 83 (16.6%) had both evidence of radiocontrast exposure and documentation compatible with a hypersensitivity reaction noted in the EHR. There were 69 (13.8%) who had evidence of radiocontrast exposure and did have nonhypersensitivity reactions documented, 19 (27.5%) with benign isolated swelling, 38 (55.1%) with "concerns about renal insufficiency," and 12 (17.4%) with various benign isolated symptoms such as warmth, flushing, nausea, or taste perversion. The authors found that 224 (44.8%) had evidence of radiocontrast exposure but no documentation supporting any hypersensitivity or nonhypersensitivity reaction. The final 124 individuals (24.8%) had no evidence of any radiocontrast exposure or reaction. Mammarappallil et al[16] also found that asking the patient was often not helpful because the patient was unsure of what, if anything, happened and were just told they were "allergic" to radiocontrast material, even if they had no documented exposure. The authors concluded that it is necessary to train the medical community to document accurately and completely when radiocontrast-associated reactions occur.

Berti and coworkers[17] from Italy reported in 2016 that 35 patients with breakthrough reactions to radiocontrast agents had a lower incidence of positive skin test reactions than 28 patients with an initial hypersensitivity reaction. This is evidence that most breakthrough reactions are not IgE mediated.

Lee and coworkers[18] from Korea reported in 2016 on a group of 453 (3.0%) individuals (of 14,785 seen between January 2014 and December 2015) with a history of mild radiocontrast-associated acute-onset hypersensitivity who had another nonionic radiocontrast study. The authors retrospectively identified 273 individuals (60.3%) who had been pretreated with chlorpheniramine maleate 4 mg, 30 to 60 minutes before their repeated radiocontrast exposure. There was no randomization, and the decision to pretreat was made by the physician using his or her judgment. There was no difference in the recurrence of an acute hypersensitivity reaction between the pretreated and the nonpretreated groups (10.6% vs 11.7%, $p = 0.729$). There was also no difference in the time to recurrent reaction or reaction severity. There was no effort made to change the specific nonionic radiocontrast material used.

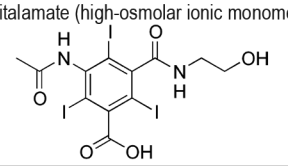
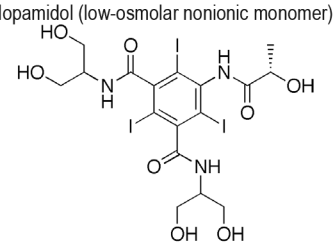
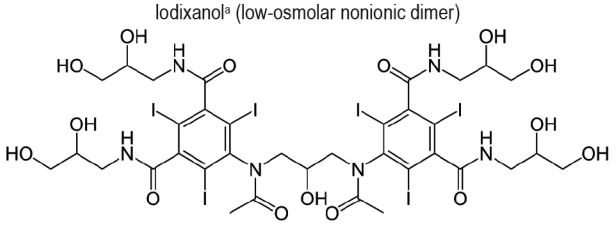
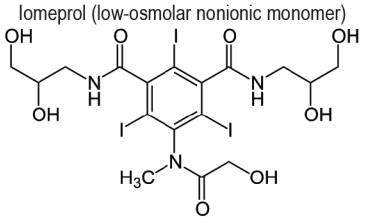
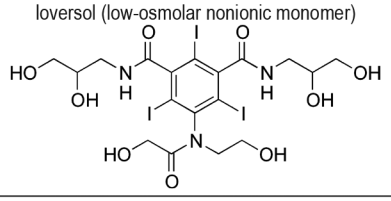
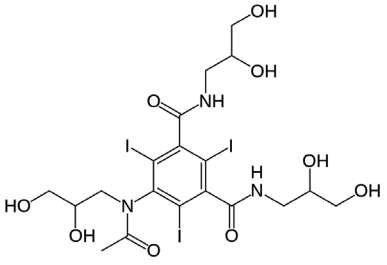
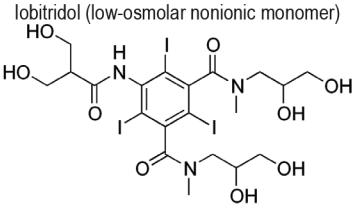
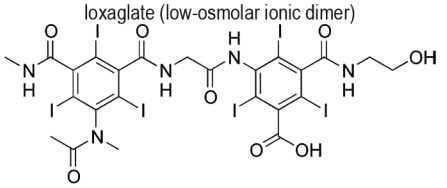
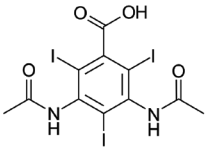
Lerondeau and coworkers[19] from France reported in 2016 on 340 patients referred for evaluation of radiocontrast agent hypersensitivity. Of these, 234 (71.5%) had normal ("negative") test and rechallenge results. Another 97 (28.5%) had abnormal ("positive") test or rechallenge results. Of those with abnormal results, there were 55 (56.7%) whose test or rechallenge was positive to the index radiocontrast agent. There were 33 (34.0%) whose test was negative to the index radiocontrast material, but of these, 3 (9.1%) uniquely tested positive to an excipient and 30 (90.9%) were test or challenge positive to 1 or more other radiocontrast agents. Finally, there were 9 (9.3%) in the abnormal results group who had an unknown index radiocontrast medium, but who were test or challenge positive to an excipient or to 1 or more radiocontrast agents. The authors concluded that their data were only useful in evaluating the risks of recurrent delayed-onset reactions.[19] They identified 3 groups of radiocontrast agents that were very unlikely to cross-react for presumed T-cell-mediated, delayed-type hypersensitivity. Group A included ioxitalamate, iopamidol, iodixanol, iomeprol, ioversol, and iohexol. Group B included iobitridol and ioxaglate. Group C included only amidotrizoate/diatrizoate.[19] Unfortunately, iobitridol and ioxaglate are not currently approved for use in the US, and amidotrizoate/diatrizoate is an old-style ionic high-osmolality radiocontrast agent.

Davenport and Cohan[20] reported in 2017 that the morbidity associated with corticosteroid prophylaxis for acute-onset radiocontrast agent hypersensitivity currently outweighs any population benefit in hospitalized patients. They noted that the number needed to treat to prevent 1 severe acute reaction was approximately 569, and to prevent 1 lethal acute reaction was likely greater than 50,000. The authors concluded that corticosteroid prophylaxis, with the goal of preventing recurrent severe acute-onset reactions in high-risk inpatients, is likely associated with substantial costs and indirect harm related to longer hospital stay.

Böhm and coworkers[21] reported in 2017 on 300 patients with a history of "iodine allergy" entered into their medical record, compared with 2 age-, sex-, and procedure-matched groups with a nonspecific or specific radiocontrast agent "allergy." Patients with the "iodine allergy" were more likely to get a suboptimal unenhanced CT scan when an enhanced CT image was clinically indicated. They also experienced higher rates of recurrent radiocontrast-associated reactions.

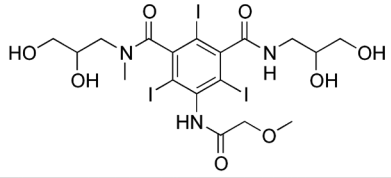
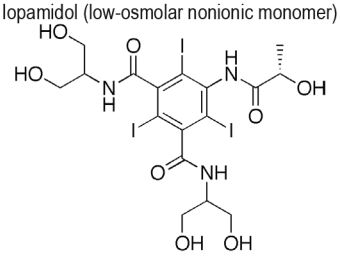
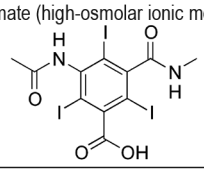
The radiocontrast materials that are noncross-reacting for delayed-onset hypersensitivity are displayed in Table 2. The other nongrouped radiocontrast agents available in the US are displayed in Table 3. Most of the agents are monomers. They all have very similar core structures, have a tri-iodinated benzene ring, and vary only by their hydrophilic side chains. They all have very low protein binding; thus, they are unable to haptenate serum proteins and induce IgE-mediated acute-onset hypersensitivity.

Table 2. Noncross-reacting radiocontrast agent groups for presumed T-cell-mediated, delayed-onset reactions

Group	Radiocontrast material
Group A	
	Ioxitalamate (high-osmolar ionic monomer) 
	Iopamidol (low-osmolar nonionic monomer) 
	Iodixanol[a] (low-osmolar nonionic dimer) 
	Iomeprol (low-osmolar nonionic monomer) 
	Ioversol (low-osmolar nonionic monomer) 
	Iohexol[a] (low-osmolar nonionic monomer) 
Group B	
	Iobitridol (low-osmolar nonionic monomer) 
	Ioxaglate (low-osmolar ionic dimer) 
Group C	
	Amidotrizoate/diatrizoatea (high-osmolar ionic monomer) 

[a] Used in Kaiser Permanente Southern California.

Table 3. Other ungrouped nonionic radiocontrast materials available in the US

Radiocontrast material
Iopromide (low-osmolar nonionic monomer) 
Iopamidol (low-osmolar nonionic monomer) 
Iothalamate (high-osmolar ionic monomer) 

Kelly and coworkers[22] in 2010 reported on the processing-dependent and processing-independent pathways for recognition of radiocontrast agents by specific human T cells. They concluded that radiocontrast media can activate T cells by direct binding to the major histocompatibility-T-cell receptor complex or by binding after uptake and processing by antigen-presenting cells. This calls into question the assumed inert nature of current radiocontrast agents.

HOW TO MANAGE SPECIFIC CLINICAL SCENARIOS

Specific clinical scenarios of radiocontrast-associated hypersensitivity and their management are displayed in Table 4. Additional detail is provided beyond the general recommendation in the American College of Radiology's *ACR Manual on Contrast Media, Version 10.3*.[2]

If either iobitridol or ioxaglate is ever approved for use in the US, they would be the agents of first choice over amidotrizoate/diatrizoate in patients with a history of a severe delayed-onset reaction to iohexol or iodixanol. If corticosteroids are used to help prevent delayed-onset reactions, clinicians should consider starting the dosing at least 24 hours before the radiocontrast exposure, to allow enough time for the corticosteroids to induce new regulatory proteins, and use a several-day course, such as prednisone at 40 mg/d for 5 days.

If the patient had a severe acute-onset reaction to an unknown contrast agent before 1990 and only amidotrizoate/diatrizoate is now available, then pretreatment with oral prednisone 40 mg, 16 hours, 6 hours, and 1 hour prior, and oral diphenhydramine 50 mg, 1 hour before exposure, has been shown to reduce recurrent severe acute reactions.[22]

If any mild acute reaction occurs, such as flushing or hives, treat with diphenhydramine 50 mg. If there are any signs or symptoms of anaphylaxis, immediately use adrenaline, 0.3 mL of 1:1000 concentration intramuscularly. This can be easily performed by having adrenaline autoinjectors available and all radiology staff trained in their use.[23] If adrenaline is used, check the patient's acute serum tryptase level.

Tell patients to report all delayed-onset rashes. Always list the exact radiocontrast agent used and supply enough detail in the drug "allergy" field of the EHR to allow other medical professionals treating the patient in the future to determine time of onset and severity.[24]

CONCLUSION

Radiocontrast-associated acute-onset hypersensitivity reactions occur after about 0.4% of all exposures. Delayed-onset reactions are probably as common or more common than acute-onset reactions, but are underreported. Most acute and delayed-onset reactions are mild. Premedication with corticosteroids and antihistamines fails to prevent many, if not most, recurrent acute or delayed-onset reactions. Corticosteroid prophylaxis for prevention of acute hypersensitivity currently appears to result in more morbidity than benefit. The specific radiocontrast agent associated with the adverse reaction must be displayed in the drug intolerance or drug "allergy" field of the EHR to enable effective management and prevention of future reactions. The time to onset of the reaction and the nature of the reaction should be noted in enough detail in the comment fields to determine the potential mechanism for the reaction, and to enable selection of an alternative radiocontrast medium for future exposures. The term *iodine allergy* should never be used in the context of radiocontrast-associated adverse reactions because it leads to poorer clinical outcomes. Most acute and delayed-onset reactions can be effectively managed by selecting an alternative radiocontrast material, without any premedication. Radiology Departments, catheterization laboratories, and all physicians who use parenteral radiocontrast agents must have management plans in place to treat serious acute reactions when they occur. Patients must be informed that delayed-onset reactions, mostly rashes occurring within one week of exposure, are as common or more common than acute

Table 4. Management of future contrast exposures in individuals with previous radiocontrast-associated hypersensitivity

Clinical history	Preferred radiocontrast material
Severe acute-onset reaction to an unknown radiocontrast agent before 1990	Iohexol or iodixanol without any premedication
Severe delayed-onset reaction to an unknown radiocontrast agent before 1990	Iohexol or iodixanol without any premedication
Acute-onset reaction to an unknown radiocontrast agent after 1990, assumed to be iohexol	Iodixanol without any premedication
Acute-onset reaction to iohexol	Iodixanol without any premedication
Acute-onset reaction to iodixanol	Iohexol without any premedication
Mild delayed-onset reaction to iohexol	Iodixanol without any premedication
Mild delayed-onset reaction to iodixanol	Iohexol without any premedication
Severe delayed-onset reaction to iohexol or iodixanol	Amidotrizoate/diatrizoate or consider iopromide or iopamidol and prednisone (40 mg/d for 5 d starting 1 d before exposure)

reactions. Future radiocontrast-associated acute- and delayed-onset reactions can be minimized, but probably never completely avoided, by using an appropriate alternative agent. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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References

1. Matthews EP. Adverse effects of iodine-derived intravenous radiopaque contrast media. Radiol Technol 2015 Jul-Aug;86(6):623-38.
2. ACR Committee on Drugs and Contrast Media. ACR manual on contrast media. Version 10.3. Reston, VA: American College of Radiology; 2017 May 31.
3. Soyyiit A, Gksel Z, Aydn M, Gentrk Z, Bavbek S. What is the clinical value of negative predictive values of skin tests to iodinated contrast media? Allergy Asthma Proc 2016 Nov;37(6):482-8. DOI: https://doi.org/10.2500/aap.2016.37.4000.
4. Corbaux C, Seneschal J, Taïeb A, Cornelis F, Martinet J, Milpied B. Delayed cutaneous hypersensitivity reactions to iodinated contrast media. Eur J Dermatol 2017 Apr 1;27(2):190-1. DOI: https://doi.org/10.1684/ejd.2016.2935.
5. Baldwin BT, Lien MH, Khan H, Siddique M. Case of fatal toxic epidermal necrolysis due to cardiac catheterization dye. J Drug Dermatol 2010 Jul;9(7):837-40.
6. Li X, Liu H, Zhao L, et al. Clinical observation of adverse drug reactions to non-ionic iodinated contrast media in population with underlying diseases and risk factors. Br J Radiol 2017 Feb;90(1070):20160729. DOI: https://doi.org/10.1259/bjr.20160729.
7. Macy E, Ho NJ. Multiple drug intolerance syndrome: Prevalence, clinical characteristics, and management. Ann Allergy Asthma Immunol 2012 Feb;108(2):88-93. DOI: https://doi.org/10.1016/j.jaci.2011.12.499.
8. Scheinfeld MH, Sprayregen S, Jerschow E, Dym RJ. Contrast is the new penicillin, and possibly worse. J Am Coll Radiol 2015 Sep;12(9):942-3. DOI: https://doi.org/10.1016/j.jacr.2014.09.032.
9. Dean KE, Starikov A, Giambrone A, Hentel K, Min R, Loftus M. Adverse reactions to intravenous contrast media: An unexpected discrepancy between inpatient and outpatient cohorts. Clin Imaging 2015 Sep-Oct;39(5):863-5. DOI: https://doi.org/10.1016/j.clinimag.2015.04.014.
10. Palmiere C, Reggiani Bonetti L. Risk factors in fatal cases of anaphylaxis due to contrast media: A forensic evaluation. Int Arch Allergy Immunol 2014;164(4):280-8. DOI: https://doi.org/10.1159/000366204.
11. Brown M, Yowler C, Brandt C. Recurrent toxic epidermal necrolysis secondary to iopromide contrast. J Burn Care Res 2013 Jan-Feb;34(1):e53-6. DOI: https://doi.org/10.1097/bcr.0b013e318257d88e.
12. Kolbe AB, Hartman RP, Hoskin TL, et al. Premedication of patients for prior urticarial reaction to iodinated contrast medium. Abdom Imaging 2014 Apr;39(2):432-7. DOI: https://doi.org/10.1007/s00261-013-0058-9.
13. Mervak BM, Davenport MS, Ellis JH, Cohan RH. Rate of breakthrough reactions in inpatients at high risk receiving premedication before contrast-enhanced CT. AJR Am J Roentgenol 2015 Jul;205(1):77-84. DOI: https://doi.org/10.2214/ajr.14.13810.
14. Jung JW, Choi YH, Park CM, Park HW, Cho SH, Kang HR. Outcomes of corticosteroid prophylaxis for hypersensitivity reactions to low osmolar contrast media in high-risk patients. Ann Allergy Asthma Immunol 2016 Sep;117(3):304-309.e1. DOI: https://doi.org/10.1016/j.anai.2016.07.010.
15. Abe S, Fukuda H, Tobe K, Ibukuro K. Protective effect against repeat adverse reactions to iodinated contrast medium: Premedication vs changing the contrast medium. Eur Radiol 2016 Jul;26(7):2148-54. DOI: https://doi.org/10.1007/s00330-015-4028-1.
16. Mammarappallil JG, Hiatt KD, Vincent W, Bettmann MA. How accurate is the label "allergic to iodinated contrast agents"? Acta Radiol 2016 Jan;57(1):47-50. DOI: https://doi.org/10.1177/0284185114568049.
17. Berti A, Della-Torre E, Yacoub M, et al. Patients with breakthrough reactions to iodinated contrast media have low incidence of positive skin tests. Eur Ann Allergy Clin Immunol 2016 Jul;48(4):137-44.
18. Lee SH, Park HW, Cho SH, Kim SS. The efficacy of single premedication with antihistamines for radiocontrast media hypersensitivity. Asia Pac Allergy 2016 Jul;6(3):164-7. DOI: https://doi.org/10.5415/apallergy.2016.6.3.164.
19. Lerondeau B, Trechot P, Waton J, et al. Analysis of cross-reactivity among radiocontrast media in 97 hypersensitivity reactions. J Allergy Clin Immunol 2016 Feb;137(2):633-635.e4. DOI: https://doi.org/10.1016/j.jaci.2015.07.035.
20. Davenport MS, Cohan RH. The evidence for and against corticosteroid prophylaxis in at-risk patients. Radiol Clin North Am 2017 Mar;55(2):413-21. DOI: https://doi.org/10.1016/j.rcl.2016.10.012.
21. Böhm I, Nairz K, Morelli JN, Keller PS, Heverhagen JT. Iodinated contrast media and the alleged "iodine allergy": An inexact diagnosis leading to inferior radiologic management and adverse drug reactions. Rofo 2017 Apr;189(4):326-32. DOI: https://doi.org/10.1055/s-0042-122148.
22. Kelly JF, Patterson R, Lieberman P, Mathison DA, Stevenson DD. Radiographic contrast media studies in high-risk patients. J Allergy Clin Immunol 1978 Sep;62(3):181-4. DOI: https://doi.org/10.1016/0091-6749(78)90104-5.
23. Restauri N, Lio E, Glueck D, et al. Best practice for safe and effective administration of epinephrine for the treatment of anaphylaxis in the radiology department. J Am Coll Radiol 2016 Mar;13(3):303-6. DOI: https://doi.org/10.1016/j.jacr.2015.08.018.
24. Blumenthal KG, Park MA, Macy EM. Redesigning the allergy module of the electronic health record. Ann Allergy Asthma Immunol 2016 Aug;117(2):126-31. DOI: https://doi.org/10.1016/j.anai.2016.05.017.

What Would It Be Like In A Radiologist's Shoes?

To spend most of my day dealing with images of people: Plain black-and-white x-ray images, or speckled images caused by sound waves bouncing off organs, or images caused by dyes outlining arteries and veins, or contrast medium filling loops of bowel, or images reconstructed by computers into cross sections of the body …

— *My Own Country,* Abraham Verghese, MBBS, b 1955, Indian-American physician-author

Viking Dreams
photograph

Sapna Reddy, MD

A beautiful rainbow frames this picturesque fishing village in Lofoten, Norway. The fishermen use cod liver oil mixed with ochre to paint their cabins a bright red.

Dr Reddy is a Radiologist at the Walnut Creek Medical Center in CA and is pursuing a dual career as a landscape/nature photographer. More of her work can be seen at www.sapnareddy.com, and in this and other issues of *The Permanente Journal*.

REVIEW ARTICLE

Complex Ventral Hernias: A Review of Past to Present

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ABSTRACT

With the incidence of ventral hernias increasing, surgeons are faced with greater complexity in dealing with these conditions. Proper knowledge of the history and the advancements made in managing complex ventral hernias will enhance surgical results. This review article highlights the literature regarding complex ventral hernias, including a shift from a focus that stressed surgical technique toward a multimodal approach, which involves optimization and identification of suboptimal characteristics.

INTRODUCTION

Complex abdominal wall defects represent one of the more challenging dilemmas faced by general surgeons. The natural history of abdominal hernias has demonstrated that with time a patient's quality of life will worsen.[1] More importantly, complex abdominal wall defects propagate additional morbidity and can result in substantial complications if left untreated.[2] As a ventral hernia progresses, studies have demonstrated that this condition impinges on psychological well-being, with patients reporting lower satisfaction with body image and mental health.[1] This same study demonstrated that patients with ventral hernias were less sexually active, had greater rates of body pain, and had diminished social and physical functioning.[1]

As the most common complication after laparotomy, incisional hernias are typically the inciting factor in the development of these complex defects.[3,4] With an estimated 4 million laparotomies performed annually in the US alone, the incidence of these defects is on the rise.[3,4] Hernias can derive from a variety of sources, including a history of trauma, previous surgery, congenital defects, infection, and even cancer.[1,3] A survey in 2016 showed 65% of experts surveyed agreeing that loss of domain and hernia volumes greater than 30% of abdominal contents are mandatory characteristics for defining large, complex abdominal wall defects.[5] However, the true complexity of such defects cannot be measured solely by a standard definition. The difficulty seen in repairing these defects ultimately depends on a multitude of factors.[2] These include the location, size, depth, and condition of the surrounding tissue associated with the defect.[2]

The surgical management of ventral hernias has evolved. Primary closure of fascial defects was originally the mainstay of therapy in hernia repair. Unfortunately, recurrence rates were unacceptable, with some studies reporting rates greater than 50%.[6,7] This led to the advent of a tension-free repair with use of prosthetic mesh. First introduced in the 1950s,[8] the use of mesh repair has expanded over time, and with improved recurrence rates, the tension-free mesh repair eventually became the gold standard for repair.[7,9] However, despite the improved recurrence rates seen with mesh use, it can subject patients to unwanted mesh-related complications, and as such, the surgical field has yet to obtain an ideal repair for complex hernias.[6,7,9,10]

At the inception of laparoscopic techniques for herniorrhaphy in 1993, certain advantages were deemed to be inherent to this approach. In general, laparoscopic techniques are associated with reduced hospital stay, faster recovery, and a 3% recurrence rate at roughly 2 years postoperatively.[11] However, certain hernia characteristics, such as loss of domain, previously placed mesh, and extensive abdominal surgical history may preclude the use of laparoscopy.[12] For such defects, expansion on the open primary repair was pursued by Ramirez et al,[13] with a technique founded on the principle of myofascial advancement and manipulation. The component separation, as it was eventually coined, has since had modifications made to its approach, with each variation possessing unique pros and cons.

However, despite operative innovation, recurrence rates remain far from acceptable. For this reason, surgeons are now shifting their focus away from operative technique and heightened emphasis on optimizing patient-related factors. This has become one of the newest developments in the history of this condition's management. In relation, the adaptation of multimodal recovery pathways, originally developed by colorectal surgeons, has shown promising effects on postoperative outcomes.[14] This same philosophy is now being employed in managing patients who are undergoing abdominal wall reconstruction. With a focus on perioperative optimization, it is hoped that these trends translate to improved success. This article aims to review, expand, and highlight the progression of technique, as well as the management strategies used in treating complex abdominal wall defects.

PREOPERATIVE CONSULTATION

Preoperative assessment of large ventral hernia defects is the cornerstone of success. It allows for identification of

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factors that may preclude certain operative interventions and promotes presurgical steps to optimize a patient's status before undergoing such a repair. Rosen[15] corroborates this and holds the preoperative consultation critical to managing patients undergoing ventral herniorrhaphy. Because extensive morbidity and mortality are associated with repair of complex abdominal defects, it is critical to understand associated morbidity and to educate patients during the presurgical evaluation.[16] Preoperative assessment therefore should define, as well as align, the patient's and surgeon's goals and expectations.[12] If presurgical evaluation detects any substantial comorbidity or disease process, surgeons should consider consultation with an internal medicine physician to facilitate optimization.[16]

Preoperative evaluation should begin with a thorough history and physical examination. Special attention should be given to the size and location of the hernia as well as prior incisions or stomas.[6] Overlying skin changes such as ulceration, thinning, and cellulitis should also be noted, as should the presence of draining sinuses or exposed mesh.[6] Because patients with these characteristics have a ten-fold increase in soft-tissue infection rates, identification is of the utmost importance, and proper treatment is necessary before repair.[15] During physical examination, patients should be evaluated in the standing and supine positions.[16] Valsalva maneuver should also be used during examination because it can enhance the sensitivity of the physical examination findings.[16] Inability to reduce herniated contents, especially of large size, below the level of the fascia should raise suspicion for a loss of domain.[15]

Surgical history, as well as previous operative reports, should be reviewed. It has been demonstrated that patients with a history of prior abdominal hernia repair have an increased risk of infection, 42% vs 12%, with a repeated operation.[15] The operative history should pinpoint previous repairs, types of mesh used (if any at all), and into which plane the mesh was placed because these factors will influence surgical therapy greatly.[6] Active reconnaissance should be used if deemed necessary and can include discussions with previous surgeons in addition to requesting operative reports. Additionally, the number of previous ventral hernia repairs is an independent risk factor for recurrence, complication rates, and reoperation rates, further highlighting the importance of the preoperative assessment.[17] Investigating the cause of previous surgical failures should encompass identification of suboptimal conditions and subsequent optimization.

The context of a patient's hernia is paramount to the preoperative assessment because presentation will often dictate urgency and method of repair. In general, indications to repair ventral hernias are subjective, but most commonly include symptom relief, cosmesis, and prevention of future morbidities such as pain, incarceration, enlargement, and skin changes associated with the defect.[18] The urgent or emergent nature of presentation can affect morbidity and mortality, with mortality rates reported to be 0.3% for elective repairs compared with 1.1% for complicated cases.[19] However, whenever feasible, surgeons should continue to exercise careful and meticulous presurgical assessment, unless precluded by an emergent presentation.

In general, the operative approach chosen should be based on the anticipated complexity as well as the experience and comfort a surgeon possesses with the operation.[12] However, as a guide, the presence of extensive adhesions or history of previous major operations potentiate the risk of intestinal injuries during laparoscopic adhesiolysis.[12] Additional factors to consider are presence of active infection, coagulable states, loss of domain, poor skin quality over the defect, and patient expectations, specifically scar revision or panniculectomy desires.[15] The use of an open procedure in the presence of these characteristics should be strongly considered because the likelihood of conversion from laparoscopic to open repair is exceptionally high and may add undue morbidity.[12]

PREOPERATIVE OPTIMIZATION

Comorbidities should be assessed and medically optimized before any surgical repair because the presence of these are associated with higher recurrence and complication rates.[6] The presence of coronary artery disease, chronic obstructive pulmonary disease, corticosteroid use, and low preoperative albumin levels were found to be significant independent predictors of wound infection and hospital length of stay.[20] Effective patient optimization generally includes smoking cessation at least 4 weeks before surgery, tight glycemic control (glucose level below 110 mg/dL; hemoglobin A_{1C} concentration less than 7.0%), nutritional optimization, and aggressive medical therapy with bronchodilators to improve oxygenation in those patients with chronic obstructive pulmonary disease or chronic hypoxia.[4,20-22] Nutritional optimization, effective glycemic control, weight loss in obese patients, and smoking cessation are cost-effective methods that should be routinely used to optimize patients preoperatively.[4] An overview of these measures appears in Table 1.[4,6,15,20-25]

Table 1. Preoperative optimization[4,6,15,20-25]

Condition	Recommendation
Diabetes mellitus	HbA_{1C} < 7%; perioperative glucose level ranges from 140 mg/dL to 160 mg/dL ideally
Smoking	Cessation at least 4 weeks before surgery
Obesity	BMI > 50 kg/m^2: Not recommended for elective repair BMI > 45 kg/m^2: Consider bariatric surgery referral BMI > 30 kg/m^2: Weight loss and diet counseling
Malnourishment	Albumin > 3 g/dL, nutritional drink (eg, IMPACT Advanced Recovery, Nestlé Health Science)
COPD/emphysema	Bronchodilator therapy; pulmonary consultation
MRSA	Preoperative screening
Cardiac history	Cardiology consultation; obstructive sleep apnea screening

BMI = body mass index; COPD = chronic obstructive pulmonary disease; HbA_{1c} = hemoglobin A_{1c}; MRSA = methicillin-resistant *Streptococcus aureus*.

Smoking cessation is imperative because smokers have higher risks of wound morbidity and hernia recurrence.[15] Smoking diminishes oxygen tension in tissues, ultimately decreasing collagen deposition during wound healing.[4] Lindström et al[22] assessed the benefits of perioperative smoking cessation, finding a 49% risk reduction in all postoperative complications in those abstaining from smoking at least 4 weeks preoperatively. Nutritional optimization is another essential aspect of preoperative evaluation because the presence of malnutrition or brittle diabetes mellitus can be detrimental to surgical success. Poor glycemic control in the perioperative and postoperative period, up to 60 days after surgery, has repeatedly been shown to increase the risk of wound infections.[4] A range of 140 mg/dL to 160 mg/dL in blood glucose levels during the perioperative period is advocated as the optimal target by Martindale and Deveney.[4]

Malnourished patients and those with obesity must be optimized to prevent operative failure. Numerous studies have demonstrated preoperative albumin levels to be one of the strongest predictors of overall 30-day postsurgical mortality and morbidity.[4,20,23,24] A Veterans Affairs study demonstrated preoperative albumin levels less than 3.0 g/dL to be the most important predictor of postsurgical complications.[24] Additionally, albumin levels have been found to correlate with the length of hospital stay as well as wound infection rates.[20] Presence of obesity can have extensive implications on surgical outcomes. Patients with a body mass index greater than 45 kg/m^2 should consider bariatric evaluation before undergoing elective hernia repair.[6] Martindale and Deveney[4] have essentially excluded elective hernia repair as an option for those with a body mass index greater than 50 kg/m^2 because the recurrence risk is prohibitively high. For those with a body mass index greater than 30 kg/m^2, an increased risk of skin and soft-tissue infections, as well as higher wound dehiscence rates, have been reported.[21,25]

PREOPERATIVE IMAGING

Computed tomography (CT) of the abdominal wall is an excellent tool in assessing ventral hernia characteristics. According to Earle et al,[12] CT imaging can define musculature integrity and assess defect relationship to intraabdominal structures, enhancing a surgeon's ability to determine the safest and most ideal approach for mesh placement. For the most part, no intravenous or oral contrast agent is necessary; however, the surgeon should use discretion on the basis of the presentation or when certain anatomical aspects of the hernia are unclear.[6] The use of CT is especially helpful in morbidly obese patients, those with history of recurrent hernias, if loss of domain is suspected, or with defects near bony structures.[15] Rosen[15] advocates for CT assessment to further evaluate possible loss of domain, which typically has extensive volume of abdominal contents localized to the hernia sac. A survey among specialists found that CT scanning, functional respiratory evaluation, and cardiology consultation are indispensable parts of the preoperative evaluation, with CT the most commonly employed.[5] The use of preoperative imaging is especially beneficial in patients with recurrences, for evaluating vasculature and tissue planes, to better delineate nonmidline hernias or for identifying defects unnoticed on physical examination.[4,12]

Although not useful in determining the extent of intraabdominal adhesions, preoperative CT imaging can detect signs of occult inflammation or infected fluid cavities that may alter mesh utilization and surgical approach.[6,12] One study showed an occult hernia detection rate of 48% in those who underwent laparoscopic hernia repairs, which originally went undetected on physical examination.[26] An additional study found significantly better results in the detection of hernia recurrence after mesh repair using CT scanning when compared with physical examination alone, with 98% and 88% detection rates, respectively.[27] The possibility of infection or additional hernias encountered unexpectedly in the operating room make CT imaging a lucrative tool during preoperative consultation.

OPTIONS FOR OPERATIVE REPAIR

Rives-Stoppa Repair

The Rives-Stoppa repair was first described in the 1980s and uses a retrorectus dissection plane. This operation has demonstrated extensive durability with avoidance of subcutaneous flap creation.[6] The operation releases the posterior rectus sheath off the rectus muscles and allows for further mobilization.[6] This is typically accomplished by incising the posterior rectus sheath within 0.5 cm from its medial border and dissecting bluntly toward the semilunar line.[6] As one dissects laterally, it is important to identify the neurovascular bundles running between the internal oblique and transversus abdominis muscles because they can lead to unnecessary morbidity if damaged.[6,15] Mesh is then often placed in a retromuscular fashion, anterior to the posterior fascial plane.[6]

Recurrence rates after Rives-Stoppa repair at midterm and long-term follow-up have been reported to be 3% and 6%, respectively.[15] This operation also maintains the functional and anatomic integrity of the abdominal wall musculature, which is considered crucial to successful abdominal wall reconstruction.[28] However, despite its excellent record, the limited lateral dissection used in this technique limits its applicability.[6] With this said, certain situations are inherently not suited for the Rives-Stoppa repair and include nonmidline ventral hernias lateral to the linea semilunaris, limited amount of retrorectus space needed for mesh placement, and insufficient medial advancement of the posterior rectus sheath and musculature.[6] Because of these limitations, additional operative techniques have been developed.

Posterior Component Separation with Transversus Abdominis Release

The transversus abdominis release has demonstrated utility in repairing complex and nonmidline defects that the Rives-Stoppa repair fails to address. This approach uses a retrorectus dissection plane, similar to the Rives-Stoppa repair with added lateral mobilization and mesh overlap.[6] Near the margin of the semilunar line, usually 0.5 cm medial, the posterior rectus sheath is incised, exposing the underlying transversus abdominis muscle.[6,15] The underlying fascia is then dissected off the muscle plane as far laterally as the psoas muscle if needed.[6,15]

The use of transversus abdominis release provides extensive benefits during

repair. First, it maximizes preservation of abdominal wall blood flow and limits the creation of large skin flaps.[29] It alleviates the tension created by the laterally connecting thoracolumbar fascia, which allows for further medial advancement of the posterior rectus sheath.[15] It also allows for further expansion of the abdominal cavity, improving tension off-loading.[15] These effects are possible because the transversus abdominis muscle extends more medially than the remaining oblique muscles and is essentially the main contributor to intraabdominal pressure, ultimately allowing enhanced tension-free repair.[15] The posterior component separation with transversus abdominis release has consistently shown a recurrence rate less than 10% in numerous studies.[29-31]

Anterior Component Separation

The anterior component separation uses a dissection anterior to the rectus muscles. During the operation, a subcutaneous plane is formed by incising the external oblique fascia, just lateral to the lateral aspect of the rectus muscles.[6,15] Additional dissection to the margin of the anterior axillary line can be performed if tension-free approximation is not attained at first.[6,15] This technique provides for extensive medial mobilization of the abdominal wall musculature while allowing effective midline reconstruction.[6]

Despite exceptional medial coverage, the limiting factor in the use of this approach is the sequelae that follow the creation of skin flaps. Krpata et al[29] found an increased rate of wound morbidity and complication rates when an anterior component separation was performed. Compared with the use of a posterior component separation, the anterior component separation had a significantly higher total complication rate (48.2% vs 25.4%, $p = 0.01$).[29] The authors attributed this finding to the extensive dead space created by the subcutaneous dissection.[29] Furthermore, after mobilization, the subcutaneous tissue is left relatively ischemic, predisposing it to infection and seroma formation.[6,15] This study also observed a trend toward higher rates of recurrence when compared with posterior component separation; however, the difference failed to meet statistical significance (14.3% vs 3.6%, $p = 0.09$).[29]

POSTOPERATIVE CARE

Historically, important aspects of recovery have involved proper airway management, pain control, and nutritional support. However, practices in immediate postoperative care in all surgical fields have vastly changed in the last decade. The use of routine narcotic pain administration and subjective diet advancement is being replaced by standardized regimens tailored to improve and speed recovery.

With present-day quality constraints, cost inflation, and subpar medical accessibility, the use of standardized recovery can have an extensive impact on more than just hernia results. In relation, a study published in 2016 demonstrated significant benefit in the use of a standardized recovery pathway.[32] Between traditional and enhanced recovery protocols, respectively, authors reported significantly shorter times to diet advancement (liquids: 2.7 vs 1.1 days; regular diet: 4.8 vs 3.0 days, $p < 0.001$), return of bowel function (5.2 vs 3.6 days, $p < 0.001$), length of stay (4.0 vs 6.1 days, $p < 0.001$), and reduced 90-day readmission rate (16% vs 4%, $p < 0.001$).[32] This protocol aimed at mitigating the metabolic consequences associated with postsurgical recovery.[32] The authors state that the pathway is based on the key principles of pain management and acceleration of intestinal recovery.[32] Summary recommendations from this study are listed in Table 2.[32]

With the impressive findings seen in recovery, the use of standardization, although promising, may not always be ideal. One of the most critical aspects to manage in nonideal circumstances in the early postoperative course is proper airway management and identifying patients at risk of respiratory failure. Long operative times increase open abdomen exposure, enhancing insensible losses and fluid shifts.[15] Patients undergoing lengthy procedures with extensive surgery or those with a history of severe pulmonary disease are generally admitted to the intensive care unit.[15] One study found respiratory complications to occur in 20% of patients after open component separation surgery.[33] Intubation is therefore advocated when plateau airway pressures increase more than 6 cm H_2O intraoperatively or postoperatively because increased airway pressures represent a 9-fold increased risk in pulmonary complications.[33] The persistent elevation of airway or abdominal pressures may indicate the need for paralysis up to 48 hours.[6,33] If, however, the patient is not critically ill, adequate pain control, chest physiotherapy, and aggressive use of incentive spirometry should be routinely employed.[6,15,33]

Postoperatively, diet and nutritional support should be optimized to ensure adequate healing. Conservative diet advancement is typically employed in patients undergoing complex hernia repair. Overly aggressive diet progression can induce retching and vomiting, which can jeopardize repair and propagate aspiration.[6] As a caveat, nasogastric tube decompression is generally reserved for patients who have intestinal resections, major intestinal manipulation, or prolonged adhesiolysis.[15] At times, a subtle presentation mimicking that of ileus can confound the diagnosis of early postoperative bowel obstruction. It should be noted that more than 90% of early postoperative bowel obstructions are partial and tend to resolve spontaneously.[16] However, any signs or concerns for early bowel obstruction should prompt CT imaging to further evaluate the abdomen.[6] Early reexploration is warranted if findings suggest a completely obstructed or strangulated bowel on workup because of the likelihood of irreversible mechanical obstruction.[6,16]

Additional aspects of postoperative recovery include mobility and drain care. In general, intraoperatively placed subcutaneous drains are removed on the basis of consistency and when output is less than 50 mL/d for 2 consecutive days.[6] Ambulation is encouraged as soon as possible but should be considered on a case-by-case basis.[15] On discharge, patients are given instructions on activity restrictions and should not lift more than 4.5 kg (10 lb) for up to 6 weeks postoperatively.[15] This is advocated to minimize increases in intraabdominal pressure, one of the major factors attributed to hernia recurrences.[15]

Abdominal binders have historically been used in the postoperative period for comfort.[6] Certain advocates for its use believe abdominal binders may actually lessen the risk of seroma formation, improve

postoperative pain control, and enhance postural stability.[34] A study performed in 2014 investigated the effects of abdominal binder use on postoperative recovery after major abdominal surgery.[34] This study showed no significant evidence linking binder use to pulmonary function, seroma formation, or improved postoperative pain control.[34] However, the study did demonstrate significant benefits in psychological distress levels as well as physical functioning and mobilization after postoperative day 5 when binders were used.[34]

CONCLUSION

With the large number of abdominal operations performed each year, the incidence of ventral hernias is on the rise. Open ventral hernia repair remains the primary option for surgeons when faced with complex abdominal wall reconstruction. The advancements in tension-free repair as well as component separation have improved success rates. However, despite improvement, certain aspects of surgical repair have yet to translate to acceptable results.

To improve successful correction rates of complex abdominal defects, emphasis has shifted from surgical technique and toward a multimodal approach involving optimization and identification of suboptimal characteristics. Although the technical experience and procedural method used by the surgeon is of importance, assessing patient-related factors and comorbidities may provide the missing aspect necessary for an ideal operative approach. With enhanced recovery pathways being incorporated into the management of complex abdominal wall defects, it is hoped that these advancements can assist surgeons in greatly improving repair success and patient quality of life. ❖

Table 2. Summary of enhanced recovery after surgery pathway for ventral hernia repair

Phase of care	Pathway component
Preoperative	Weight loss counseling Diabetic control (HbA_{1C} < 8%) Smoking cessation > 4 weeks Obstructive sleep apnea screening Preoperative nutritional shake MRSA screening
Perioperative	Subcutaneous heparin, 5000 U once, with sequential compression devices to lower extremities Oral alvimopan,12 mg once Oral gabapentin, 100-300 mg once First-generation cephalosporin or vancomycin for screen positive for MRSA
Intraoperative	Pain control: • Limit use of narcotics and paralytics • Intraoperative TAP block, 20 mL of liposomal bupivacaine diluted to 200 mL (100 mL per side)
Postoperative	Pain control: • IV hydromorphone PCA: 0.2 mg every 6-10 min, no breakthrough dose; no basal rate; stopped on POD 2 once a clear liquid diet is begun • Oral oxycodone, 5-10 mg every 4 h as needed, started once off IV PCA • Oral acetaminophen, 650 mg, every 6 h, started immediately postoperatively • Oral gabapentin, 100-300 mg 3x daily, started on POD 1 • IV/oral diazepam, 5 mg every 6 h as needed: 2.5-mg dose for patients > age 65 y; hold for patients with obstructive sleep apnea, sedation, or any respiratory compromise • Oral NSAIDs, 600-800 mg orally every 6-8 h as needed, can use IV ketorolac, 15-30 mg every 6 h for up to 72 h; hold for patients with renal dysfunction Intestinal recovery: • No routine nasogastric tube placement • NPO except medications on operative day only • Scheduled diet advancement: POD 1, limited clear liquids (< 250 mL/shift); POD 2, clear liquids ad libitum; POD 3, regular diet • Oral alvimopan, 12 mg twice daily, until discharge or POD 7 Fluids: Fluid conservative strategy: lactated Ringer's at 100 mL/h on operative day; 5% dextrose in half normal saline at 75 mL/h on POD 1; saline lock IVF on POD 2

[a] Source: Majumder et al.[32]

HbA_{1c} = hemoglobin A_{1c}; IV = intravenous; IVF = intravenous fluid; MRSA = methicillin-resistant *Staphylococcus aureus;* NPO = nothing by mouth; NSAID = nonsteroidal anti-inflammatory drug; PCA = patient-controlled analgesia; POD = postoperative day; TAP = transversus abdominis plane.

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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References

1. van Ramshorst GH, Eker HH, Hop WC, Jeekel J, Lange JF. Impact of incisional hernia on health-related quality of life and body image: A prospective cohort study. Am J Surg 2012 Aug;204(2):144-50. DOI: https://doi.org/10.1016/j.amjsurg.2012.01.012.
2. Lowe JB 3rd, Lowe JB, Baty JD, Garza JR. Risk associated with "components separation" for closure of complex abdominal wall defects. Plast Reconstr Surg 2003 Mar;111(3):1276-83. DOI: https://doi.org/10.1097/01.prs.0000047021.36879.fd.
3. Heller L, Chike-Obi C, Xue AS. Abdominal wall reconstruction with mesh and components separation. Semin Plast Surg 2012 Feb;26(1):29-35. DOI: https://doi.org/10.1055/s-0032-1302463.
4. Martindale RG, Deveney CW. Preoperative risk reduction: Strategies to optimize outcomes. Surg Clin North Am 2013 Oct;93(5):1041-55. DOI: https://doi.org/10.1016/j.suc.2013.06.015.
5. Passot G, Villeneuve L, Sabbagh C, et al; Fédération de Recherche en Chirurgie (FRENCH). Definition of giant ventral hernias: Development of standardization through a practice survey. Int J Surg 2016 Apr;28:136-40. DOI: https://doi.org/10.1016/j.ijsu.2016.01.097.
6. Pauli EM, Rosen MJ. Open ventral hernia repair with component separation. Surg Clin North Am 2013 Oct;93(5):1111-33. DOI: https://doi.org/10.1016/j.suc.2013.06.010.
7. Luijendijk RW, Hop WC, van den Tol MP, et al. A comparison of suture repair with mesh repair for incisional hernia. N Engl J Med 2000 Aug 10;343(6):392-8. DOI: https://doi.org/10.1056/NEJM200008103430603.

8. Usher FC, Ochsner J, Tuttle LL Jr. Use of marlex mesh in the repair of incisional hernias. Am Surg 1958 Dec;24(12):967-74.
9. Hawn MT, Snyder CW, Graham LA, Gray SH, Finan KR, Vick CC. Long-term follow-up of technical outcomes for incisional hernia repair. J Am Coll Surg 2010 May;210(5):648-55. DOI: https://doi.org/10.1016/j.jamcollsurg.2009.12.038.
10. Gonzalez R, Rehnke RD, Ramaswamy A, Smith CD, Clarke JM, Ramshaw BJ. Components separation technique and laparoscopic approach: A review of two evolving strategies for ventral hernia repair. Am Surg 2005 Jul;71(7):598-605.
11. Heniford BT, Ramshaw BJ. Laparoscopic ventral hernia repair: A report of 100 consecutive cases. Surg Endosc 2000 May;14(5):419-23. DOI: https://doi.org/10.1007/s004640000179.
12. Earle D, Roth JS, Saber A, et al; SAGES Guidelines Committee. SAGES guidelines for laparoscopic ventral hernia repair. Surg Endosc 2016 Aug;30(8):3163-83. DOI: https://doi.org/10.1007/s00464-016-5072-x.
13. Ramirez OM, Ruas E, Dellon AL. "Components separation" method for closure of abdominal-wall defects: An anatomic and clinical study. Plast Reconstr Surg 1990 Sep;86(3):519-26. DOI: https://doi.org/10.1097/00006534-199009000-00023.
14. Geltzeiler CB, Rotramel A, Wilson C, Deng L, Whiteford MH, Frankhouse J. Prospective study of colorectal enhanced recovery after surgery in a community hospital. JAMA Surg 2014 Sep;149(9):955-61. DOI: https://doi.org/10.1001/jamasurg.2014.675.
15. Rosen MJ. Atlas of abdominal wall reconstruction. Philadelphia, PA: Elsevier Saunders; 2012.
16. Townsend CM Jr, Beauchamp RD, Evers BM, Mattox KL. Sabiston textbook of surgery: The biological basis of modern surgical practice. 19th ed. Philadelphia, PA: Elsevier Saunders; 2012.
17. Holihan JL, Alawadi Z, Martindale RG, et al. Adverse events after ventral hernia repair: The vicious cycle of complications. Am J Coll Surg 2015 Aug;221(2):478-85. DOI: https://doi.org/10.1016/j.jamcollsurg.2015.04.026.
18. Sauerland S, Walgenbach M, Habermalz B, Seiler CM, Miserez M. Laparoscopic versus open surgical techniques for ventral or incisional hernia repair. Cochrane Database Syst Rev 2011 Mar 16;(3):CD007781. DOI: https://doi.org/10.1002/14651858.CD007781.pub2.
19. Santora TA, Roslyn JJ. Incisional hernia. Surg Clin North Am 1993 Jun;73(3):557-70. DOI: https://doi.org/10.1016/s0039-6109(16)46037-8.
20. Dunne JR, Malone DL, Tracy JK, Napolitano LM. Abdominal wall hernias: Risk factors for infection and resource utilization. J Surg Res 2003 May 1;111(1):78-84. DOI: https://doi.org/10.1016/s0022-4804(03)00077-5.
21. Breuing K, Butler CE, Ferzoco S, et al; Ventral Hernia Working Group. Incisional ventral hernias: Review of the literature and recommendations regarding the grading and technique of repair. Surgery 2010 Sep;148(3):544-58. DOI: https://doi.org/10.1016/j.surg.2010.01.008.
22. Lindström D, Sadr Azodi O, Wladis A, et al. Effects of a perioperative smoking cessation intervention on postoperative complications: A randomized trial. Ann Surg 2008 Nov;248(5):739-45. DOI: https://doi.org/10.1097/sla.0b013e3181889d0d.
23. Gibbs J, Cull W, Henderson W, Daley J, Hur K, Khuri SF. Preoperative serum albumin level as a predictor of operative mortality and morbidity: Results from the National VA Surgical Risk Study. Arch Surg 1999 Jan;134(1):36-42. DOI: https://doi.org/10.1001/archsurg.134.1.36.
24. Daley J, Khuri SF, Henderson W, et al. Risk adjustment of the postoperative morbidity rate for the comparative assessment of the quality of surgical care: Results of the National Veterans Affairs Surgical Risk Study. J Am Coll Surg 1997 Oct;185(4):328-40. DOI: https://doi.org/10.1016/s1072-7515(97)00090-2.
25. Regner JL, Mrdutt MM, Munoz-Maldonado Y. Tailoring surgical approach for elective ventral hernia repair based on obesity and National Surgical Quality Improvement Program outcomes. Am J Surg 2015 Dec;210(6):1024-9. DOI: https://doi.org/10.1016/j.amjsurg.2015.08.001.
26. Saber AA, Rao AJ, Itawi EA, Elgamal MH, Martinez RL. Occult ventral hernia defects: A common finding during laparoscopic ventral hernia repair. Am J Surg 2008 Apr;195(4):471-3. DOI: https://doi.org/10.1016/j.amjsurg.2007.04.013.
27. Gutiérrez de la Peña C, Vargas Romero J, Diéguez García JA. The value of CT diagnosis of hernia recurrence after prosthetic repair of ventral incisional hernias. Eur Radiol 2001;11(7):1161-4. DOI: https://doi.org/10.1007/s003300000743.
28. Nau P, Clark CJ, Fisher M, et al. Modified Rives-Stoppa repair for abdominal incisional hernias. Health 2010;2(2):162-9. DOI: https://doi.org/10.4236/health.2010.22024.
29. Krpata DM, Blatnik JA, Novitsky YW, Rosen MJ. Posterior and open anterior components separations: A comparative analysis. Am J Surg 2012 Mar;203(3):318-22. DOI: https://doi.org/10.1016/j.amjsurg.2011.10.009.
30. Novitsky YW, Elliott HL, Orenstein SB, Rosen MJ. Transversus abdominis muscle release: A novel approach to posterior component separation during complex abdominal wall reconstruction. Am J Surg 2012 Nov;204(5):709-16. DOI: https://doi.org/10.1016/j.amjsurg.2012.02.008.
31. Iqbal CW, Pham TH, Joseph A, Mai J, Thompson GB, Sarr MG. Long-term outcome of 254 complex incisional hernia repairs using the modified Rives-Stoppa technique. World J Surg 2007 Dec;31(12):2398-404. DOI: https://doi.org/10.1007/s00268-007-9260-7.
32. Majumder A, Fayezizadeh M, Neupane R, Elliott HL, Novitsky YW. Benefits of multimodal enhanced recovery pathway in patients undergoing open ventral hernia repair. J Am Coll Surg 2016 Jun;222(6):1106-15. DOI: https://doi.org/10.1016/j.jamcollsurg.2016.02.015.
33. Blatnik JA, Krpata DM, Pesa NL, et al. Predicting severe postoperative respiratory complications following abdominal wall reconstruction. Plast Reconstr Surg 2012 Oct;130(4):836-41. DOI: https://doi.org/10.1097/prs.0b013e318262f160.
34. Rothman JP, Gunnarsson U, Bisgaard T. Abdominal binders may reduce pain and improve physical function after major abdominal surgery—a systematic review. Dan Med J 2014 Nov 6;61(11):A4941.

Multiplicity of Hot Irons

If practitioners, since the time of Albucasis, had been contented with his doctrine, and never had ventured to think for themselves, surgery had not been what it now is, and its great merit would still have consisted in the multiplicity of its hot irons.

— Percivall Pott, 1714-1788, English surgeon, one of the founders of orthopedics

Slot Canyon
photograph

Tyler Kern, MD

This photograph was taken in Antelope Canyon in AZ. Antelope Canyon consists of a series of slot canyons believed to be created by the erosion of sandstone from flash floods. Walking through these canyons is a surreal experience.

Dr Kern is a Urology Resident at the Los Angeles Medical Center in CA. He has pursued his passion for nature and wildlife photography throughout his life and hopes to inspire others to get outside, explore, and thrive.

REVIEW ARTICLE

Hip Osteoarthritis: A Primer

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ABSTRACT

The objective of this article is to deliver a concise up-to-date review on hip osteoarthritis. We describe the epidemiology (disease distribution), etiologies (associated risk factors), symptoms, diagnosis and classification, and treatment options for hip osteoarthritis. A quiz serves to assist readers in their understanding of the presented material.

INTRODUCTION

Please see the Sidebar: Quiz to Assess Knowledge of Hip Osteoarthritis (True/False/Depends) with Answers.

Osteoarthritis (OA), often referred to as "wear-and-tear" arthritis, age-related arthritis, or degenerative joint disease, is the most common form of joint disorder in the US, and it is estimated that more than 27 million Americans are affected.[1] As a degenerative disorder, OA can involve any joint, and it primarily affects the articular cartilage and surrounding tissues.[2] OA can be broadly classified into primary and secondary types. In primary OA, the disease is of idiopathic origin (no known cause) and usually affects multiple joints in a relatively elderly population. Secondary OA usually is a monoarticular condition and develops as a result of a defined disorder affecting the joint articular surface (eg, trauma).[3] This review will focus on primary hip OA with a discussion of secondary hip OA.

The hip joint is one of the body's largest weight-bearing joints, only secondary to the knee joint, and is commonly affected by OA.[4] The current accepted understanding of hip OA is that although articular cartilage is mainly affected, the entire joint also is affected. The OA process involves progressive loss of articular cartilage, subchondral cysts, osteophyte formation, periarticular ligamentous laxity, muscle weakness, and possible synovial inflammation.[2] There is a growing consensus that OA is not the result of a singular process affecting the joints but rather results from a number of distinct conditions, each associated with unique etiologic factors and possible treatments that share a common final pathway.[5] The effects of OA on the large joints of the lower extremities, including the hips, can result in reduced mobility and marked physical impairment that can lead to loss of independence and to increased use of health care services. As such, OA may have a profound effect on activities of daily living and lead to substantial disability and dependency in walking, stair climbing, and rising from a seated position. Several risk factors are linked to the development of hip OA including age, gender, genetics, obesity, and local joint risk factors. However, the exact primary hip OA etiology remains unknown,[6-8] and a universal protocol is lacking for its diagnosis and treatment. In this report, we describe hip OA epidemiology (disease distribution), etiologies (associated risk factors), symptoms, diagnosis and classification, and treatment options.

PREVALENCE

The difference between the clinical and radiographic prevalence of hip OA remains unclear; however, most epidemiologic studies of hip OA involve radiographic parameters to establish disease prevalence.[9,10] Research suggests that hip OA is epidemiologically distinguishable from OA affecting other joints.[11] For example, only a small percentage of patients who underwent total hip arthroplasty (THA) to address primary hip OA required a total knee arthroplasty (3%-7%) and vice versa.[12] In a prominent US-based population study,[13] prevalence of symptomatic hip OA was reported at 9.2% among adults age 45 years and older, with 27% showing radiologic signs of disease; prevalence was slightly higher among women. A systematic review of radiographic hip OA prevalence demonstrated an increase in mean prevalence with advancing age for both men and women.[10] Men have a higher prevalence of hip OA before age 50, whereas women have a higher prevalence thereafter.[14] Caucasian populations also have a higher hip OA prevalence that ranges between 3% and 6% as compared with 1% or less in Asians, blacks, East Indians, or native Americans,[15,16] suggesting a genetic predisposition. According to the Centers for Disease Control and Prevention, lifetime risk for symptomatic hip OA is 18.5% for men and 28.6% for women.[5]

ETIOLOGIES AND RISK FACTORS

OA is a chronic disorder affecting synovial joints. Although sometimes referred to as "degenerative joint disease," this term is a misnomer. The degenerative process manifested by progressive loss of articular cartilage is accompanied by a reparative process with reactive bone formation, osteophyte growth, and remodelling.[5] The dynamic process of destruction and repair determines the final disease picture. OA is not primarily an inflammatory process, and synovial inflammation, when found, usually is not accompanied by a systemic rise in inflammatory markers. Primary OA (also termed *idiopathic*), generally is a diagnosis of exclusion and is believed to account for

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the majority of all hip OA.[10] Aging is assumed to contribute to the development of hip OA mainly because of the inability to specifically define an underlying anatomic abnormality or specific disease process leading to the degenerative process.

Genetic factors also may play a role in hip OA, possibly by the inheritance of an anatomical abnormality such as acetabular dysplasia. A sibling study demonstrated a higher risk for hip OA among those who had an affected sibling, as demonstrated by structural changes noted on hip radiographs.[17] Secondary (from a known cause) OA results from conditions that change the cartilage environment. These conditions include trauma, congenital or developmental joint abnormalities, metabolic defects, infection, endocrine disease, neuropathic conditions, and disorders that affect the normal structure and function of hyaline cartilage. Secondary hip OA occurs when a condition results in an anatomic abnormality, which can be relatively subtle, that predisposes the hip to mechanical factors that lead to degenerative changes.[5]

Risk factors associated with hip OA can be divided into local risk factors that act on the joint level and more general risk factors.

Local Risk Factors

Joint Dysplasia

Conditions such as acetabular dysplasia and other developmental disorders leading to structural joint abnormalities are believed to play a major role in development of hip OA later in life.[5] Mild dysplastic changes often can go unnoticed and predispose to hip OA.

Trauma

Fractures involving the joint articular surface can lead to secondary posttraumatic arthritis. It is unclear whether isolated labral tears contribute to hip OA.[18,19]

Quiz to Assess Knowledge of Hip Osteoarthritis (True/False/Depends) with Answers:

1. **Aging and other risk factors contribute to hip osteoarthritis (OA).**
   Answer: *True.* However, not all hip OA is related to the aging process. Young people can develop secondary hip OA from trauma, congenital dysplasia and developmental disorders, infection, metabolic conditions, and other causes.
2. **Patients should wait as long as possible before undergoing total hip arthroplasty (THA).**
   Answer: *False.* Patients who fail nonsurgical treatment should not delay undergoing THA because delay correlates with worse clinical outcomes even after surgery is performed.
3. **Hip OA primarily is a disease of cartilage.**
   Answer: *True.* Progressive loss of articular cartilage often is accompanied by a reparative process that involves sclerosis and osteophyte formation.
4. **Joint stiffness in hip OA may not improve for several hours, or it may last throughout an entire day.**
   Answer: False. Morning stiffness helps to differentiate OA from rheumatoid arthritis. In rheumatoid arthritis, joint stiffness may not improve for several hours or it may last throughout the entire day. In OA, stiffness typically lasts for only a few minutes and subsides in 30 minutes or less. Movement and physical activity that loosens the joint generally improve OA.
5. **Certain radiographic parameter measurements as described by Kellgren and Lawrence[1] can help clinicians assess hip OA severity.**
   Answer: *False.* Currently, there is no gold standard with which to measure and report the prevalence of radiographic primary hip OA. The Kellgren and Lawrence method of diagnosis is the most common method with which to measure radiographic OA severity. A limitation associated with this system is its reliance on the presence of osteophytes, which correlate poorly with hip pain.
6. **Studies demonstrate that viscosupplementation injections slow OA symptom progression.**
   Answer: *False.* Most clinical studies show that these treatments are no more effective than a placebo and are not recommended as hip OA treatment.
7. **Nonsteroidal anti-inflammatory drugs (NSAIDs) are effective first-line hip OA treatments.**
   Answer: *True.* Both topical NSAIDs (such as capsaicin) and oral NSAIDs may be considered as an adjunct for symptomatic pain relief in addition to core treatments for patients with OA. Diclofenac and etoricoxib are the most efficacious NSAIDs for pain relief in hip OA, producing a moderate to large effect size. However, NSAIDs should be used with caution to avoid potential complications associated with long-term use.

1. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957 Dec;16(4):494-502. DOI: https://doi.org/10.1136/ard.16.4.494.

General Risk Factors

Age

The Research on Osteoarthritis/Osteoporosis Against Disability study,[20] which prospectively followed 745 Japanese men and 1470 Japanese women for 3 years, revealed that age greater than 60 years is an important risk factor for radiographic OA. However, it is also clear that aging of joint tissues and OA development are distinct processes. Chondrocalcinosis, an age-related matrix change observed in radiographs of arthritic joints, may contribute to OA by stimulating production of proinflammatory mediators.[20]

Sex

Hip OA prevalence is higher among men younger than age 50 years, whereas women have the highest prevalence after age 50 years.[21] This finding may be attributable to postmenopausal changes[21,22] and is supported by observations from multiple studies that report protective effects of estrogen replacement therapy and hip OA.[21]

Obesity

Excess body weight is a risk factor for OA not only in weight-bearing joints, but also in the hand.[23,24] Excess weight produces increased load on the joint, but there is growing evidence for a metabolic contribution to OA as well.[25]

Genetics

Several studies suggest that genetics have an important role in the etiopathogenesis of hip OA, and a twin study reported on a 60% risk for hip OA attributable to genetic factors.[26] Another study demonstrated that having a first-, second-, or third-degree relative who undergoes THA for hip OA increases a person's risk for having the procedure.[27]

Occupation

Certain occupations involving heavy manual work and high-impact sports activities are linked to OA in the hip and other joints later in life.[28,29] Repetitive stress and biomechanical overload, especially in the setting of a preexisting hip joint anatomical abnormality, are likely causes.[30] Farmers are particularly prone to hip OA.[31] However, no credible evidence demonstrates that exercise and physical activity are directly related to hip OA in the general population.

SYMPTOMS

The most common symptom of hip OA is pain around the hip joint (generally located in the groin area). The pain can develop slowly and worsen over time (most common) or pain can have a sudden onset. Pain and stiffness can develop in the morning or after sitting or resting. Stiffness typically lasts for only a few minutes and subsides over 30 or fewer minutes. Movement and activity that loosen the joint generally improve OA symptoms. Later in the progression of the disease, painful symptoms may occur more frequently, including during rest or at night (see Sidebar: Common Hip Osteoarthritis Symptoms).

DIAGNOSIS AND CLASSIFICATION

Hip OA often can be diagnosed upon clinical presentation alone, although imaging investigations can be useful to both confirm a diagnosis and to monitor disease progression (Figure 1A-C).[5] After taking a careful medical history that includes a review of associated hip OA risk factors, a clinician should perform a focused clinical examination of the affected hip. The examination should include an inspection and comparison of leg length between the affected and opposite sides, an evaluation of a possible joint fixed position denoting deformity, and a gait assessment. These steps should be followed by palpation of regional bony prominences and tendons to assess for tenderness and/or injuries. A neurovascular assessment of both lower extremities and range of motion of the affected joint should be performed with a comparison to the contralateral side. Additional tests may provide more information regarding underlying conditions that lead to hip OA.

Common Hip Osteoarthritis Symptoms

- Pain and stiffness that is worse in the morning or after sitting or resting
- Pain in the groin or thigh that radiates into the buttocks or knee
- Pain that flares with vigorous activity
- Stiffness in the hip joint that makes it difficult to walk or bend
- "Locking" or "sticking" of the joint and a grinding noise (crepitus) during movement caused by loose cartilage fragments and other tissues interfering with smooth hip motion
- Decreased range of motion in the hip that affects the ability to walk and may cause a limp

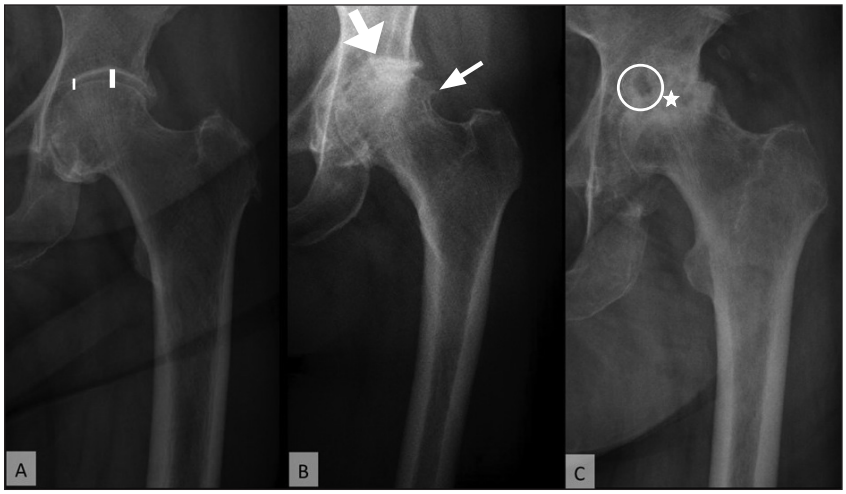

Figure 1. Anteroposterior hip radiograph. A. Narrowing of the superomedial joint space is seen in the region marked by white lines. B. Bone-on-bone osteoarthritis (thicker arrow) with osteophyte formation (thinner arrow). C. End-stage osteoarthritis with femoral head deformation (star) and cyst formation (circle).

In 1957, Kellgren and Lawrence[32] described a grading scale for the radiologic assessment of OA that remains the most widely used classification system; however, this scale is not specific for hip OA grading. In 1963, Kellgren[33,34] described four grades of hip OA based on the degree of joint space narrowing, osteophyte formation, arthritic changes affecting the bone margins, and gross deformity as the following: Grade 1, doubtful OA with possible joint space narrowing medially and subtle osteophyte formation around the femoral head. Grade 2, mild OA with definite joint space narrowing inferiorly with definite osteophyte formation and slight subchondral sclerosis. Grade 3, moderate OA with marked narrowing of the joint space, small osteophytes, some sclerosis and cyst formation, and deformity of the femoral head and acetabulum. Grade 4, obliterated joint space with features seen in grades 1 to 3, large osteophytes, and gross deformity of the femoral head and acetabulum. Several other radiographic classification systems exist such as Croft's grade,[35] minimal joint space,[35] and the Tönnis classification.[36]

Other imaging studies such as computerized tomography and magnetic resonance imaging typically are not required for diagnosis and usually are reserved for the identification of secondary causes or presurgical planning. Blood tests may be ordered to help confirm a diagnosis and to rule out other inflammatory conditions such as rheumatoid arthritis, especially if joint symptoms are associated with morning stiffness and synovial inflammatory changes. Complete blood count, erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, and cyclic citrullinated peptide antibody tests are among the most common laboratory studies ordered; when testing for hip OA, however, these test results are expected to fall within defined limits. The American College of Rheumatology has established clinical criteria and radiologic parameters that are commonly used for hip OA diagnosis in clinical practice.

An important contrast between patient symptoms and radiographic findings may be observed. Patients with marked radiographic changes may not necessarily demonstrate severe correlating clinical symptoms and vice versa. Some patients with high-grade radiographic hip OA may be asymptomatic.[37]

TREATMENT OPTIONS

Nonpharmacologic Treatments

Exercise

An exercise program that does not involve high-impact activities usually is advocated and is associated with pain reduction.[38] Aquatic exercises also improve function.[38,39] Exercises that strengthen and stretch the muscles around the hip can support the hip joint and ease hip strain. Certain activities and exercises

Common Activities that Exacerbate Osteoarthritis Hip Pain

- Prolonged inactivity
- Abduction and external and internal rotation
- Bending
- Getting into and out of a car
- Prolonged physical activity

that can aggravate the hip joint should be recognized and avoided (see Sidebar: Common Activities that Exacerbate Osteoarthritis Hip Pain). Activities that necessitate twisting at the hip such as golf or are high impact such as jogging should be replaced with activities that exert less stress on the hip joint such as gentle yoga, cycling, or swimming. Manipulation and stretching should be considered as adjuncts to core treatments, particularly for hip OA.[37]

Physical Therapy

Physical therapy is the mainstay of treatment in mild and early hip OA and is aimed at strengthening hip muscles and maintaining joint mobility. Physical therapy that is provided during the later stages of hip OA may provide little or no benefit.[40]

Weight Reduction

Gaining 10 pounds can exert an extra 60 pounds of pressure upon a hip with each step.[41] Unloading the joint through weight loss can slow cartilage loss and decrease joint impact. Weight recommendations that address hip OA are based upon findings from many cohort studies.[42-45] An individualized exercise program combined with effective behavioral strategies aimed at weight loss may be most beneficial in reducing pain for overweight patients.

Transcutaneous Electrical Nerve Stimulation

Transcutaneous electrical nerve stimulation should be considered as an adjunct to core treatments for pain relief for patients with hip OA.[46]

Temperature Extremes

Hot and cold treatments sometimes are effective pain relief modalities. Heat treatments enhance circulation and soothe stiff joints and tired muscles. Cold treatments slow circulation, reduce swelling, and alleviate acute pain. A patient may need to experiment and/or alternate use of heat and cold therapies to determine which is most effective.

Proper Footwear and Bracing/Joint Supports/Insoles

Patients should be educated about appropriate footwear that features shock-absorbing properties to address lower limb OA.[46] Patients with OA who have biomechanical joint pain or instability may be considered for assessment of bracing/joint supports/insoles as an adjunct treatment.[46] Bracing may have a role in modifying biomechanics to treat hip OA, although more research in this area is necessary.[5]

Assistive Devices

Walking sticks, tap turners, canes, and other devices should be considered as adjuncts to core treatments for people with OA who have specific problems with activities of daily living. If needed, patients can be referred for further evaluation and treatment from occupational and physical therapists and/or specialized disability device and equipment companies.[46]

Acupuncture is not recommended as OA treatment. Patient education can help to incorporate multiple approaches into hip OA treatment and minimize risk factors.

Pharmacologic Treatments

Acetaminophen and Nonsteroidal Anti-Inflammatory Drugs

Acetaminophen typically is recommended as a first-line medication for OA.[47] However, the role of acetaminophen for short-term relief of hip OA pain remains equivocal.[47] Topical Nonsteroidal anti-inflammatory drugs (NSAIDs) (such as capsaicin) may be considered as an adjunct therapy for pain in addition to core treatments. Acetaminophen and topical NSAIDs should be considered ahead of oral NSAIDs, cyclooxygenase 2 inhibitors, or opioids.[46] Topical capsaicin should be considered as an adjunct to core treatments for knee or hand OA but has limited use in hip OA because of hip joint depth.[46] If acetaminophen is insufficient for pain relief, NSAIDs may be more efficacious.[45] Diclofenac and etoricoxib are the most efficacious NSAIDs for pain relief in hip OA, producing moderate to large effects.[46] However, NSAIDs should be used with caution to avoid potential complications such as gastrointestinal tract bleeding and adverse cardiovascular events associated with long-term use.[46,47] If acetaminophen and/or NSAIDs provide insufficient pain relief, opioid analgesics may be considered. Opioid medications, however, are not routinely used because of concerns regarding their side effects and long-term addiction potential.[48] Risks and benefits should be considered, particularly for older patients.[46]

Rubefacients

Topical rubefacients should not be used to treat OA.[46]

Glucosamine/Chondroitin

Use of glucosamine or chondroitin products for OA treatment is not recommended.[46]

Intra-Articular Injections

Corticosteroids; hyaluronic acids; and, relatively recently, platelet-rich plasma injections, are the most common modalities to treat pain associated with hip OA. Corticosteroids offer short-term pain relief,[47] and guidelines recommend their use as an adjuvant to other nonsurgical treatment modalities.[45] Although the literature in this area is scarce and data are weak, recent evidence suggests that caution should be exercised when using multiple intra-articular steroid hip injections before THA because multiple injections have been associated with a significantly higher risk for prosthetic joint infection than a single injection administered before THA.[44,49,50] Clinical trials do not provide strong support for the clinical use and value of hyaluronic acid injections.[46,47] The use of platelet-rich plasma remains under investigation in clinical trials, and data available from small studies do not provide substantial evidence for a clear clinical role.[5]

Surgical Treatments

Hip Arthroscopy

Studies on the use of arthroscopy in hip OA are not high quality. Arthroscopy, which primarily is performed during early OA stages, provides temporary relief and is associated with a high conversion rate to THA (9.5%-50%).[51]

Total Hip Arthroplasty

THA is today's surgical modality for patients with intractable pain, for those who have failed nonsurgical treatment, and for those with severe functional impairment. Approximately 1 million THA procedures are performed globally each year for patients with advanced hip OA.[52] This procedure repeatedly demonstrates cost-effectiveness in clinical trials.[53] Hip implant longevity has

been demonstrated, with as many as 95% of prostheses remaining functional at 10 years, which is consistent in certain populations where the patient has good overall general physical health, ability to exercise, remains active and maintains a good weight for which more than 80% of prostheses can remain functional at 25 years.[53-55] Primary care providers should advise symptomatic patients who fail nonsurgical treatment to avoid waiting unnecessarily to undergo THA because evidence demonstrates that prolonged delays correlate with worse clinical outcomes after THA.[53] Progressive pain, disability, and functional impairment can cause further unnecessary damage to tissues and joints that affect the biomechanical environment in other joints. Interference with usual activities of daily living can be unnecessarily affected; this can be especially problematic for younger patients who work and are more socially and physically active.

Hip Resurfacing

Although originally developed as a substitute for THA for younger patients who failed nonsurgical treatment, current evidence indicates that hip resurfacing is suitable for a very specific subset of patients, usually young active men with large femoral heads, as an alternative to THA.[55-57]

CONCLUSION

OA is a chronic disorder affecting synovial joints and a leading cause of disability in the US and worldwide. Current thought is that hip OA results from a number of distinct conditions, each associated with unique etiologic factors and possible treatments that share a common final pathway. The most common symptom of hip OA is pain around the hip joint (generally located in the groin area). Most of the time, the pain develops slowly and worsens over time, or pain can have a sudden onset. Aging and genetic factors are important contributing causes of hip OA. The European League against Rheumatism 2005 Recommendations for the Management of Hip Osteoarthritis advocate a multidisciplinary approach for the management of hip OA (see Sidebar: European League against Rheumatism 2005 Recommendations for the Management of Hip Osteoarthritis) Nonpharmacologic (low impact exercises, weight reduction, and adjunct therapies), pharmacologic (mainly acetaminophen and topical NSAID medication) and surgical options (hip arthroscopy in early OA, total hip arthroplasty and hip resurfacing in advanced OA) may be used in the treatment of hip OA. It is important for clinicians to avoid unnecessary delay in referring patients with advanced hip OA for surgical consideration appropriately to prevent worse clinical outcomes after THA. ❖

European League against Rheumatism 2005 Recommendations for the Management of Hip Osteoarthritis

The European League against Rheumatism published comprehensive recommendations in 2005 for the management of hip osteoarthritis (OA).[1] The group adopted a multidisciplinary approach (involving rheumatologists, orthopedic surgeons, and an epidemiologist) and represented 14 European countries proposing evidence-based treatment interventions for the treatment of hip OA. Powered by an extensive literature review, experts proposed key hip OA recommendations:

1. The best approach to hip OA treatment is to combine pharmacologic and nonpharmacologic (physical therapy and activity modification) modalities.
2. The treatment plan should involve managing risk factors, such as weight loss for obesity, and should be tailored to patient needs and expectations.
3. Acetaminophen is the oral analgesic of first choice for mild to moderate symptoms and long-term pain control. Nonsteroidal anti-inflammatory drugs may be added or substituted for patients with severe OA who do not respond to acetaminophen. Opioid analgesics are an alternative if nonsteroidal anti-inflammatory drugs are ineffective or poorly tolerated.
4. Symptomatic slow-acting drugs for OA such as glucosamine sulfate, chondroitin sulfate, and others have no or limited clinical value in managing hip OA.
5. For patients with acute flare-ups who fail medical management, intra-articular corticosteroid injections may be an option. However, evidence supporting their efficacy in hip OA is lacking.
6. Joint preservation surgery may be considered for patients with conditions such as hip dysplasia and deformities who are not yet candidates for total hip arthroplasty.
7. Total hip arthroplasty is an effective treatment for patients with refractory pain and symptoms and radiological evidence of hip OA.

1. Zhang W, Doherty M, Arden N, et al. EULAR evidence based recommendations for the management of hip osteoarthritis: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2005;64:669–81. DOI: https://doi.org/10.1136/ard.2004.028886.

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References

1. Barbour KE, Helmick CG, Boring M, Brady TJ. Vital signs: Prevalence of doctor-diagnosed arthritis and arthritis-attributable activity limitation—United States, 2013-2015. MMWR Morb Mortal Wkly Rep 2017 Mar 10;66(9):246-53. DOI: https://doi.org/10.15585/mmwr.mm6609e1.
2. Hutton CW. Osteoarthritis: The cause not result of joint failure? Ann Rheum Dis 1989 Nov;48(11):958-61. DOI: https://doi.org/10.1136/ard.48.11.958.
3. Aronson J. Osteoarthritis of the young adult hip: Etiology and treatment. Instr Course Lect 1986;35:119-28.
4. Zhang Y, Jordan JM. Epidemiology of osteoarthritis. Clin Geriatr Med 2010 Aug;26(3):355-69. DOI: https://doi.org/10.1016/j.cger.2010.03.001. Erratum in: Clin Geriatr Med 2013 May;29(2):ix. DOI: https://doi.org/10.1016/j.cger.2013.01.013.
5. Murphy NJ, Eyles JP, Hunter DJ. Hip osteoarthritis: Etiopathogenesis and implications for management. Adv Ther 2016 Nov;33(11):1921-46. DOI: https://doi.org/10.1007/s12325-016-0409-3.
6. Ganz R, Leunig M, Leunig-Ganz K, Harris WH. The etiology of osteoarthritis of the hip: An integrated mechanical concept. Clin Orthop Relat Res 2008 Feb;466(2):264-72. DOI: https://doi.org/10.1007/s11999-007-0060-z.
7. Harris WH. Etiology of osteoarthritis of the hip. Clin Orthop Relat Res 1986 Dec;(213):20-33. DOI: https://doi.org/10.1097/00003086-198612000-00004.
8. Murray RO. The aetiology of primary osteoarthritis of the hip. Br J Radiol 1965 Nov;38(455):810-24. DOI: https://doi.org/10.1259/0007-1285-38-455-810.
9. Frankel S, Eachus J, Pearson N, et al. Population requirement for primary hip-replacement surgery: A cross-sectional study. Lancet 1999 Apr 17;353(9161):1304-9. DOI: https://doi.org/10.1016/S0140-6736(98)06451-4.
10. Dagenais S, Garbedian S, Wai EK. Systematic review of the prevalence of radiographic primary

hip osteoarthritis. Clin Orthop Relat Res 2009 Mar;467(3):623-37. DOI: https://doi.org/10.1007/s11999-008-0625-5.

11. Cushnaghan J, Dieppe P. Study of 500 patients with limb joint osteoarthritis. I. Analysis by age, sex, and distribution of symptomatic joint sites. Ann Rheum Dis 1991 Jan;50(1):8-13. DOI: https://doi.org/10.1136/ard.50.1.8.
12. Shao Y, Zhang C, Charron KD, Macdonald SJ, McCalden RW, Bourne RB. The fate of the remaining knee(s) or hip(s) in osteoarthritic patients undergoing a primary TKA or THA. J Arthroplasty 2013 Dec;28(10):1842-5. DOI: https://doi.org/10.1016/j.arth.2012.10.008.
13. Jordan, J, Helmick C, Renner J, Luta G. Prevalence of hip symptoms and radiographic symptomatic hip osteoarthritis in African-Americans and Caucasians: The Johnston County Osteoarthritis Project. J Rheumatol 2009 Apr; 36(4):809-15.
14. Felson DT. Preventing knee and hip osteoarthritis. Bull Rheum Dis 1998 Nov;47(7):1-4.
15. Lawrence JS, Sebo M. The geography of osteoarthritis. In: Nuki G, editor. The aetiopathogenesis of osteoarthrosis. London, UK: Pitman; 1980 Apr. p 155-83.
16. Mukhopadhaya B, Barooah B. Osteoarthritis of hip in Indians an anatomical and clinical study. Indian Journal of Orthopaedics 1967;1(1):55-62.
17. Lanyon P, Muir K, Doherty S, Doherty M. Assessment of a genetic contribution to osteoarthritis of the hip: Sibling study. BMJ 2000 Nov 11;321(7270):1179-83. DOI: https://doi.org/10.1136/bmj.321.7270.1179.
18. Neumann G, Mendicuti AD, Zou KH, et al. Prevalence of labral tears and cartilage loss in patients with mechanical symptoms of the hip: Evaluation using MR arthrography. Osteoarthritis Cartilage 2007 Aug;15(8):909-17. DOI: https://doi.org/10.1016/j.joca.2007.02.002.
19. McCarthy JC, Busconi B. The role of hip arthroscopy in the diagnosis and treatment of hip disease. Can J Surg 1995 Feb;38 Suppl 1:S13-7.
20. Muraki S, Akune T, Oka H, et al. Incidence and risk factors for radiographic knee osteoarthritis and knee pain in Japanese men and women: A longitudinal population-based cohort study. Arthritis Rheum 2012 May;64(5):1447-56. DOI: https://doi.org/10.1002/art.33508.
21. Felson DT. Epidemiology of hip and knee osteoarthritis. Epidemiol Rev 1988;10:1-28. DOI: https://doi.org/10.1093/oxfordjournals.epirev.a036019.
22. Andrianakos AA, Kontelis LK, Karamitsos DG, et al; ESORDIG Study Group. Prevalence of symptomatic knee, hand, and hip osteoarthritis in Greece. The ESORDIG study. J Rheumatol 2006 Dec;33(12):2507-13.
23. Oliveria SA, Felson DT, Cirillo PA, Reed JI, Walker AM. Body weight, body mass index, and incident symptomatic osteoarthritis of the hand, hip, and knee. Epidemiology 1999 Mar;10(2):161-6. DOI: https://doi.org/10.1097/00001648-199903000-00013.
24. Johnson VL, Hunter DJ. The epidemiology of osteoarthritis. Best Pract Res Clin Rheumatol 2014 Feb;28(1):5-15. DOI: https://doi.org/10.1016/j.berh.2014.01.004.
25. Sellam J, Berenbaum F. Is osteoarthritis a metabolic disease? Joint Bone Spine 2013 Dec;80(6):568-73. DOI: https://doi.org/10.1016/j.jbspin.2013.09.007.
26. MacGregor AJ, Antoniades L, Matson M, Andrew T, Spector TD. The genetic contribution to radiographic hip osteoarthritis in women: Results of a classic twin study. Arthritis Rheum 2000 Nov;43(11):2410-6. DOI: https://doi.org/10.1002/1529-0131(200011)43:11<2410::AID-ANR6>3.0.CO;2-E.
27. Pelt CE, Erickson JA, Peters CL, Anderson MB, Cannon-Albright L. A heritable predisposition to osteoarthritis of the hip. J Arthroplasty 2015 Sep;30(9 Suppl):125-9. DOI: https://doi.org/10.1016/j.arth.2015.01.062.
28. Harris P, Hart D, Jawad S. Risks of osteoarthritis associated with running: A radiological survey of ex-athletes. Arthritis Rheum 1994.
29. Kujala UM, Kaprio J, Sarna S. Osteoarthritis of weight bearing joints of lower limbs in former élite male athletes. BMJ 1994 Jan 22;308(6923):231-4. DOI: https://doi.org/10.1136/bmj.308.6923.231. Erratum in: BMJ 1994 Mar 26;308(6932):819. DOI: https://doi.org/10.1136/bmj.308.6932.819.
30. Sulsky SI, Carlton L, Bochmann F, et al. Epidemiological evidence for work load as a risk factor for osteoarthritis of the hip: A systematic review. PLoS One 2012;7(2):e31521. DOI: https://doi.org/10.1371/journal.pone.0031521.
31. Harris EC, Coggon D. Hip osteoarthritis and work. Best Pract Res Clin Rheumatol 2015 Jun;29(3):462-82. DOI: https://doi.org/10.1016/j.berh.2015.04.015.
32. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957 Dec;16:494-502. DOI: https://doi.org/10.1136/ard.16.4.494.
33. Kellgren, J. Atlas of standard radiographs in arthritis. In: The Epidemiology of Chronic Rheumatism vol. 2. Oxford: Blackwell Scientific; 1963.
34. Atlas of standard radiographs of arthritis. Oxford, UK: Blackwell Scientific; 1963.
35. Croft P, Cooper C, Wickham C, Coggon D. Defining osteoarthritis of the hip for epidemiologic studies. Am J Epidemiol 1990 Sep;132(3):514-22. DOI: https://doi.org/10.1093/oxfordjournals.aje.a115687.
36. Tönnis D. Congenital dysplasia and dislocation of the hip in children and adults. New York, NY: Springer-Verlag; 1987 Feb.
37. Pereira D, Peleteiro B, Araújo J, Branco J, Santos RA, Ramos E. The effect of osteoarthritis definition on prevalence and incidence estimates: A systematic review. Osteoarthritis Cartilage 2011 Nov;19(11):1270-85. DOI: https://doi.org/10.1016/j.joca.2011.08.009.
38. Fransen M, McConnell S, Hernandez-Molina G, Reichenbach S. Exercise for osteoarthritis of the hip. Cochrane Database Syst Rev 2014 Apr 22;(4):CD007912. DOI: https://doi.org/10.1002/14651858.CD007912.pub2.
39. Bartels, E, Juhl, C, Christensen, R, Hagen, K, Danneskiold-Samsøe B, Dagfinrud, H, Lund, H. Aquatic exercise for the treatment of knee and hip osteoarthritis. 2016 Mar 23;3:CD005523. DOI: https://doi.org/10.1002/14651858.CD005523.pub3.
40. Zhang W, Doherty M, Arden N, et al; EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). EULAR evidence based recommendations for the management of hip osteoarthritis: Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2005 May;64(5):669-81. DOI: https://doi.org/10.1136/ard.2004.028886.
41. Reyes C, Leyland KM, Peat G, Cooper C, Arden NK, Prieto-Alhambra D. Association between overweight and obesity and risk of clinically diagnosed knee, hip, and hand osteoarthritis: A population-based cohort study. Arthritis Rheumatol 2016 Aug;68(8):1869-75. DOI: https://doi.org/10.1002/art.39707.
42. Curtis GL, Chughtai M, Khlopas A, et al. Impact of physical activity in cardiovascular and musculoskeletal health: Can motion be medicine? J Clin Med Res 2017 May;9(5):375-81. DOI: https://doi.org/10.14740/jocmr3001w.
43. Felson DT, Niu J, Clancy M, Sack B, Aliabadi P, Zhang Y. Effect of recreational physical activities on the development of knee osteoarthritis in older adults of different weights: The Framingham Study. Arthritis Rheum 2007 Feb 15;57(1):6-12. DOI: https://doi.org/10.1002/art.22464.
44. Bennell K. Physiotherapy management of hip osteoarthritis. J Physiother 2013 Sep;59(3):145-57. DOI: https://doi.org/10.1016/S1836-9553(13)70179-6.
45. da Costa BR, Reichenbach S, Keller N, et al. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: A network meta-analysis. Lancet 2017 Jul 8;390(10090):e21-33. DOI: https://doi.org/10.1016/S0140-6736(17)31744-0.
46. Hochberg MC, Altman RD, April KT, et al; American College of Rheumatology. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken) 2012 Apr;64(4):465-74. DOI: https://doi.org/10.1002/acr.21596.
47. Osteoarthritis: Care and management. Clinical guideline [CG177] [Internet]. London, UK: NICE; 2014 Feb [cited 2017 Aug 11]. Available from: www.nice.org.uk/guidance/cg177.
48. da Costa BR, Nüesch E, Kasteler R, et al. Oral or transdermal opioids for osteoarthritis of the knee or hip. Cochrane Database Syst Rev 2014 Sep 17;(9):CD003115. DOI: https://doi.org/10.1002/14651858.CD003115.pub4.
49. McCabe PS, Maricar N, Parkes MJ, Felson DT, O'Neill TW. The efficacy of intra-articular steroids in hip osteoarthritis: A systematic review. Osteoarthritis Cartilage 2016 Sep;24(9):1509-17. DOI: https://doi.org/10.1016/j.joca.2016.04.018.
50. Chambers AW, Lacy KW, Liow MHL, Manalo JPM, Freiberg AA, Kwon YM. Multiple hip intra-articular steroid injections increase risk of periprosthetic joint infection compared with single injections. J Arthroplasty 2017 Jun;32(6):1980-3. DOI: https://doi.org/10.1016/j.arth.2017.01.030.
51. Piuzzi NS, Slullitel PA, Bertona A, et al. Hip arthroscopy in osteoarthritis: A systematic review of the literature. Hip Int 2016 Jan-Feb;26(1):8-14. DOI: https://doi.org/10.5301/hipint.5000299.
52. Pivec R, Johnson AJ, Mears SC, Mont MA. Hip arthroplasty. Lancet 2012 Nov 17;380(9855):1768-77. DOI: https://doi.org/10.1016/S0140-6736(12)60607-2.
53. Daigle ME, Weinstein AM, Katz JN, Losina E. The cost-effectiveness of total joint arthroplasty: A systematic review of published literature. Best Pract Res Clin Rheumatol 2012 Oct;26(5):649-58. DOI: https://doi.org/10.1016/j.berh.2012.07.013.
54. Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. J Bone Joint Surg Am 2007 Apr;89(4):780-5. DOI: https://doi.org/10.2106/JBJS.F.00222.
55. Marshall DA, Pykerman K, Werle J, et al. Hip resurfacing versus total hip arthroplasty: A systematic review comparing standardized outcomes. Clin Orthop Relat Res 2014 Jul;472(7):2217-30. DOI: https://doi.org/10.1007/s11999-014-3556-3.
56. Sehatzadeh S, Kaulback K, Levin L. Metal-on-metal hip resurfacing arthroplasty: An analysis of safety and revision rates. Ont Health Technol Assess Ser 2012;12(19):1-63.
57. Matharu GS, Pandit HG, Murray DW, Treacy RB. The future role of metal-on-metal hip resurfacing. Int Orthop 2015 Oct;39(10):2031-6. DOI: https://doi.org/10.1007/s00264-015-2692-z.

Secondary Syphilis Associated with Membranous Nephropathy and Acute Hepatitis in a Patient with HIV: A Case Report

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ABSTRACT

Introduction: We present a case of membranous nephropathy associated with a secondary syphilis infection in a patient with HIV.

Case Presentation: A 37-year-old white man with HIV who was receiving highly active antiretroviral therapy presented to the Emergency Department with 6 weeks of rectal pain. He had a CD3-CD4 count of 656 cells/mm^3 and an undetectable viral load. On admission, he was found to have an anal ulcer, a serum creatinine of 1.4 mg/dL (baseline 0.7 to 1.0 mg/dL), elevated transaminases, positive rapid plasmin reagin, and a urine protein/creatinine ratio revealing nephrotic-range proteinuria. Renal biopsy demonstrated membranous nephropathy with features suggestive of a secondary cause. Our patient was treated with penicillin for secondary syphilis, with normalization of renal function, resolution of the nephrotic syndrome, and improvement of his elevated transaminases.

Discussion: This case is a reminder that patients with HIV are not infrequently coinfected with *Treponema pallidum* and that secondary syphilis can have systemic manifestations, including elevated transaminases and nephrotic syndrome. Prompt diagnosis and treatment will result in resolution of these problems.

INTRODUCTION

Syphilis, as a disease entity, became widely known in the Western world during the Renaissance, when large outbreaks occurred that rapidly spread throughout Europe and Asia.[1] The etiologic agent, *Treponema pallidum*, was identified in 1905,[2] and with the development of medications, particularly of penicillin, and of serologic testing, syphilis became a relatively small public health issue. Since 2000, however, when the historically lowest incidence rates of syphilis in the US were observed, rates have doubled from 2.1 cases/100,000 population in 2000 to 5.3 cases/100,000 in 2013.[3] The largest increase in incidence is seen among men who have sex with men in all age groups and among all ethnicities.[3]

Because of its shared mode of transmission, coinfection of syphilis with HIV is frequent.[4] The presence of mucosal syphilitic ulcers facilitates the transmission of HIV. Moreover, the presence of immunodeficiency caused by HIV may result in syphilis presenting atypically, with a more rapid clinical course and aggressive manifestations, including neurologic and ophthalmologic involvement.[5] Serologic diagnosis of syphilis using nontreponemal testing followed by confirmation using more specific treponemal testing is applicable regardless of HIV status.[6] In 2010, Horberg et al[7] examined the Kaiser Permanente Northern California patient population and reported that the adjusted incidence rate ratio on syphilis infection in HIV vs non-HIV-infected individuals was 86.0, and that this ratio increased with time.

Nephrotic syndrome is well known to be associated with HIV infection. Although the disease entity termed HIV-associated nephropathy (HIVAN), which is characterized by collapsing focal and segmental glomerulosclerosis and acute interstitial nephritis with microcystic tubular dilatation, is predominantly seen among African American patients with high viral loads and low CD4 counts,[8] nephrotic syndrome in patients with HIV may be caused by any number of glomerular pathologies, including immune complex glomerulonephritis, minimal change disease, and immunoglobulin A (IgA) nephropathy, among others.[9,10] Thus, it would be a mistake to assume that all nephrotic syndromes presenting in an HIV-positive patient is necessarily caused by HIVAN. This is particularly true if the patient is coinfected with either syphilis, hepatitis B, or hepatitis C, each of which may cause other distinct glomerular diseases.

The following case serves as a reminder that nephrotic syndrome in a patient with HIV may not necessarily be caused by the HIV.

CASE PRESENTATION

Presenting Concerns

A 37-year-old white man with a medical history of HIV who was receiving highly active antiretroviral therapy presented to the Emergency Department with 6 weeks of rectal pain. He had been evaluated both in the Emergency Department and the urgent care clinic several times before his admission. Initially, his symptoms were thought to be caused by unprotected anal intercourse exacerbated by hard bowel movements. Seven days before his admission, the patient presented to the urgent care clinic with persistent rectal pain and subjective fevers. Examination revealed a 1-cm indurated anal lesion for which he received oral cephalexin. A biopsy of the lesion was performed. He received intravenous metronidazole before the biopsy and subsequently received trimethoprim/sulfamethoxazole when an intraoperative wound culture returned *enterococcus*, *Pseudomonas aeruginosa*, and *Bacteroides fragilis*. On the day of admission, he returned to the Emergency Department with reports of nausea, vomiting, dark urine, and nonbloody

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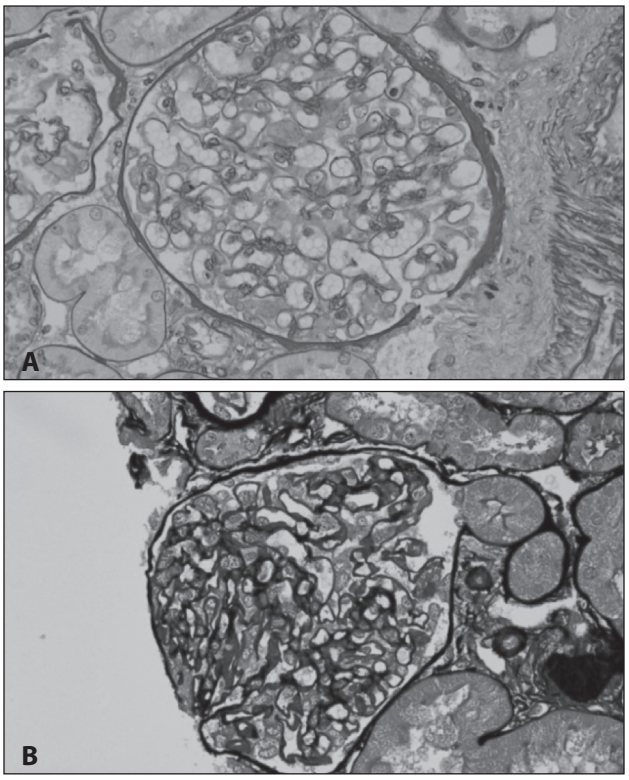

Figure 1. Renal biopsy by light microscopy, A) periodic acid-Schiff stain and B) Jones silver stain, showing mild acute tubular necrosis and mild arterial and arteriolar nephrosclerosis.

diarrhea for 3 days. His subjective fevers had resolved since cephalexin had been started.

His medical history was significant for depression and HIV diagnosed in 2004, which was treated with highly active antiretroviral therapy. His last CD3-CD4 count was 656 cells/mm^3, and his HIV viral load was undetectable 3 months before admission. He had previously been treated for gonorrhea and syphilis. He had a history of surgical removal of anal condylomata. He was allergic to abacavir, which caused rash. He drank 2 to 3 glasses of wine and 1 to 2 beers weekly and occasionally used recreational marijuana. He never smoked tobacco. His medications before admission included efavirenz-emtricitabine-tenofovir (600-200-300 mg combination) 1 tablet daily, cephalexin (500 mg) 4 times daily, sertraline (50 mg) daily, diltiazem 2% in petrolatum ointment, dibucaine 1% ointment, and docusate sodium (250 mg) daily. He took no over-the-counter or herbal medications.

On presentation, his temperature was 37.3°C, blood pressure was 115/68 mmHg without orthostatic changes, pulse was 56 beats/min, respiratory rate was 19 breaths/min, and oxygen saturation was 99% on room air. In general, he was a well-appearing man in no acute distress. He had no scleral icterus, and cardiopulmonary and abdominal exams were unremarkable. No abdominal tenderness was demonstrated. He had no peripheral edema. He had significant bilateral inguinal but no cervical or axillary lymphadenopathy. He had no skin rash. His rectal examination revealed ulceration at the posterolateral external anal sphincter, which was tender to palpation. Initial laboratory analysis revealed white blood cell count of 7.2 x 10^3/mL, hemoglobin 12.9 g/dL, mean corpuscular volume 91.5 fL, platelet 451 x 10^3/L, sodium 132 mEq/L, potassium 3.8 mEq/L, chloride 99 mEq/L, bicarbonate 27 mEq/L, blood urea nitrogen 17 mg/dL, and creatinine of 1.4 mg/dL. His baseline creatinine the previous year was 0.7 mg/dL to 1.0 mg/dL. Other laboratory test results included aspartate aminotransferase 221 U/L, alanine aminotransferase 255 U/L, total bilirubin 1.1 mg/dL, alkaline phosphatase 881 U/L, gamma-glutamyl transpeptidase 920 U/L, and lipase 26 U/L. Serum total protein was 4.6 g/dL and albumin was 1.1 g/dL. Prothrombin time international normalized ratio was 1.0. Both C3 and C4 complement factors were normal, as was rheumatoid factor and antinuclear antibody. Urinalysis revealed a specific gravity of > 1.050 and no leukocyte esterase or nitrite; urine protein was > 600 mg/dL, urine hemoglobin 0.20 mg/dL, urobilinogen 4.0 mg/dL, and urine bilirubin 6.0 mg/dL. Urine microscopy demonstrated urine white blood cell count > 25/high-power field, urine red blood cell 4 to 10/high-power field, and 5 to 10 hyaline casts, with 0 to 2 granular casts/low-power field. Urine culture was negative. Hansel's stain of the urine demonstrated no urinary eosinophils. Urine electrolytes yielded a urine sodium 37 mEq/L, urine potassium 92 mEq/L, urine chloride 45 mEq/L, and urine creatinine > 400 mg/dL. The urinary protein/creatinine ratio was 8.2 g/g. Urine was negative for detectable acetaminophen or salicylates.

Therapeutic Intervention and Treatment

Our patient presented with several medical issues that included elevated transaminases, acute kidney injury, nephrotic range proteinuria, and rectal ulceration. He received intravenous fluid hydration for presumed prerenal azotemia. Trimethoprim/sulfomethoxazole was continued. Abdominal ultrasound did not find signs of biliary obstruction or cholecystitis but did find bilateral echogenic kidneys without hydronephrosis. Antimitochondrial

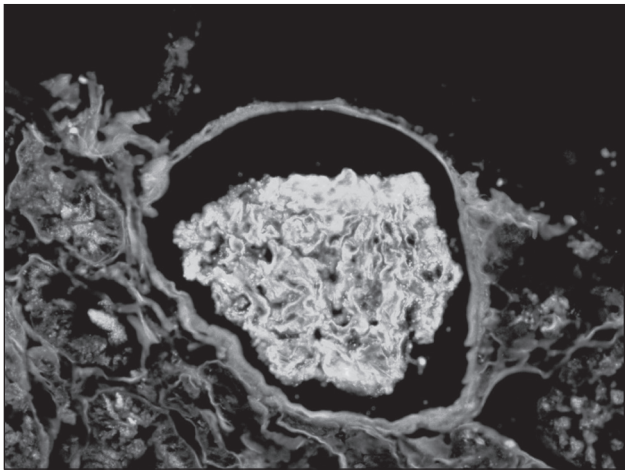

Figure 2. Renal biopsy by immunofluorescence microscopy, showing positive staining for immunoglobulin G, immunoglobulin M, C3, C1q, and kappa and lambda light chains in the capillary walls and mesangial regions.

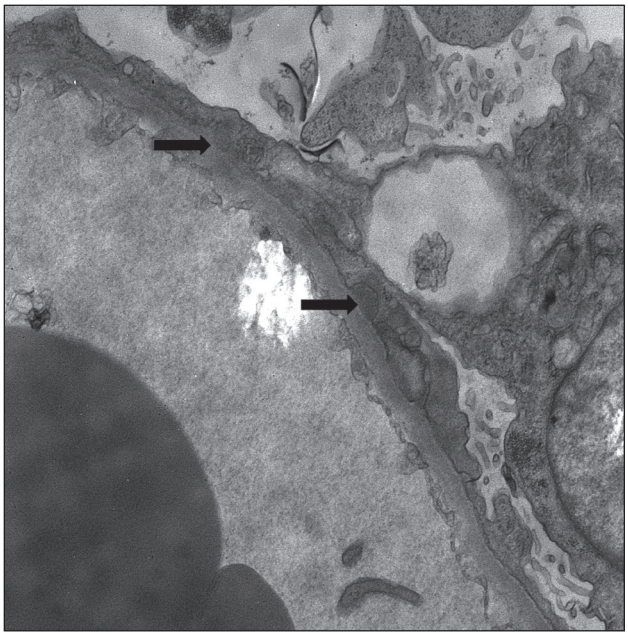

Figure 3. Renal biopsy by electron microscopy. Arrows indicate subepithelial electron-dense deposits in the subepithelial and paramesangial regions.

and antismooth-muscle antibodies were negative; ceruloplasmin and iron saturation were normal. Treponemal enzyme immuoassay antibody was positive, and rapid plasmin reagin was 1:16. His rapid plasmin reagin 3 months before admission was negative although his treponemal antibody was positive, confirming past infection. Hepatitis B surface antigen, core antibody, and surface antibody, and hepatitis C antibody were negative; however, hepatitis A immunoglobulin M (IgM) was positive. Herpes simplex viral culture of the anal lesion was negative. The anal ulcer biopsy revealed lymphoplasmacytoid cell proliferation without evidence of clonality or lymphoma. On hospital day 2, the patient's serum creatinine rose to 1.58 mg/dL. The patient underwent a percutaneous renal biopsy for acute kidney injury and nephrotic syndrome. The kidney biopsy demonstrated mild acute tubular necrosis, mild arterial and arteriolar nephrosclerosis, and findings consistent with early secondary membranous nephropathy.

Pathology

Figures 1 to 3 demonstrate the results of the renal biopsy. By light microscopy (Figures 1A and 1B), there were 14 glomeruli in the biopsy specimen. All were normal in appearance. There were no crescents or segments of sclerosis. Mild acute tubular necrosis and mild arterial and arteriolar nephrosclerosis were observed. Immunofluorescence microscopy, however, demonstrated positive staining for immunoglobulin G (IgG) (4+), IgM (1-2+), C3 (3-4+), C1q (3+), and both kappa and lambda light chains (2-3+) in the capillary walls in a granular pattern and in mesangial regions. Strong granular capillary wall and mesangial staining for IgG is illustrated in Figure 2. By electron microscopy, small electron-dense deposits were identified in subepithelial and paramesangial regions (Figure 3). Podocyte foot processes were extensively effaced, and tubuloreticular inclusions were not identified.

Follow-up and Outcomes

Benzathine penicillin 2,400,000 IU once per week for 3 weeks was started for treatment of secondary syphilis. Nephrotic syndrome resolved. Follow-up laboratory tests 6 weeks after

Table 1. Case timeline

Date	Venue	Summary	Diagnostic test results	Intervention
19 December 2013	Emergency Department	37-y-old man with HIV presents with 3-4 w of anal pain	Examination: anal ulcer	Psyllium; zinc oxide; dibucaine cream
6 January 2014	Emergency Department	Anal pain and subjective fevers	Examination: anal ulcer	Surgical consult; cephalexin
9 January 2014	Surgery center	Anal pain but fevers resolved	Examination: under anesthesia, anal ulcer	Cultures; punch biopsies
11 January 2014	Emergency Department	Nausea and vomiting	Examination: anal ulcer; inguinal adenopathy; creatinine 1.4; +3 protein; alanine transaminase 255; alkaline phosphatase 881; bilirubin 1.1; abdominal ultrasound	Hospitalization; hydration; switch to trimethoprim/sulfamethoxazole on basis of culture results
13 January 2014	Hospital	Nausea and vomiting resolved	Creatinine 1.58; urine protein/creatinine 8.2; rapid plasma reagin 1:16	Nephrology, Gastroenterology, Infectious Disease consults; switch to penicillin
16 January 2014	Hospital	Asymptomatic	Renal biopsy	None
2 February 2014	Nephrology clinic	Asymptomatic	Creatinine 0.99; urine protein/creatinine < 0.13; alanine transaminase 62; alkaline phosphatase 265	Prescribed to complete total of 3 w of penicillin therapy
6 March 2014	Nephrology clinic	Asymptomatic	Creatinine 0.88; urine protein/creatinine < 0.15; alanine transaminase 50; alkaline phosphatase 96	None

Renal Manifestations of Syphilis

Glomerular
- Minimal change disease/focal sclerosis[1-3]
- Membranous nephropathy[4-14]
- Crescentic glomerulonephritis[15]
- Postinfectious glomerulonephritis[14,16]
- Amyloidosis[17]

Tubular
- Acute tubular necrosis[18,19]
- Interstitial nephritis[20,21]

Vascular
- Renal artery stenosis[22-24]
- Endarteritis[13]

Mass lesion
- Renal gumma[25]

starting penicillin therapy demonstrated a serum creatinine of 0.88 mg/dL, serum albumin 3.8 mg/dL, alanine aminotransferase 50 U/L, alkaline phosphatase 96 U/L, urine protein/creatinine ratio of < 0.15 mg/mg, and normal urinalysis. See Table 1 for a timeline of the patient's case.

DISCUSSION

Membranous nephropathy is among the most common diagnoses for adults with nephrotic syndrome in the general population and accounts for approximately 20% of cases of nephrotic syndrome.[11] Histologically, membranous nephropathy is characterized by diffuse thickening of the glomerular basement membrane with immune complex deposits located in the subepithelial space, and the absence of significant inflammatory or proliferative changes. Membranous nephropathy can be either idiopathic or secondary to an underlying cause, such as solid malignant tumors, medications (eg, penicillamine, gold, nonsteroidal anti-inflammatory drugs), autoimmune diseases (eg, lupus, rheumatoid arthritis, mixed connective tissue disease), or infections (eg, hepatitis B, hepatitis C). In our case, the renal biopsy confirmed a diagnosis of early membranous nephropathy. Although the glomeruli in early membranous nephropathy may look completely normal under light microscopy, as it did in our case, the diagnosis of membranous nephropathy was confirmed by further examination of the specimen using both immunofluorescence and electron microscopy. Moreover, in our case, the immunofluorescence pattern and the presence of both subepithelial and mesangial immune complex deposits suggested that membranous nephropathy was secondary to an underlying condition, which we presumed to be syphilis.

Renal manifestations of syphilis are varied and include not only membranous nephropathy, but also a host of other glomerular and nonglomerular conditions (see the Sidebar: Renal Manifestations of Syphilis). Membranous nephropathy is the most common glomerular lesion seen with syphilis patients.[12] Circulating immune complexes have been seen among patients with secondary syphilis,[13] and immune complexes containing antitreponemal antibodies have been eluted from renal biopsy specimens.[14,15] As opposed to idiopathic membranous nephropathy, where IgG and C3 staining are typically seen by immunofluorescence studies on renal biopsies, membranous nephropathy secondary to syphilis typically has staining not only for IgG and

1. Hartley AJ, Rajakariar R, Sheaff M, Buckland M, Goh B, O'Connell R. Syphilis masquerading as focal segmental glomerulosclerosis. Int J STD AIDS 2014 Jun;25(7):529-31. DOI: https://doi.org/10.1177/0956462413516940.
2. Stubanus M, Göbel H, Rieg S, Walz G, Gerke P. Quiz page. Minimal change glomerulonephritis associated with secondary syphilis. Am J Kidney Dis 2007 Jun;49(6):A49-50.
3. Krane NK, Espenan P, Walker PD, Bergman SM, Wallin JD. Renal disease and syphilis: A report of nephrotic syndrome with minimal change disease. Am J Kidney Dis 1987 Feb;9(2):176-9. DOI: https://doi.org/10.1016/s0272-6386(87)80096-3.
4. Hunte W, al-Ghraoui F, Cohen RJ. Secondary syphilis and the nephrotic syndrome. J Am Soc Nephrol 1993 Jan;3(7):1351-5.
5. Sølling J, Sølling K, Jacobsen KU, Olsen S, From E. Circulating immune complexes in syphilitic nephropathy. A case report. Br J Vener Dis 1978 Feb;54(1):53-6. DOI: https://doi.org/10.1136/sti.54.1.53.
6. Gamble CN, Reardon JP. Immunopathogenesis of syphilitic glomerulonephritis. Elution of antitreponemal antibody from glomerular immune-complex deposits. New Engl J Med 1975 Feb 27;292(9):449-54. DOI: https://doi.org/10.1056/nejm197502272920903.
7. O'Regan S, Fong JS, de Chadarévian JP, Rishikof JR, Drummond KN. Treponemal antigens in congenital and acquired syphilitic nephritis: Demonstration by immunofluorescence studies. Ann Intern Med 1976 Sep;85(3):325-7. DOI: https://doi.org/10.7326/0003-4819-85-3-325.
8. Handoko ML, Duijvestein M, Scheepstra CG, de Fijter CW. Syphilis: A reversible cause of nephrotic syndrome. BMJ Case Rep 2013 Feb 8;2013. DOI: https://doi.org/10.1136/bcr-2012-008279.
9. Chen YM, Marcos LA, Liapis H, Steinberg TH, Morrison AR. An unusual cause of membranous glomerulonephritis in a patient with HIV. Int Urol Nephrol 2012 Jun;44(3):983-6. DOI: https://doi.org/10.1007/s11255-011-9945-6.
10. Mora Mora MT, Gallego Domínguez MS, Castellano Cerviño MI, Novillo Santana R, Gómez-Martino Arroyo JR. Membranous glomerulonephritis in a patient with syphilis. [Article in English, Spanish]. Nefrologia 2011;31(3):372-3. DOI: https://doi.org/10.3265/Nefrologia.pre2011.Mar.10819.
11. Bani-Hani S, Patel V, Larsen CP, Walker PD, Cooke CR, Showkat A. Renal disease in AIDS: It is not always HIVAN. Clin Exp Nephrol 2010 Jun;14(3):263-7. DOI: https://doi.org/10.1007/s10157-009-0253-8.
12. Satoskar AA, Kovach P, O'Reilly K, Nadasdy T. An uncommon cause of membranous glomerulonephritis. Am J Kidney Dis 2010 Feb;55(2):386-90. DOI: https://doi.org/10.1053/j.ajkd.2009.06.015.
13. Hruby Z, Kuźniar J, Rabczyński J, Bogucki J, Steciwko A, Weyde W. The variety of clinical and histopathologic presentations of glomerulonephritis associated with latent syphilis. Int Urol Nephrol 1992;24(5):541-7. DOI: https://doi.org/10.1007/bf02550123.
14. Bhorade MS, Carag HB, Lee HJ, Potter EV, Dunea G. Nephropathy of secondary syphilis. A clinical and pathological spectrum. JAMA 1971 May 17;216(7):1159-66. DOI: https://doi.org/10.1001/jama.216.7.1159.
15. Walker PD, Deeves EC, Sahba G, Wallin JD, O'Neill WM Jr. Rapidly progressive glomerulonephritis in a patient with syphilis. Identification of antitreponemal antibody and treponemal antigen in renal tissue. Am J Med 1984 Jun;76(6):1106-12. DOI: https://doi.org/10.1016/s0022-5347(17)49052-5.
16. Yoshikawa K, Aida Y, Seki N, et al. Early syphilitic hepatitis concomitant with nephrotic syndrome followed by acute kidney injury. Clin J Gastroenterol 2014 Aug;7(4):349-54. DOI: https://doi.org/10.1007/s12328-014-0499-x.
17. Dowling GB. Syphilitic nephritis. Br Med J 1925 Sep 26;2(3378):551-2. DOI: https://doi.org/10.1136/bmj.2.3378.551.
18. Nelson TV, Blaceri S, Biederman JI. Rhabdomyolysis and acute renal failure with syphilitic myositis. Kidney Int 2016 May;89(5):1169. DOI: https://doi.org/10.1016/j.kint.2015.09.004.
19. Estévez RF. Neurosyphilis presenting as rhabdomyolysis and acute renal failure with subsequent irreversible psychosis and dementia. Psychosomatics 2006 Nov-Dec;47(6):538-9. DOI: https://doi.org/10.1176/appi.psy.47.6.538.
20. Zhou J, Hu C, Zheng F, Cheng H, Xuan J, Li H. Nephrogenic diabetes insipidus secondary to syphilis infection. J Clin Endocrinol Metab 2013 Jul;98(7):2663-6. DOI: https://doi.org/10.1210/jc.2013-1074.
21. Chen YC, Lee N, Chang CT, Wu MS. Salt loss and hyponatraemia in a patient with syphilitic nephritis. Nephrol Dial Transplant 2005 Jun;20(6):1248-50. DOI: https://doi.org/10.1093/ndt/gfh778.
22. Kharge J, Bharatha A, Raghu TR, Manjunath CN. Bilateral coronary ostial stenosis with bilateral renal ostial stenosis in cardiovascular syphilis: De novo percutaneous coronary intervention and in-stent restenosis. Eur Heart J 2013 Sep;34(34):2682. DOI: https://doi.org/10.1093/eurheartj/eht036.
23. Joshi SV, Desai R, Agarwal N, et al. Successful management of ruptured suprarenal aortic aneurysm with left artery stenosis (a case report). J Postgrad Med 1988 Apr;34(2):105-7.
24. Price RK, Skelton R. Hypertension due to syphilitic occlusion of the main renal arteries. Br Heart J 1948 Jan;10(1):29-33. DOI: https://doi.org/10.1136/hrt.10.1.29.
25. de Carvalho JG, Slongo EL, Sobral AC. Kidney mass and osteolytic lesion: Is it always malignancy? Nephrol Dial Transplant 2007 Feb;22(2):645-8.

C3, but also occasionally with IgA, IgM, and C1q ("full house pattern"),[10,14] which, with the exception of IgA staining, were seen in our case. At the time of this case presentation, immunostaining for phospholipase A2 receptor, frequently positive in primary, as opposed to secondary, membranous nephropathy,[16] was not yet available in our facility. Our patient's rapid clinical response to antitreponemal treatment also speaks in favor of syphilis as being the underlying cause of his membranous nephropathy.

Membranous nephropathy has also been seen in patients infected with HIV. Although the predominant glomerular lesion seen in nephrotic HIV-infected patients is collapsing focal and segmental glomerulosclerosis with interstitial inflammation and tubular microcystic changes, also known as HIVAN, other immune complex glomerulonephritides have been reported in HIV-infected patients, including membranous nephropathy.[9,10] In a study of patients with HIV who underwent renal biopsies, those patients who had non-HIVAN renal disease had a slower rate of progression to renal replacement therapy than did those patients with HIVAN. Moreover, in contrast to those with HIVAN, patients with non-HIVAN renal disease had a clinical course that was not significantly affected by intensification of antiretroviral therapy or the absence of a detectable viral load.[10] The treatment of HIV-associated membranous nephropathy remains uncertain. There is one case report of a patient with HIV-associated membranous nephropathy who responded dramatically to prednisone[17] and another report of a patient who responded to intensification of antiviral therapy.[18] In our case, although we cannot rule out HIV-associated membranous nephropathy, our patient's rapid response to antibiotic therapy and the absence of detectable glomerular endothelial tubuloreticular structures, which is frequently seen in HIV-associated renal disease, speak against HIV as playing a major role in our patient's nephrotic syndrome.

Syphilis has also been associated with acute hepatitis particularly among HIV-infected patients.[19,20] Although our patient had only moderately elevated transaminases without jaundice or clinical signs or symptoms of acute hepatitis, florid acute hepatitis with jaundice caused by syphilis has been reported, which resolved completely with antimicrobial therapy.[21] Liver biopsies have demonstrated periportal hepatocyte necrosis and pericholangiolar inflammation.[22] As such, serum alkaline phosphatase is typically elevated out of proportion to either bilirubin or transaminase levels,[19-21] as it was in our patient. Interestingly, primary syphilitic proctitis, as was presumably seen in our patient, has been associated with liver involvement, perhaps because of their common venous drainage.[23] Our patient also had a detectable IgM against hepatitis A virus. The prolonged presence of antihepatitis A virus IgM following infection has been reported and indeed, false positive antihepatitis A virus IgM, confirmed by the absence of detectable viral RNA, has also been seen.[24] Our patient's clinical course with rapid resolution after treatment was not consistent with an acute hepatitis A infection.

Our patient was also taking medications that could have affected his renal function. Tenofovir is well known to have nephrotoxic effects and may present with evidence of proximal tubular dysfunction (ie, glycosuria in the absence of hyperglycemia, phosphaturia, amino aciduria, renal tubular acidosis—termed Fanconi syndrome) and proteinuria.[25] Sulfa antibiotics are frequently implicated in cases of acute interstitial nephritis.[26] Sulfadiazine, a sulfa antibiotic used in toxoplasmosis, is sparingly soluble and has been associated with crystal-induced acute renal failure.[27] Moreover, sulfamethoxisole, similar to cimetidine, inhibits the tubular secretion of creatinine, resulting in an elevated serum level without an effect on the actual glomerular filtration rate.[28] Finally, synthetic marijuana use has been associated with cases of acute kidney injury, presumably caused by acute tubular necrosis.[29]

CONCLUSION

HIV-infected patients are frequently coinfected with other pathogens, such as syphilis, hepatitis B, and/or hepatitis C. Although similar cases have been reported,[30-34] our recent case serves as a reminder that syphilis, the "great mimicker," is commonly seen in patients with HIV and can lead to disease states such as nephrotic syndrome and hepatitis. Prompt diagnosis and treatment is essential to prevent morbidity and mortality. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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References

1. Frith J. Syphilis—its early history and treatment until penicillin and the debate on its origins. Journal of Military and Veterans' Health 2012;20(4):40-58.
2. de Souza EM. A hundred years ago, the discovery of Treponema pallidum. An Bras Dermatol 2005 Sep/Oct;80(5):547-8. DOI: https://doi.org/10.1590/S0365-05962005000600017.
3. Patton ME, Su JR, Nelson R, Weinstock H; Centers for Disease Control and Prevention (CDC). Primary and secondary syphilis—United States, 2005-2013. MMWR Morb Mortal Wkly Rep 2014 May 9;63(18):402-6.
4. Wasserheit JN. Epidemiological synergy. Interrelationships between human immunodeficiency virus infection and other sexually transmitted diseases. Sex Transm Dis 1992 Mar-Apr;19(2):61-77. DOI: https://doi.org/10.1097/00007435-199219020-00001.
5. Lynn WA, Lightman S. Syphilis and HIV: A dangerous combination. Lancet Infect Dis 2004 Jul;4(7):456-66. DOI: https://doi.org/10.1016/s1473-3099(04)01061-8.
6. Centers for Disease Control and Prevention, Workowski KA, Berman SM. Sexually transmitted diseases treatment guidelines, 2006. MMWR Recomm Rep 2006 Aug 4;55(RR-11):1-94. Erratum in: MMWR Recomm Rep 2006 Sep 15;55(36):997.
7. Horberg MA, Ranatunga DK, Quesenberry CP, Klein DB, Silverberg MJ. Syphilis epidemiology and clinical outcomes in HIV-infected and HIV-uninfected patients in Kaiser Permanente Northern California. Sex Transm Dis 2010 Jan;37(1):53-8. DOI: https://doi.org/10.1097/olq.0b013e3181b6f0cc.
8. Kimmel PL, Barisoni L, Kopp JB. Pathogenesis and treatment of HIV-associated renal diseases: Lessons from clinical and animal studies, molecular pathologic correlations, and genetic investigations. Ann Intern Med 2003 Aug 5;139(3):214-26. DOI: https://doi.org/10.7326/0003-4819-139-3-200308050-00011.
9. Szczech LA, Gupta SK, Habash R, et al. The clinical epidemiology and course of the spectrum of renal diseases associated with HIV infection. Kidney Int 2004 Sep;66(3):1145-52. DOI: https://doi.org/10.1111/j.1523-1755.2004.00865.x.

10. D'Agati V, Appel GB. Renal pathology of human immunodeficiency virus infection. Semin Nephrol 1998;18(4):406-21.
11. Braden GL, Mulhern JG, O'Shea MH, Nash SV, Ucci AA Jr, Germain MJ. Changing incidence of glomerular diseases in adults. Am J Kidney Dis 2000 May;35(5):878-83. DOI: https://doi.org/10.1016/s0272-6386(00)70258-7.
12. Hunte W, al-Ghraoui F, Cohen RJ. Secondary syphilis and the nephrotic syndrome. J Am Soc Nephrol 1993 Jan;3(7):1351-5.
13. Sølling J, Sølling K, Jacobsen KU, Olsen S, From E. Circulating immune complexes in syphilitic nephropathy. A case report. Br J Vener Dis 1978 Feb;54(1):53-6. DOI: https://doi.org/10.1136/sti.54.1.53.
14. Gamble CN, Reardon JP. Immunopathogenesis of syphilitic glomerulonephritis. Elution of antitreponemal antibody from glomerular immune-complex deposits. New Engl J Med 1975 Feb 27;292(9):449-54. DOI: https://doi.org/10.1056/nejm197502272920903.
15. O'Regan S, Fong JS, de Chadarévian JP, Rishikof JR, Drummond KN. Treponemal antigens in congenital and acquired syphilitic nephritis: Demonstration by immunofluorescence studies. Ann Intern Med 1976 Sep;85(3):325-7. DOI: https://doi.org/10.7326/0003-4819-85-3-325.
16. Larsen CP, Messias NC, Silva FG, Messias E, Walker PD. Determination of primary versus secondary membranous glomerulopathy utilizing phospholipase A2 receptor staining in renal biopsies. Mod Pathol 2013 May;26(5):709-15. DOI: https://doi.org/10.1038/modpathol.2012.207.
17. Mattana J, Siegal FP, Schwarzwald E, et al. AIDS-associated membranous nephropathy with advanced renal failure: Response to prednisone. Am J Kidney Dis 1997 Jul;30(1):116-9. DOI: https://doi.org/10.1016/s0272-6386(97)90573-4.
18. Alarcón-Zurita A, Salas A, Antón E, et al. Membranous glomerulonephritis with nephrotic syndrome in a HIV positive patient—remarkable remission with triple therapy. Nephrol Dial Transplant 2000 Jul;15(7):1097-8. DOI: https://doi.org/10.1093/ndt/15.7.1097.
19. Crum-Cianflone N, Weekes J, Bavaro M. Syphilitic hepatitis among HIV-infected patients. Int J STD AIDS 2009 Apr;20(4):278-84. DOI: https://doi.org/10.1258/ijsa.2008.008324.
20. Mullick CJ, Liappis AP, Benator DA, Roberts AD, Parenti DM, Simon GL. Syphilitic hepatitis in HIV-infected patients: A report of 7 cases and review of literature. Clin Infect Dis 2004 Nov 15;39(10):e100-5. DOI: https://doi.org/10.1086/425501.
21. Sabbatani S, Manfredi R, Attard L, Salfi N, Chiodo F. Secondary syphilis presenting with acute severe hepatic involvement in a patient with undiagnosed HIV disease. AIDS Patient Care STDS 2005 Sep;19(9):545-9. DOI: https://doi.org/10.1089/apc.2005.19.545.
22. Sobel HJ, Wolf EH. Liver involvement in early syphilis. Arch Pathol 1972 Jun;93(6):565-8.
23. Le Marchant JM, Ferrand B. [Primary syphilitic proctitis associated with liver involvement (author's transl)]. [Article in French]. Sem Hop 1981 Sep 18-25;57(33-36):1434-8.
24. Centers for Disease Control and Prevention (CDC). Positive test results for acute hepatitis A virus infection among persons with no recent history of acute hepatitis—United States, 2002-2004. MMWR Morb Mortal Wkly Rep 2005 May 13;54(18):453-6.
25. Scherzer R, Estrella M, Li Y, et al. Association of tenofovir exposure with kidney disease risk in HIV infection. AIDS 2012 Apr 24;26(7):867-75. DOI: https://doi.org/10.1097/qad.0b013e328351f68f.
26. Garvey JP, Brown DM, Chotirmall SH, Dorma AM, Conlon PJ, Walshe JJ. Trimethoprim-sulfamethoxazole induced acute interstitial nephritis in renal allografts: Clinical course and outcome. Clin Nephrol 2009 Nov;72(5):331-6. DOI: https://doi.org/10.5414/cnp72331.
27. Díaz F, Collazos J, Mayo J, Martínez E. Sulfadiazine-induced multiple urolithiasis and acute renal failure in a patient with AIDS and toxoplasma encephalitis. Ann Pharmacother 1996 Jan;30(1):41-2. DOI: https://doi.org/10.1177/106002809603000108.
28. Berglund F, Killander J, Pompeius R. Effect of trimethoprim-sulfamethoxazole on the renal excretion of creatinine in man. J Urol 1975 Dec;114(6):802-6. DOI: https://doi.org/10.1016/s0022-5347(17)67149-0.
29. Kazory A, Aiyer R. Synthetic marijuana and acute kidney injury: An unforeseen association. Clin Kidney J 2013 Jun;6(3):330-3. DOI: https://doi.org/10.1093/ckj/sft047.
30. Tatu AL, Popescu M, Rotarescu R, Popescu SD. A rare case of syphilis associated with renal and hepatic involvement. Dermatol Pract Concept 2013 Oct 31;3(4):53-4. DOI: https://doi.org/10.5826/dpc.0304a13.
31. Morrison EB, Normal DA, Wingo CS, Henrich WL. Simultaneous hepatic and renal involvement in acute syphilis. Case report and review of the literature. Dig Dis Sci 1980 Nov;25(11):875-8. DOI: https://doi.org/10.1007/bf01338531.
32. Tsai YC, Chen LI, Chen HC. Simultaneous acute nephritis and hepatitis in secondary syphilis. Clin Nephrol 2008 Dec;70(6):532-6. DOI: https://doi.org/10.5414/cnp70532.
33. Tang AL, Thin RN, Croft DN. Nephrotic syndrome and hepatitis in early syphilis. Postgrad Med J 1989 Jan;65(759):14-5. DOI: https://doi.org/10.1136/pgmj.65.759.14.
34. Makker J, Bajantri B, Nayudu SK. Secondary syphilis with hepatitis and nephrotic syndrome: A rare concurrence. J Clin Med Res 2016 Jul;8(7):550-4.

A Disease of an Unusual Nature

A disease of an unusual nature has invaded Italy and many other regions. In the beginning pustules are on the private parts, soon on the whole body … Moreover to this disease the physicians of our time do not yet give a name, but is called by the common name of French disease, as if this contagion were imported from France into Italy or because Italy was invaded at the same time both by the disease itself and the armies of the French.

— Niccolò Leoniceno, 1428-1524, Italian physician and humanist

Migraine Headache Treated with Famciclovir and Celecoxib: A Case Report

Bradford Lee NaPier, MD; Maki Morimoto, MD; Erin NaPier

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ABSTRACT

Introduction: Herpes simplex virus (HSV) has been speculated to play a role in migraine headache pathophysiology. We present the first successful migraine headache treatment with therapy specifically targeting HSV infection.

Case Presentation: A previously healthy 21-year-old white woman presented with a severe headache and was diagnosed with severe migraine headache disorder. She initially was treated with standard migraine headache medications without symptomatic improvement. She was then given famciclovir and celecoxib. The patient fully recovered within days and continues to enjoy significant reduction in severity and frequency of symptoms.

Discussion: Famciclovir and celecoxib may work synergistically against HSV. The virus may play a role in the pathophysiology of migraine headaches, and this is the first case report of successful migraine headache treatment with these medications. Further studies are needed to elucidate the efficacy of these medications in treating migraine disorder.

INTRODUCTION

Migraine headache pathophysiology has not been fully elucidated. Previous studies point to multifactorial genetic, chemical, and anatomic origins.[1] Researchers have observed that migraine tends to run in families and is considered to be at least partially heritable in nature.[1] Others describe the actual physical phenomena observed among patients with migraine as consisting of trigeminovascular system activation, cortical spreading depression, and neuronal sensitization.[2] It appears that a triggering event in a genetically predisposed patient can initiate a cascade resulting in the headache experience.[1] Specifically, trigeminal ganglion activation seems to be a common early observation among patients with migraine.[1] Herpes simplex virus (HSV) has been known to reside within the trigeminal ganglion and is speculated to play a role in migraine headache pathophysiology.[3] Treatments to target HSV infection may be important in migraine headache management.

CASE PRESENTATION

Presenting Concerns

A previously healthy 21-year-old white female college student woke up one morning with a visual aura consisting of scintillating scotoma followed by headache onset. At presentation she described the headache as severe and throbbing in nature with accompanying nausea and mild confusion. The scotoma resolved in 1 hour; however, the headache persisted for the next 24 hours. Nausea and cognitive dysfunction lasted for 3 and 9 days, respectively. The patient started taking nonsteroidal anti-inflammatory drugs during this time. Approximately 2 days after resolution of the initial presentation, her symptoms recurred. A neurologist was consulted, and the diagnosis of acute migraine headache was made. A magnetic resonance imaging scan of the patient's brain revealed several nonspecific hyperintensities in the pericortical frontal lobe on T2-weighted images (Figure 1). Possibilities of stroke, multiple sclerosis, or other neurologic disorders were excluded on the basis of symptoms and imaging studies. The patient had no history of cold sores. HSV serology was not performed.

Therapeutic Interventions and Treatment

During the next three months, the patient began a trial of several migraine headache treatments including triptans, beta blockers, prednisone, and injections of botulinum toxin. Most of the treatments provided only mild symptomatic improvement. Her difficulty with higher cognitive functions, especially concentration, persisted. She started to experience difficulty with her college coursework and had to take an excused absence for the semester. Concurrently, her sleep quality deteriorated significantly.

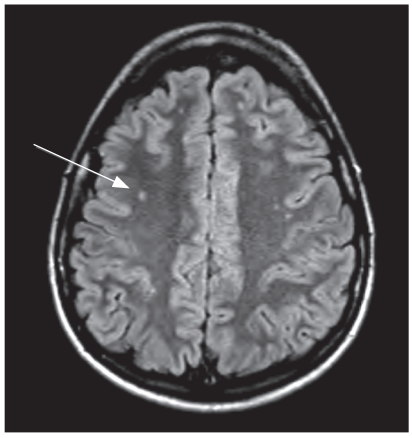

Figure 1. Axial, T2-weighted magnetic resonance image of the patient's brain. The arrow indicates nonspecific hyperintensities in the pericortical frontal lobe.

Follow-up and Outcomes

Seven months after her initial presentation, our patient began to take famciclovir and celecoxib, as prescribed by her treating physician. She reported substantial relief of her symptoms within 5 days and an immediate improvement in sleep quality. Her mental clarity returned with subjective improvement of headache symptoms, and she was able to return to her full college course load while taking maintenance doses of famciclovir and celecoxib. At 3 years after onset of symptoms, and 15 months after starting famciclovir and celecoxib therapy, our patient has experienced

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Table 1. Case timeline

Date	Events and intervention
October 2014	First migraine
November 2014-August 2015	4 migraines, each with severe symptoms lasting 5-6 d
November 2015	10 d/mo severe symptoms
December 2015	25 d/mo severe symptoms Standard treatment initiated: triptans, beta blockers, prednisone, botox injections
January 2016-April 2016	15-20 d/mo severe symptoms
May 2016	Famciclovir and celecoxib initiated
May 2016-June 2017	< 2 d/mo mild symptoms
June 2017	Famciclovir and celecoxib discontinued
June 2017-September 2017	< 2 d/mo mild symptoms

marked reduction in severity and frequency of migraine symptoms, allowing her to complete her undergraduate coursework and to work fulltime without interruption. After 12 months of treatment, she discontinued scheduled famciclovir and celecoxib therapy, and as of this writing has not reported any increase in severity or frequency of symptoms. A timeline of her case is presented in Table 1.

DISCUSSION

Migraine, which affects approximately 15% of the general population in the US,[4] is a severe headache disorder associated with physical, psychological, and financial morbidity.[5] Migraine accounts for an average of 8.3 days of absenteeism and 11.2 days of reduced productivity per affected individual each year, with an overall estimated cost to employers of $3309 per affected employee.[4]

Currently available treatment modalities consist of acute abortive pharmacotherapies, prophylactic pharmacotherapies, and adjunctive therapies. Acute abortive pharmacotherapies include nonsteroidal anti-inflammatory medications, acetaminophen, glucocorticoids, opioids, triptans, and ergots. Prophylactic pharmacotherapies consist of beta blockers, calcium channel blockers, tricyclic antidepressants, selective norepinephrine reuptake inhibitors, and antiepileptic medications. Adjunctive therapies such as acupuncture, biofeedback, massage therapies, and onabotulinumtoxin-A injections also have been described.[6]

There has been much speculation about the relationship between migraine headaches and HSV, which already has been implicated in some forms of cranial nerve (CN) disorders. In 1991, Adour[7] demonstrated that patients with acute herpes labialis also exhibited CN deficiencies involving CNs V, VII, IX, and X. This phenomenon was termed *HSV-related polyganglionitis.* In 2003, Thiel et al[8] examined the presence of HSV in postmortem ganglions. By using a specific immunostaining technique, the investigators revealed that HSV-1 and HSV-3 latently resided in the CN V (trigeminal) ganglions.[8] It was then speculated that chronic infection and inflammation of the ganglion by HSV were present in many patients. In 2013, VanElzakker[3] hypothesized that pathologically activated glial cells in the vagal sensory ganglia could cause an exaggerated sickness response that is found in chronic fatigue syndrome. If VanElzakker's hypothesis is true, then we must ask whether glial cells in the intracranial trigeminal ganglia, pathologically activated by HSV, could initiate migraine.

HSV infection commonly is treated with a ganglioside analog medication. Famciclovir is an example of this class of medication. Cyclooxygenase-2 inhibitors such as celecoxib also have been used to treat HSV infection. In 2005, Gebhardt et al[9] successfully demonstrated that celecoxib inhibited the heat-stressed herpes virus reactivation in mice. Synergy between famciclovir and celecoxib in treating HSV infection has been proposed and studied. A phase 2A randomized study of chronic fatigue syndrome revealed a twofold to threefold symptom improvement in patients treated with famciclovir (Famvir, Novartis International AG, Basel, Switzerland) and celecoxib when compared with placebo.[10]

CONCLUSION

In this case, a substantial improvement in migraine headache symptoms was achieved with the use of famciclovir and celecoxib (both medications with direct antiviral activity toward HSV). This combination of medications was used with definite effect initially as an abortive therapy and subsequently as a prophylactic therapy. On the basis of the current understanding of the pathophysiology of migraine headaches, specifically the role of HSV-mediated trigeminal inflammation in migraine symptomatology and the antiviral characteristics of famciclovir and celecoxib, we believe these medications may work synergistically to treat migraine disorder. We also hypothesize that migraine may be attributable to a reactivation of a latent HSV residing within the trigeminal ganglion. Further prospective trials using famciclovir and celecoxib must be performed in isolation and in combination to elucidate the respective role each may play in treating migraine disorder. ❖

Disclosure Statement

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References

1. Cutrer FM. Pathophysiology of migraine. Semin Neurol 2010 Apr;30(2):120-30. DOI: https://doi.org/10.1055/s-0030-1249222.
2. Charles A. Advances in the basic and clinical science of migraine. Ann Neurol 2009 May;65(5):491-8. DOI: https://doi.org/10.1002/ana.21691.
3. VanElzakker MB. Chronic fatigue syndrome from vagus nerve infection: A psychoneuroimmunological hypothesis. Med Hypotheses 2013 Sep;81(3):414-23. DOI: https://doi.org/10.1016/j.mehy.2013.05.034.
4. de Lissovoy G, Lazarus SS. The economic cost of migraine. Present state of knowledge. Neurology 1994 Jun;44(6 Suppl 4):S56-62.
5. Mennini FS, Gitto L, Martelletti P. Improving care through health economics analyses: Cost of illness and headache. J Headache Pain 2008 Aug;9(4):199-206. DOI: https://doi.org/10.1093/med/9780199584680.003.012.
6. Welch KM. Drug therapy of migraine. N Engl J Med 1993 Nov 11;329(20):1476-83. DOI: https://doi.org/10.1056/nejm199311113292008.
7. Adour KK. Medical management of idiopathic (Bell's) palsy. Otolaryngol Clin North Am 1991 Jun;24(3):663-73.
8. Thiel D, Derfuss T, Paripovic I, et al. Latent herpesvirus infection in human trigeminal ganglia causes chronic immune response. Am J Pathol 2003 Dec;163(6):2179-84. DOI: https://doi.org/10.1016/s0002-9440(10)63575-4.
9. Gebhardt BM, Varnell ED, Kaufman HE. Inhibition of cyclooxygenase 2 synthesis suppresses herpes simplex virus type 1 reactivation. J Ocul Pharmacol Ther 2005 Apr;21(2):114-20. DOI: https://doi.org/10.1089/jop.2005.21.114.
10. Pridgen WL, Duffy C, Gendreau JF, Gendreau RM. A famciclovir + celecoxib combination treatment is safe and efficacious in the treatment of fibromyalgia. J Pain Res 2017 Feb 22;10:451-60. DOI: https://doi.org/10.2147/jpr.s127288.

This is a story and illustration from the upcoming book *100 Little Stories of Big Moments* published by The Permanente Press.

The stories were written by physicians in 15 minutes in writing workshops about meaningful moments in their work and life of practicing medicine. Professional artists were asked to create a visual representation of the story.

Letting Me Off the Hook

James T Hardee, MD

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Margaret was 82 years old and had a plethora of usual and not-so-usual medical conditions. Diabetes, hypertension, congestive heart failure, arthritis, and GERD to name a few. She also had a Pacemaker and an artificial knee. I would see her 4-5 times a year for various ailments—some new and others chronic. Fatigue. Dizziness. Back pain. Shortness of breath. Tingling. Numbness. And so on …

While I always thought she was a "nice lady," I would at times find myself frustrated because most of her ailments were not fixable. There was no "cure" for her back pain. The fatigue was so multifactorial that no intervention would likely help much. I found myself occasionally annoyed during some of her visits, wanting to say bluntly, "You're 80 years old with a problem list a mile long and on 13 medications … what do you expect?" I wanted, just once, to call it out and state the obvious. But I never did.

At the end of one particularly long visit with her, while I felt the usual exasperation, she commented something that has stuck with me ever since. "Dr Hardee, you never fix me, but I always enjoy talking with you!"

This was the break in the case I needed. This gave *me* relief and the permission that it was "okay" not to fix her. There was benefit to our meetings beyond labs, x-rays, injections, meds, and referrals.

That she enjoyed the interactions let me off the hook, as it were, and helped me not feel quite so obligated to try to fix her. I found myself enjoying her visits more, since knowing the "goals" of care were looser … more negotiable.

I use her quote from time to time with other patients in similar situations now to reprioritize and recognize what I can and cannot do. ❖

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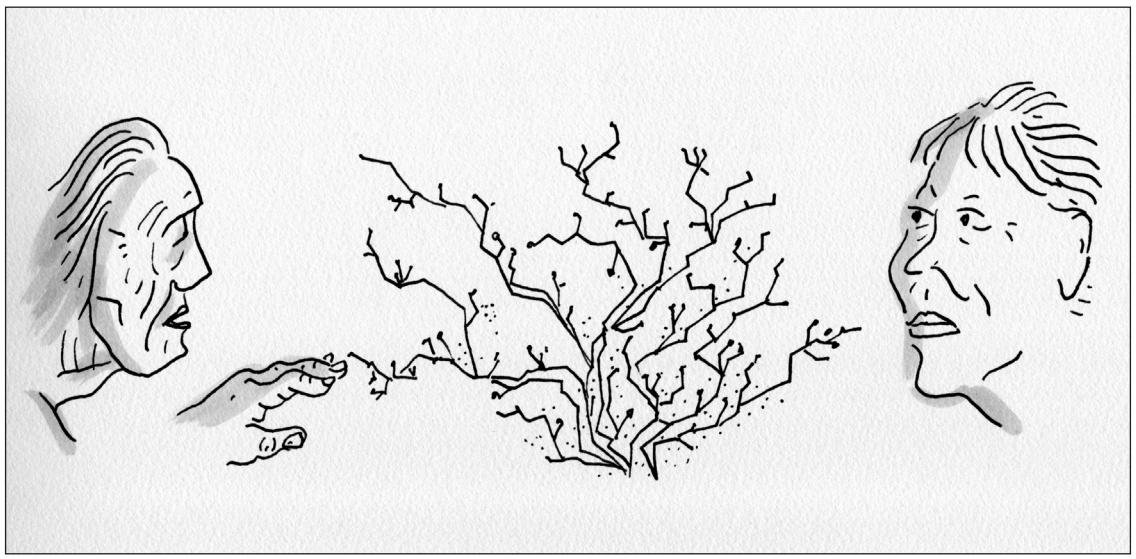

Accompanying artwork: **Monica by Susan MacLeod**

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Susan MacLeod has been a freelance cartoonist, writer, and graphic facilitator in Halifax, Nova Scotia, Canada for the past seven years. She is currently working on a humorous graphic novel about navigating her mother through nine years of long-term care.

COMMENTARY

Toward Better HIV Care: A Thought Leader Interview

Brian Raymond, MPH; Benjamin Wheatley, MPP

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ABSTRACT

The two largest providers of HIV care in the US are the Veterans Administration and Kaiser Permanente. Both organizations are significantly outperforming the general population in implementing the HIV Care Continuum, which involves 1) testing and diagnosis, 2) linkage to care, 3) retention in care, 4) initiation and continuation of antiretroviral therapy, and 5) achievement of viral suppression. Adherence to the care continuum allows people living with HIV to achieve viral suppression to levels where the virus is undetectable. Such individuals are less likely to transmit the virus than are other infected individuals not receiving medical care. In this interview article, leaders from the two comprehensive integrated health care systems share insight about how their organizations achieve top-quality HIV care outcomes, as well as their ongoing efforts to identify and close gaps in care.

INTRODUCTION

People living with HIV who receive comprehensive HIV treatment and take antiretroviral medications as prescribed can achieve viral suppression, meaning that the virus is undetectable in their bodies. This result is sustainable over time. Such individuals are at less risk of the development of AIDS or of transmitting the virus than are other infected individuals who are not receiving medical care.

The two largest providers of HIV care in the US are the US Department of Veterans Affairs (VA) and Kaiser Permanente (KP). Compared with the general US population, HIV patients in these integrated delivery systems had significantly better outcomes along the five steps of the HIV care cascade (also called HIV treatment cascade and HIV care continuum). This care cascade involves 1) testing and diagnosis, 2) linkage to care, 3) retention in care, 4) initiation and continuation of antiretroviral (ARV) therapy, and 5) achievement of viral suppression (Figure 1).[1] Independently published results from both organizations demonstrate that improved outcomes along the HIV care cascade are being achieved in these integrated health care systems.[2-4]

Here, edited and condensed for space, is a recent conversation with experts from the VA and KP (see Sidebar: Subject Matter Experts) about how their organizations achieve top-quality HIV care outcomes and how these results might be replicated elsewhere.

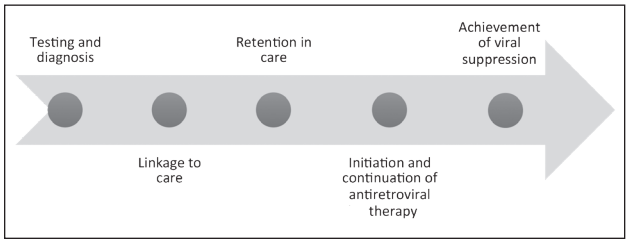

Figure 1. HIV care cascade.[a]

[a] The HIV care cascade (or continuum) "is a model that outlines the sequential steps or stages of HIV medical care that people living with HIV go through from initial diagnosis to achieving the goal of viral suppression (a very low level of HIV in the body)."[1] Each step in the cascade has been associated with lower mortality, improved patient health, and even lower transmission of HIV.[2]

1. Backus L, Czarnogorski M, Yip G, et al. HIV care continuum applied to the US Department of Veterans Affairs: HIV virologic outcomes in an integrated health care system. J Acquir Immune Defic Syndr 2015 Aug 1;69(4):474-80. DOI: https://doi.org/10.1097/QAI.0000000000000615.
2. What is the HIV care continuum? [Internet]. Washington, DC: HIV.gov; last updated 2015 Aug 4 [cited 2017 Sep 29]. Available from: www.aids.gov/federal-resources/policies/care-continuum/.

CHALLENGES

Institute for Health Policy (IHP): In the general population, more than 50% of individuals diagnosed with HIV are not engaged in care. Why is this number so high?

Pam Belperio: One key reason is that many people living with HIV in the general population may not have insurance coverage, particularly comprehensive prescription plans, like what is available through the VA and KP. They may not regularly seek out a health care practitioner because they pay out of pocket, especially for younger populations. For the same reason, they may not be engaged in health care in general.

Michael Horberg: I also think you have to break this down by demographic groups. When we start talking about Latino or

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African American populations, I think there are still disparities and a lack of trust toward the health care system, reflecting a lack of access to care. And I think certainly if you start talking about the rural South, you're talking about lack of easy access to quality care.

And when you also talk about the men-having-sex-with-men population, there has always been a certain amount of homophobia, whether internal or external—that has precluded good access to health care.

Lisa Backus: We know that men in general don't have quite as much health care-seeking behavior, so getting them diagnosed and engaged in care is more difficult. Inadequate insurance coverage for that population is often a big barrier to care. And of course, there's the big stigma issue. Being engaged in care may readily identify you as having HIV, so the stigma associated with accessing care might be a reason as well.

IHP: What has been the most challenging segment of the HIV care cascade for your organization to make improvements on and why?

Backus: For the VA, the biggest challenges at this point are still getting people diagnosed, and then retention in care. In general, we do an incredibly good job once people are retained in care—getting them "on" ARV therapy and getting them virally suppressed. The challenge that remains for us is in the diagnosis and then in getting them to stay in care once they are initially linked to care.

Horberg: For KP, initial linkage to care has been really high; we average 97%. We can get patients in for their first set of labs [laboratory studies], but then of course the challenge is retaining them. The VA (77%) and KP (80%) have exceptionally high numbers for retention in HIV care—really, this is exceptional [Figure 2]. It's important to note that we've got many patients who don't meet the classic definition of care retention—which is 2 face-to-face visits per year with their HIV specialist or primary care physician—but they have been taking their medications, getting their refills and even getting their labs. Many are virally suppressed, especially those who have been in care longer.

Of course, we are always concerned about follow-up and about patients whose viral loads go up, or who develop other illnesses. So, when we say they don't meet the classic definition of retention, that doesn't mean there is no contact. We are using video visits and secure messaging to maintain close contact. We recently presented data from the KP Mid-Atlantic Region showing that patients with one face-to-face visit annually, plus e-mail contact or e-mail plus video visit, had viral suppression comparable to those with at least two face-to-face visits annually.

But again, it's all about the demographic groups. For example, a particularly challenging population for us has been heterosexual black women. Retaining them in care has been difficult for a lot of the reasons, including stigma, childcare obligations, and distrust of the health system.

Among the younger population of men who have sex with men, there are some with a sense of immortality. And frankly, there's a sense among some individuals that health care providers are doing so well in treating HIV that if they delay being treated, they will still be okay. KP and the VA are two integrated health systems that are very good at providing the care, but you have to want to be cared for. That's not to put the blame on the patient; sometimes health care providers aren't good at communicating why retention in care is important.

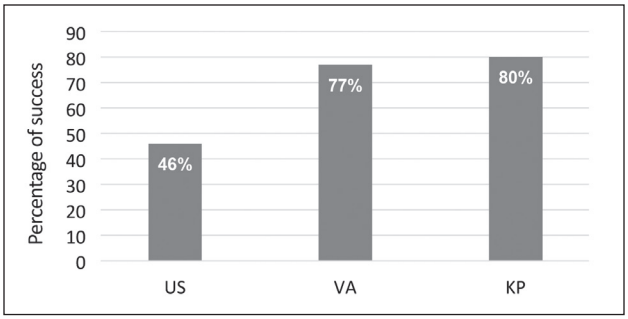

Figure 2. Retention in care.

KP = Kaiser Permanente; VA = US Department of Veterans Affairs.

Belperio: Yes, I think that's right on target. If you look at data published by the VA, it is that younger population that really is the most challenging.

ACHIEVING POSITIVE OUTCOMES

IHP: Both the VA and KP perform substantially better in engaging patients in care than the US general population [Figure 2]. Can you describe what your organization does to get such good results?

Belperio: We've been able to maximize the use of our electronic medical record and patient registry. Once patients are identified as being HIV positive, we can monitor those patients electronically, both from a national standpoint as well as from a local VA facility standpoint. These are incredibly helpful tools that allow us to know who our population is, where they are located, and if they are indeed engaged in care.

The other thing that's a factor in both KP and the VA is that our patients are insured and have drug benefits. Within the VA, barriers to obtaining HIV medications are minimized. For example, the VA has on formulary all FDA [Food and Drug Administration]-approved HIV antiretrovirals. [The VA] has very low or no copays depending on income, refills can be ordered over the phone or the Internet, medications can be mailed, and the VA will provide 90-day supplies for people on stable regimens. Whereas in the general population, drug benefits are certainly not as accessible as they are within the VA and KP.

Horberg: We've also put information systems in place that empower the staff in our multidisciplinary care teams—which can include the HIV specialist, care/case manager, HIV clinical pharmacist, dedicated medical assistants, social worker, etc. Each Region and Medical Center in the biggest Regions can define the team composition differently to best meet their needs. We don't just leave care management to physicians. We have data systems in place that help us identify patients who are falling through the cracks early on, and then do appropriate outreach. Often the nonphysician clinical staff is most aware of who needs an appointment, who has not had labs done, etc.

Patients can call the team about any element of their care. The care team can see if their labs are up to date, when they were last seen, or if their AIDS Drug Assistance Program (ADAP)[a] status is current. Some KP Regions have medical financial assistance programs to help people who are insured, but their medication copays may be a hindrance to good adherence.

Additionally, we've really tried to respect the patients so that they feel welcomed and want to come to the clinic and want to engage with our staff. You know, it doesn't matter if it's HIV or any other condition. If you don't like your doctor and you don't like the clinic staff, then you're less likely to want to be engaged in care.

Do we have care gaps? Absolutely. We're not going to say, "Our retention in care is at 70% to 80%, and the US population is generally at 43%, so we're good." No, that means we have a 20% to 30% gap, and the patients in the gap are at greater risk. We try to engage them as I described earlier.

Backus: The VA also uses multidisciplinary care teams. A lot of our HIV clinics have case managers, social workers, psychologists, or psychiatrists in them because many patients with HIV have multiple diagnoses. Some have mental health disorders. Some have substance use disorders. Some have other medical comorbidities.

Additionally, a lot of the HIV physicians, nurse practitioners, or physician assistants provide complete primary care, so they can also address a patient's hypertension or coronary disease—conditions that we're now seeing in the aging HIV population. If you only have to go to one doctor and can get all your many needs addressed, that will help retain people in care.

The information systems are important. The VA does some national reporting, and we can tell facilities about how many people they have engaged in care, how many people they have on ARVs, or the population that is virally suppressed.

We know that health care professionals are basically all incredibly hard working and want to do the right thing. If you point out to them that the most important metrics are engagement in care, being on ARVs, and being virally suppressed, clinicians will then come up with the local intervention to improve those numbers. Local ownership of innovation is important because often the available clinic staff, the available clinic hours, the available clinic structure is very different across facilities. It makes a huge difference whether you're in San Francisco, [CA] or you're in Fargo, North Dakota. We've learned that if you just give local clinicians some sense of how they're doing on the HIV care cascade, they can come up with much more creative interventions to address issues than we ever could do from a national perspective. Sometimes you just have to give the care team some feedback; then they'll figure out how to address the problem.

Horberg: We're also firm believers in "think globally, act locally." We've set parameters around performance levels we expect to achieve, but we know darn well that what works in Baltimore [MD], for example, isn't necessarily going to work in [Washington] DC. Or what works in San Francisco [CA] won't necessarily be what works in Fresno [CA].

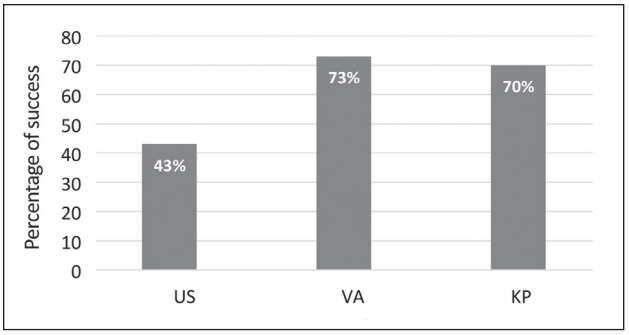

Figure 3. Initiation and continuation of antiretroviral therapy (ART).[a]

[a] Some patients received ART without meeting the classic definition of engaged in care.
KP = Kaiser Permanente; VA = US Department of Veterans Affairs.

IHP: Once engaged in care, patients from the VA and KP are much more likely to initiate and continue using ARV therapy than the US general population [Figure 3]. What are you doing right?

Horberg: Our clinical guideline is that if you're HIV positive, you should be on medications. We're putting things in place to help patients get to their appointments and to help them afford their medications if that's an issue. We're checking their test results regularly. We believe patients should get their viral load checked at least twice a year and more frequently if it's not controlled.

The HIV care cascade is a very classic method, which says you have to be retained in care … to be on medicines, leading to being virally suppressed. In KP—and I'm assuming the same is true for the VA—if you look at all of the patients, and not just those "retained" by the cascade definition, 85% to 86% are virally suppressed. So, it's a much higher number if you get rid of that restriction of having to be also seen twice a year.

Backus: The VA and KP work in very similar ways [in this regard]. We also have policy from our Central Office that says everybody should be on ARVs, and we report on the number of people on ARVs. We don't do it in the traditional care cascade, where you have to have met a prior criterion. At the end of the day, we report on everybody even if they don't meet the strict criteria of two visits a year for engagement in care. Are you on ARVs? Are you virally suppressed? That's what we care about.

The other point is that the VA population has the benefit of continuous insurance. If you're in the VA, we're going to be taking care of you. In other systems, patients have to reapply for the ADAP or sometimes end up losing their Medicaid coverage—these people might not get on ARVs.

As mentioned before, we also try to make it as easy as possible for people to get their medications and to have a supply on hand.

Belperio: Our clinical pharmacists are very actively engaged with the HIV programs within the VA. More than 80% of the facilities have a clinical pharmacist who is involved with their HIV clinic. These pharmacists work very hard in terms

of maintaining adherence and making sure people's medication refills are being addressed appropriately. They ensure that medication changes, drug interactions, and any adverse events that patients may be experiencing are managed appropriately. Questions and issues regarding medications can be addressed and handled by the pharmacists as well. Oftentimes these pharmacists are much more readily available than the patient's practitioner may be.

The VA also has an HIV community advisory board that's made up of veterans, and that group is nationally representative across the country. There are approximately 15 veterans on the rotating board, with advisory board meetings generally twice a year. Veterans bring up issues that they have heard from their communities that they would like to see addressed or resolved and provide feedback on what their experience has been with VA HIV care. We really take to heart those discussions and try to address those issues.

As an example, one of the things that prompted a 90-day HIV drug fill with refills within the VA was that patients who were on stable HIV treatment were running into issues with having to come in or contact their physician for refills, leading to gaps in their treatment. This is a really important piece that the community advisory board alerted us to.

Horberg: To improve adherence, we try to do whatever we can to provide 90-day refills in our system. We actually see higher rates of adherence among our patients who use mail-order pharmacy.

Well-functioning mail-order pharmacies are a great way to improve adherence, and I think that's also related to why we have such good viral suppression and such high adherence rates. And we try to bring "in-house" whatever we can, including full pharmacy benefits and support, our specialists, and care teams. ADAP has been really helpful because we can therefore have that medication adherence data readily available to us. You're not just guessing, "Are they picking up their medicines based on the viral loads?" You're actually seeing the patient's medication refill data.

IHP: Both the VA and KP perform substantially better in achieving viral suppression than the US general population [Figure 4]. Can you describe what your organization does to get such good results?

Backus: It's pretty much all the things that we mentioned before. It is 90-day prescription refills. It's having a mail-order pharmacy service. It's that we report on rates of viral suppression. It's that local clinicians have tools that make it easier to see who is virally suppressed and who is not.

Belperio: It's about multidisciplinary teams and addressing mental health issues. [See next question.]

Backus: Again, clinical pharmacists play a big role. At the end of the day, viral suppression is all about did you receive your medications? Did you take your medications? Have you continued to take your medications? The pharmacists are great at following-up on this stuff.

Horberg: Part of the problem is that everyone thinks there's one step. There isn't. Our data showed that the clinical pharmacist was more critical than a physician, especially when it came to adherence. But it's not just the clinical pharmacist. It's also the integration of care. It's everyone, including the full multidisciplinary care team and the patient, being empowered and feeling responsible and creating our own safety net. Of course, I'm always cautious about using that term *safety net*. If the patient is really struggling or if the patient goes in and out of incarcerations, we say one of the first things you [should] do is just get yourself to our office, and we'll take it from there. Just don't divorce yourself from the system and don't think you don't have a medical home.

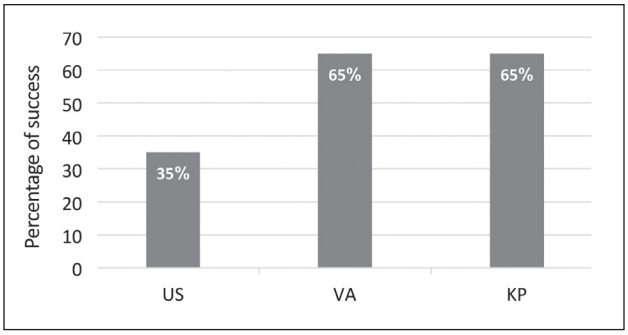

Figure 4. Achievement of viral suppression.[a]

[a] Some patients achieved viral suppression without meeting the classic definition of engaged in care.

KP = Kaiser Permanente; VA = US Department of Veterans Affairs.

IHP: Can you elaborate on the importance of mental health integration?

Belperio: Within many of the VA HIV clinics, there is mental health integration, either directly in the HIV clinic itself or through a direct connection with a particular mental health provider or clinic. Such a relationship makes for a very easy transition between addressing the patient's HIV medical needs and his/her mental health or substance use needs as well.

There's a lot of education that is done within our mental health and substance use disorder programs regarding HIV care and special needs of HIV patients as it relates to their mental health and substance use disorders. Educational outreach on the management of alcohol and substance use disorders in HIV has really been an important piece. The collaboration between HIV clinicians and the mental health and substance use disorder clinic has really made an incredible difference in making sure those needs get addressed so that they don't interfere with the medical care that's being provided to the HIV patients.

Horberg: I would add that by making mental health internal to the health program, you're also making sure that, by it being seamless, there's no drug interactions and the medical and psychiatric treatments are complementary to each other, if not even synergistic.

Belperio: It goes back to that whole idea of one-stop shopping and keeping a patient-centered focus. Bringing the

care to the patient, rather than the patient having to go to another clinic location on another day to see his/her mental health practitioner. The goal is really to center care around the patient, rather than sending the patient off into different directions for mental health services.

OBSTACLES PATIENT POPULATIONS FACE

IHP: What segments of your patient populations are most vulnerable to falling off the HIV care cascade and at which segments? What are the most important obstacles these populations face?

Backus: For the VA, I think two groups of patients are most vulnerable. First, there is a group of patients with multiple diagnoses, sometimes quadruple diagnoses. The population contends with homelessness, mental health disorders, substance use disorders, in addition to their HIV. For a lot of those people, figuring out where you're going to get your next meal or where you're sleeping far outweighs concerns about how they're going to get their HIV medications.

The other vulnerable population is the relatively newly diagnosed young individuals who are asymptomatic. Michael [Horberg] alluded to this population. They're 25 [years old], and they feel great. Their peers may tell them, "Don't worry about it. There are great drugs, and you can wait 10 years or 15 or 20 years to take the drugs."

Both of those are populations we lose on the engagement to care aspect of the care cascade. We get them linked the first time, but then they do not make it to subsequent appointments.

Horberg: We have concerns about African American women and people of color in general from the national [Centers for Disease Control and Prevention] data. The issue is that strategies to address various demographic groups are not necessarily the same. It's not a one-size-fits-all proposition. And we know the face of the epidemic and the nature of the epidemic vary geographically. So, what I might do in San Francisco [CA] may not work in other cities. And sometimes that applies even within our own self-imposed geographic Regions like Northern California or the Mid-Atlantic.

FUTURE INNOVATIONS

IHP: What innovations does your organization have on the horizon that will help to further improve HIV care in the near future?

Backus: The VA has recently expanded its use of telehealth and secure messaging to make it easier for people to connect with their clinicians. We are particularly targeting this strategy on the younger population that we think we may be missing. They want to send text messages, or they want to just communicate with their practitioner via e-mail.

Some of the homeless population have only cell phones because they don't have fixed addresses. We used to send only appointment letters to people. Well, if you're homeless, I can't send the appointment letter because you have no address. So, we have to change how we notify people about appointments and say, "Okay, we're going to send text alerts to remind people that they have appointments."

We realize that some of these innovations are generational. Some of the older people want a letter, and they don't have e-mail and don't want you calling them. So, we have to figure out the right form of patient outreach and adapt it to an individual.

We're also doing some technologic things to make data more available to care teams because we do think it makes it easier for clinicians to assess their panels and assess their performance.

To date, the VA has not been prescribing that much PrEP [preexposure prophylaxis] to prevent HIV infection. I think that's one of the other things coming in the future, and we do some better targeting of PrEP.

Belperio: Consent to testing has been a barrier to HIV testing in the past. Some of those walls have been broken down, and we are not requiring the written consent that had been required and has been a big barrier in the past. Now, HIV testing can be done with oral informed consent from the patient. That consent is documented in the electronic record by the clinician.

I will also emphasize the role of clinical video telehealth and empowering the patient to become more engaged in their care by making things easier for them to stay linked in care. If the HIV provider is not at the VA clinic location that's closest to the patient, then our video telehealth services can help them access an HIV practitioner remotely.

My HealtheVet, VA's patient portal, is a way for patients to communicate with their clinician and track their care through various electronic modalities. It empowers them to take on extra responsibility regarding their health care and makes it easy for them to contact their practitioners. The turnaround is quick, and patients seem to really like using that method of communicating with their clinician and following their own progress. They have access to all of their lab data, visits, [and] prescriptions, and they can use it to refill prescriptions electronically.

So, that's been a really positive advancement. My HealtheVet is not specific to HIV, but it's been used widely across the HIV segment within the VA.

Horberg: We are trying to get more patients on PrEP and identifying more and more patients at risk, especially among men having sex with men, women at high risk, and women [wanting] to get pregnant. A big focus going forward is a renewed emphasis on STDs [sexually transmitted diseases]—diagnosis and treatment, both among men having sex with men and HIV-positive patients. This focus includes STD self-testing of throat and rectum for the men-having-sex-with-men population. We know that urine tests didn't pick up all cases of gonorrhea and chlamydia.[4]

Like the VA, KP has a patient portal, and we're trying to encourage patients to ask their doctors or other members of the care team questions online before there's an issue or an issue boils up to a crisis. Refills of medication, requesting labs to be ordered, and communicating lab results in a more timely manner are all part of the patient portal.

We also are applying video visits in telehealth, especially for PrEP but also for some of the HIV return visits. Data from the KP Mid-Atlantic Region showed that one in-person visit with the HIV specialist plus e-mail did not have statistically

significantly different results compared with two in-person visits a year for viral suppression. So, we do know that for a lot of patients they don't need to be physically seen to be doing well.

I also think renewed emphasis on multidisciplinary care teams, especially with attention to mental health screening, alcohol and drug use, and then getting the patients into appropriate programs have been important. I'm not sure any of those in and of themselves are an "innovation," but it's like everything we've been talking about here. Every incremental bit contributes to the overall good results.

On a cautionary note, I think there has been a certain sense that things have been pretty good. So, I think there needs to be renewed emphasis on both prevention and treatment; there always needs to be. Today, there's uncertainty about federal HIV care financing. Drastic cuts have been proposed. We could see a lot of the great gains that have been made thrown into great disarray as a byproduct of that. ❖

[a] AIDS Drug Assistance Programs are a set of programs in all 50 states in the US that provide Food and Drug Administration-approved HIV treatment drugs to low-income patients in the US. The programs are administered by each state with funds distributed by the US government.

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References

1. Backus L, Czarnogorski M, Yip G, et al. HIV care continuum applied to the US Department of Veterans Affairs: HIV virologic outcomes in an integrated health care system. J Acquir Immune Defic Syndr 2015 Aug 1;69(4):474-80. DOI: https://doi.org/10.1097/QAI.0000000000000615.
2. Horberg MA, Hurley LB, Klein DB, et al. The HIV care cascade measured over time and by age, sex, and race in a large national integrated care system. AIDS Patient Care STDS 2015 Nov;29(11):582-90. DOI: https://doi.org/10.1089/apc.2015.0139.
3. CDC. Monitoring selected national HIV prevention and care objectives by using HIV surveillance data, United States and 6 dependent areas, 2012. HIV Surveillance Supplemental Report 2014:19.
4. Harrison P. Urine tests miss sexually transmitted infections [Internet]. New York, NY: Medscape; 2015 Oct 16 [cited 2017 Sep 29]. Available from: www.medscape.com/viewarticle/852800.

EDITORIAL

Access to Affordable Housing Promotes Health and Well-Being and Reduces Hospital Visits

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ABSTRACT

Clinical interventions can only partially mitigate homelessness and housing insecurity, which are threats to health and well-being. Clinicians have several opportunities to address these problems: They can refer patients who are homeless or housing insecure to support services, advocate for their employer or care group to commit resources to end homelessness and housing insecurity, and/or work with government and private sector community organizations to address and eliminate these problems. Citing examples from around the US, we will illustrate how clinics, hospitals, health plans, and public health organizations work to engage in initiatives to end homelessness and housing insecurity.

INTRODUCTION

In 2013, the lack of affordable housing was the leading cause of homelessness in America's 25 largest cities,[1] and 10% of low-income renters lived in units that lacked complete plumbing or kitchen facilities, experienced frequent breakdowns in major systems, or had to address other physical housing defects.[2] In 2014, 7 million people in poor households (2.2% of the total US population) were living with family and friends, and the number of households paying more than 50% of their income toward housing increased to 6.6 million, a 27.7% increase since 2007. On the night of the 2015 homelessness census, 1 of every 567 Americans was sleeping outdoors, in an emergency shelter, or in transitional housing.[3]

The Family Options Study reported that it costs $4800 per family per month to house a family in an emergency shelter.[4] Homelessness and housing insecurity create a vicious cycle that destroys well-being and can be fatal: Adults who are homeless or housing insecure are less likely to have goal-oriented thinking and more likely to experience psychological distress, substance use, intimate partner violence, and symptoms of trauma.[4] Children who are homeless or housing insecure exhibit more antisocial behavior, less prosocial behavior, more sleep problems, and difficulty advancing in school.[4]

Homeless people die at about four times the rate of housing-secure people in the general population,[5] and housing-insecure individuals are likely to delay medical care because of costs.[6] Lack of health insurance and the inability to follow through on the treatment of chronic conditions can exacerbate illnesses that would normally respond to medical intervention. Without affordable, accessible health care, illness or injury can interfere with employability that, in turn, increases the likelihood of poverty and homelessness.

HEALTH PROMOTION THROUGH AFFORDABLE HOUSING

Increased access to affordable housing promotes health and well-being.[4] Housing can improve the effectiveness of care for patients whose coverage is capitated through Medicaid or similar programs. Promoting health through housing will become increasingly important as health care payments transition from volume-based to value-based models. Investments that reduce homelessness are a good value relative to many clinical services that are offered as a matter of course.[7] These initiatives also can stabilize neighborhoods surrounding health care facilities and increase the comfort levels of patients, families, employers, and others who visit a health care organization.

Benefits to Patients

Stable housing for homeless patients, especially those with mental illness and/or people fleeing domestic violence, can reduce Emergency Department visits and hospitalizations.[8] Stable housing also can improve the management of chronic medical conditions.[9] Children are more likely to meet developmental milestones when raised in stable and healthy housing in which they are not exposed to lead, mold, vermin, or other threats.[10,11] Children spend more time in school when they spend less time in hospitals or in Emergency Departments. They also learn more when stable housing allows for classroom continuity.[12,13]

Benefits to Employees and their Families

The increase in worker productivity that is associated with improved housing can benefit health care organizations as employers.[14] For health care organizations located in older areas of cities in which the housing stock has deteriorated below current standards, housing initiatives can provide attractive, yet affordable, housing that reduces the need for employees and their families to commute long distances between home and work and between home and school.

Housing and Community Development Resources

Policies that regulate banks and the financial services industry have stimulated investments in affordable housing for more than 40 years. The 1977 Community

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Reinvestment Act[15] and the Low-Income Housing Tax Credit are two examples.[16,17] Since 1999, the Healthy Homes Initiatives at the US Department of Housing and Urban Development (HUD) has been leading a federal effort to address lead and other toxins in existing housing stock.

Nearly 1000 private-sector community development financial institutions work at local, regional, and national levels. These institutions are financial intermediaries that have community development as their primary mission. For example, the Local Initiatives Support Corporation (LISC) is a national community development intermediary that was established by the Ford Foundation on the heels of Community Reinvestment Act passage.[15] LISC, community development financial institutions, and other intermediaries provide capital and support capacity building to fuel production and preservation of high-quality affordable rental housing; supportive, service-enriched, mixed-income, and senior rental housing; and affordable home ownership. As a result, the community development sector—with its deep bench of thousands of community development corporations, regional and national nonprofit housing developers, socially minded private developers, and investors—provides the track record, expertise, and resources to create synergy when partnering with private health care systems and public health agencies to advance coordinated projects.

Affordability is created or preserved through a number of avenues including publicly owned housing maintained by a local public housing authority, housing privately owned by nonprofit and for-profit developers, limited-equity programs, and community land trusts. Low-Income Housing Tax Credits, HUD mortgages, the Community Development Block Grant Program, and similar programs support nonprofit and for-profit developers. Because these government programs are limited in scale, "naturally occurring" affordable housing—housing that becomes available within the private market when landlords keep rents relatively low, accept subsidy vouchers from eligible tenants, or own aging properties that cannot command market-level rents—is a helpful complement to new construction. Strategies to improve and to preserve this housing stock have come into favor among local jurisdictions, philanthropists, community residents, organizers, and those working in community development. One example of naturally occurring affordable housing is described in the following paragraph.

EXAMPLE OF MODEL PROGRAMS

Clinics

On the east side of St Paul, MN, the Federally Qualified Health Center, East Side Community Health Services, is collaborating on a housing initiative with Rolling Hills Apartments to serve recent immigrants and refugees with naturally occurring affordable housing.[18] These 2 populations have unique needs because many have experienced trauma and torture. They also tend to lack experience with and trust in Western medicine. Rolling Hills is a renovated 108-unit "housing of last resort" complex. During renovation, space was added for health services, immigration services, and social/community-building activities. The Federally Qualified Health Center provides preventive services on site and primary health care services at its nearby East Side Family Clinic. The project was made possible by the Healthy Futures Fund, a $200 million initiative formed by the LISC, Morgan Stanley, and The Kresge Foundation.

In Washington, DC, catalytic investments of $14 million to finance a clinic and $22 million for affordable housing from The Healthy Futures Fund allowed the not-for-profit So Others Might Eat and the provider of clinical services Community of Hope to develop the 320,000-square-foot Conway Center.[19] This project brings affordable housing, primary care services, employment training, and economic development opportunities together in one location. In addition to living adjacent to a Metro stop, residents and community members will have access to outreach and health education programs designed to promote healthy lifestyles.

Hospital Systems

A premier example of the "anchor institution" strategy is the Phillips Partnership in South Minneapolis.[20] Initiated by Allina Health and the Abbott-Northwestern Hospital in the 1990s, public partners, community developers, and Allina leaders developed strategies to improve investments in surrounding single-family homes for affordable home purchase and multifamily apartment building quality. An employer-assisted housing strategy complements these physical improvements by helping hospital system employees find quality affordable nearby housing.

In Indianapolis, IN, Eskenazi Hospital is improving community quality by serving as an anchor institution and by placing community health workers in neighborhoods.[21] These activities are all part of LISC's Great Places 2020 initiative. Because 79% of its patients live in neighborhoods that Eskenazi Hospital serves, the hospital is considering assuming an even larger role in its surrounding community.

In New York City, Mount Sinai Hospital is supporting the evaluation of the Two Shades of Green program. Two Shades of Green is a partnership that applies green (energy efficient and low impact), healthy (free of mold, toxins, and vermin), and cost-effective measures to property maintenance and the rehabilitation of existing affordable housing.[22] To reinforce program delivery, LISC New York City mobilized a range of affordable housing, community health, and building science stakeholders. These partners include the New York City Department of Health and Mental Hygiene, New York City Department of Housing Preservation and Development, Steven Winters Associates, Mount Sinai Hospital, and Community Development Corporation. Since 2013, Two Shades of Green has stimulated housing renovation and property maintenance in more than 1500 affordable apartments. Owners of these properties have reduced asthma risk for their residents through property management practices that minimize exposures to pests, tobacco smoke, and harsh cleaning products. Such practices also reduce operating costs, particularly for green cleaning, with several properties experiencing a cost savings as high as 50%. It was critical to collaborate with New York City's Department of Health to bring technical expertise to owners regarding

more effective pest control methods to reduce asthma risks through active design and program evaluation.

Health Plans

A Minnesota Accountable Care Organization, Hennepin Health, comprises 4 organizations (Hennepin County Human Services and Public Health Department, Hennepin County Medical Center, Metropolitan Health Plan, and NorthPoint Health & Wellness Center) to provide integrated medical and social services to low-income Medicaid patients in the county that includes Minneapolis.[23,24] Data sharing and community health workers are critical to the success of this program, which offers housing and social services navigation, job placement supports, Emergency Department triage, and intensive case management. The health plan was started in January 2012 and by December 2014 had enrolled nearly 10,000 members, many of whom were nonwhite middle-age men with unstable housing and significant mental health and substance abuse needs. During the second year of operation, the number of outpatient visits increased by 3.3%, and the rate of Emergency Department and inpatient admissions decreased by 9.1% and 3%, respectively. Quality scores for patients with diabetes, asthma, and vascular conditions improved, and 87% of enrollees expressed satisfaction with their care experience. Hennepin Health's influence on county health and social services costs is not yet known but generally is regarded as positive.

In St Paul, MN, HealthPartners collaborated with Catholic Charities and other community organizations to raise $100 million for the Higher Ground Shelter, which opened in 2016.[25] The Opportunity Center, an adjacent 6-story building in which clients will be able to receive job resources and training, access to veterans' programs, and basic health care services, opens in 2018. The new complex is integral to HealthPartners' Hospital to Home Program because it will provide permanent housing for patients who were homeless when they were admitted to Regions Hospital.[26]

United Health Group, with home offices in Minnetonka, MN, invested $20 million in Chicanos Por La Causa in Phoenix, AZ, to support its integrated health and human services programs within its affordable housing properties.[27] United Health Group also has committed $50 million to the Greater Minnesota Housing Fund to support Low-Income Housing Tax Credit investments in supportive housing.[28]

Public Health and Other Organizations

The Rhode Island State Health Department, in collaboration with the Centers for Disease Control and Prevention, has created 10 Health Equity Zones.[29] Each Health Equity Zone has a work plan that focuses on ideas to improve population health and approaches for investment in local communities. Community engagement is a priority in reaching these public health goals.

Paseo Verde in Philadelphia, PA, demonstrates the accomplishments that can be achieved when a private investor partners with a community organization.[30] This $48 million green and transit-oriented development was created through a partnership between community-based Asociación Puertorriqueños en Marcha[31] and private developer Jonathan Rose Companies. The Paseo Verde complex has a health center and pharmacy on site.

Since 2008, the Baltimore-based Green and Healthy Homes Initiative has led national efforts to integrate lead abatement, healthy homes programs, weatherization, and energy efficiency work.[32] The Green and Healthy Homes Initiative promotes integrated methods to create a whole-house approach to reducing toxins and other contaminants and improve energy efficiency in Baltimore, MD, and other US cities. The Initiative has worked in partnership with numerous health departments and health systems to measure the impact of these interventions on rates of asthma, lead poisoning, injuries, and other respiratory illnesses.

An Uncertain Future

Even with existing government and private initiatives in place, the affordable housing crisis persists for low-income families. The current political climate puts existing funding mechanisms at risk at a time when new partnerships and new perspectives are needed. President Trump's Fiscal Year 2018 budget features substantial cuts to nondefense domestic discretionary programs.[33] As housing costs continue to rise, an increasing portion of the HUD budget is being used to maintain the supply of affordable housing units and rental subsidies, which means that fewer HUD dollars are available for housing production.[34] HUD's HOME Investment Partnerships Program,[35] which provides formula grants to states and municipalities, has seen its budget reduced by more than 50% from its fiscal year 2010 watermark and was threatened with elimination as recently as last year.

These funding mechanisms must be protected if the US is to address the severe affordable housing shortage. In addition to directly participating in the construction of housing or supporting individuals and families, health care organizations can play an important role by advocating for the value of affordable housing and its related health and well-being benefits.

CONCLUSION

Despite the nation's financial recovery since the Great Recession, low-income families remain at high risk for homelessness and housing insecurity because wages are not keeping up with rent inflation.[34] Changes in federal policy are exacerbating the problem. Homelessness and housing insecurity not only reduce the effectiveness of health care and increase its cost; these problems serve as barriers to well-being for adults and children.

Clinicians help patients when they can 1) recognize homelessness and housing insecurity during encounters with patients and refer them to supportive resources, 2) advocate for their health care organizations to become involved in ending homelessness and housing insecurity, and 3) work with government and private sector community organizations to eliminate these problems. Clinic groups, hospital systems, health plans, and public health organizations can promote this "triple aim" by engaging in initiatives to end homelessness and housing insecurity. Although some approaches necessitate

a long-term investment, each approach mitigates an aspect of housing insecurity, which threatens health and well-being and cannot be eliminated even when clinical services are enhanced. ❖

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References

1. Hunger and homelessness survey. A status report on hunger and homelessness in America's cities: A 25-city survey [Internet]. Washington, DC: The United States Conference of Mayors; 2014 Dec [cited 2017 Oct 26]. Available from: www2.cortland.edu/dotAsset/655b9350-995e-4aae-acd3-298325093c34.pdf.
2. The state of the nation's housing: 2016 [Internet]. Cambridge, MA: Joint Center for Housing Studies of Harvard University; 2016 [cited 2017 Oct 26]. Available from: www.jchs.harvard.edu/sites/jchs.harvard.edu/files/jchs_2016_state_of_the_nations_housing_lowres.pdf.
3. The state of homelessness in America: 2016 [Internet]. Washington, DC: National Alliance to End Homelessness; 2016 [cited 2017 Oct 26]. Available from: http://naeh.wpengine.com/wp-content/uploads/2016/10/2016-soh.pdf.
4. Gubits D, Shinn M, Wood M, et al. Family Options Study: 3-year impacts of housing and services interventions for homeless families. Cambridge, MA: Abt Associates, Inc; 2016 Oct.
5. O'Connell JJ. Premature mortality in homeless populations: A review of the literature. Nashville, TN: National Health Care for the Homeless Council, Inc; 2005 Dec.
6. Stahre M, VanEenwyk J, Siegel P, Njai R. Housing insecurity and the association with health outcomes and unhealthy behaviors, Washington State, 2011. Prev Chronic Dis 2015 Jul 9;12:E109. DOI: https://doi.org/10.5888/pcd12.140511.
7. Ly A, Latimer E. Housing First impact on costs and associated cost offsets: A review of the literature. Can J Psychiatry 2015 Nov;60(11):475-87. DOI: https://doi.org/10.1177/070674371506001103.
8. Shumway M, Boccellari A, O'Brien K, Okin RL. Cost-effectiveness of clinical case management for ED frequent users: Results of a randomized trial. Am J Emerg Med 2008 Feb;26(2):155-64. DOI: https://doi.org/10.1016/j.ajem.2007.04.021.
9. Integrating housing & health: A health-focused evaluation of the apartments at Bud Clark [Internet]. Portland, OR: CORE (Center for Outcomes Research & Education); Providence Health & Services; 2013 Oct 7 [cited 2017 Oct 27]. Available from: https://shnny.org/images/uploads/Oregon-SH-Report.pdf.
10. Jelleyman T, Spencer N. Residential mobility in childhood and health outcomes: A systematic review. J Epidemiol Community Health 2008 Jul;62(7):584-92. DOI: https://doi.org/10.1136/jech.2007.060103.
11. Sandel M, Sheward R, Sturtevant L. Compounding stress: The timing and duration effects of homelessness on children's health. Washington, DC: Center for Housing Policy; 2015 Jun [cited 2017 Oct 27]. Available from: www.issuelab.org/resources/21731/21731.pdf.
12. Brennan M. The impacts of affordable housing on education: A research summary [Internet]. Washington, DC: Center for Housing Policy; 2011 May [cited 2017 Oct 27]. Available from: www.nchh.org/Portals/0/HHFF_Impacts_of_Affordable_Housing.pdf.
13. Scanlon E, Devine K. Residential mobility and youth well-being: Research, policy, and practice issues. Journal of Sociology & Social Welfare 2001;28(1):119-38.
14. Healy RG. Effects of improved housing on worker performance. J Hum Resour 1971 Summer;6(3):297-308. DOI: https://doi.org/10.2307/144952.
15. Community Reinvestment Act. PL 95-128, 91 Stat 1147, title VII of the Housing and Community Development Act of 1977, 12 USC § 2901 et seq.
16. Community Reinvestment Act [Internet]. Washington, DC: Board of Governors of the Federal Reserve System; 2014 Feb 11 [cited 2016 Dec 18]. Available from: www.federalreserve.gov/communitydev/cra_about.htm.
17. Low-income housing tax credits [Internet]. Washington, DC: Office of Policy Development and Research (PD&R), US Department of Housing and Urban Development; revised 2017 Jul 10 [cited 2016 Dec 18]. Available from: www.huduser.gov/portal/datasets/lihtc.html.
18. Melo F. St. Paul's east side: Rolling Hills housing complex to get $14.4M rehab [Internet]. St Paul, MN: Pioneer Press; 2015 Nov 5 [cited 2017 Oct 27]. Available from: www.twincities.com/2013/01/07/st-pauls-east-side-rolling-hills-housing-complex-to-get-14-4m-rehab/.
19. Building Hope Capital Campaign [Internet]. Washington, DC: SOME (So Others Might Eat); 2016 [cited 2016 Dec 23]. Available from: http://capitalcampaign.some.org/about/.
20. The Backyard Initiative [Internet]. Minneapolis, MN: Allina Health; c2017 [cited 2016 Feb 12]; Available from: www.allinahealth.org/About-Us/Community-involvement/Initiatives-and-programs/The-Backyard-Initiative/.
21. Great Places 2020 names two new additional neighborhoods [Internet]. Indianapolis, IN: LISC Indianapolis; 2016 [cited 2016 Dec 23]. Available from: http://liscindianapolis.org/great-places-2020-names-two-new-additional-neighborhoods/.
22. Two Shades of Green [Internet]. New York, NY: LISC NYC; 2016 [cited 2016 Dec 23]. Available from: www.lisc.org/nyc/what-we-do/green-and-healthy-neighborhoods/two-shades-green/.
23. Blewett LA, Owen RA. Accountable care for the poor and underserved: Minnesota's Hennepin Health model. Am J Public Health 2015 Apr;105(4):622-4. DOI: https://doi.org/10.2105/ajph.2014.302432.
24. Sandberg SF, Erikson C, Owen R, et al. Hennepin Health: A safety-net accountable care organization for the expanded Medicaid population. Health Aff (Millwood) 2014 Nov;33(11):1975-84. DOI: https://doi.org/10.1377/hlthaff.2014.0648.
25. Pfitzinger J. Seeking higher ground [Internet]. St Paul, MN: St Paul Magazine; 2016 Dec [cited 2017 Oct 27]. Available from: http://saintpaulmag.com/seeking-higher-ground.
26. Hospital to home: Reducing avoidable hospital emergency department visits while improving stability and health. Initial report for program expansion [Internet]. St Paul, MN: Wilder Research; 2014 Feb [cited 2017 Oct 27]. Available from: www.wilder.org/Wilder-Research/Publications/Studies/Hospital%20to%20Home/Reducing%20Hospital%20Emergency%20Dept%20Visits%20While%20Improving%20Stability%20and%20Health,%20Initial%20Report%20for%20Program%20Expansion.pdf.
27. UnitedHealthcare and Chicanos Por La Causa open myCommunity Connect Center in Maryvale to broaden access to social services for low-income residents [Internet]. Phoenix, AZ: UnitedHealth Group; 2016 [cited 2016 Dec 23]. Available from: www.unitedhealthgroup.com/Newsroom/Articles/Feed/UnitedHealthcare/2016/0218myCommunityConnectCenter.aspx.
28. 2014 annual report. Greater Minnesota Housing Fund & Minnesota Equity Fund [Internet]. St Paul, MN: Greater Minnesota Housing Fund, Minnesota Equity Fund; 2015 [cited 2017 Oct 27]. Available from: http://gmhf.com/wp-content/uploads/2016/08/2014-GMHF-AR.pdf.
29. Health equity zones [Internet]. Providence, RI: Rhode Island Department of Health; 2016 [cited 2016 Dec 23]. Available from: www.health.ri.gov/programs/detail.php?pgm_id=1108/.
30. Paseo Verde [Internet]. Philadelphia, PA: Jonathan Rose Companies, LLC; c2017 [cited 2016 Dec 23]. Available from: www.paseoverdeapts.com/.
31. Asociación Puertorriqueños en Marcha for Everyone [Internet]. Philadelphia, PA: Asociación Puertorriqueños en Marcha; 2016 [cited 2016 Dec 23]. Available from: http://apmphila.org/.
32. Green & healthy homes initiative. History and mission [Internet]. Baltimore, MD: Green & Healthy Homes Initiative; c2017 [cited 2016 Dec 26]. Available from: www.greenandhealthyhomes.org/about-us/history-and-mission.
33. President Trump's budget proposes to slash affordable housing and other essential programs [Internet]. Washington, DC: National Low Income Housing Coalition; 2017 Jun 8 [cited 2017 Nov 8]. Available from: http://nlihc.org/sites/default/files/Trump-Budget.pdf.
34. Mazzara A. New census data show rising rents, weak income growth [Internet]. Washington, DC: Center on Budget and Policy Priorites; 2015 Sep 18 [cited 2017 Jun 8]. Available from: www.cbpp.org/blog/new-census-data-show-rising-rents-weak-income-growth.
35. HOME Investment Partnerships Program [Internet]. Washington, DC: Department of Housing and Urban Development; 2016 [cited 2017 Nov 6]. Available from: www.hud.gov/program_offices/comm_planning/affordablehousing/programs/home/.

NARRATIVE MEDICINE

The Harmony of Disequilibrium

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The narrative of life that is revealed during illness and death exposes the fabric and shapes of the human spirit and the texture of human consciousness. The following three clinical encounters illustrate how tragedy, grief, and despair have no architecture: We collapse on cruel universal scars. There is, however, an unbroken flame that never flickers or goes out that brings harmony within the anarchic disequilibrium of human suffering.

CASE 1. THE IMBALANCE OF HEALTH INEQUITY

K could not answer any of my questions. Her mother, standing at the bedside, informed me that K had a seizure that morning, which was why she brought her to the Emergency Department. K grew up in a rural town in the Deep South of the US. She was able to finish high school but because of economic hardship in her family she began working soon thereafter. K became a single mother of 3 children, now between the ages of 3 and 8 years. She was working 2 different jobs to support her children up until the day before her admission to the hospital. Three years ago, as part of her obstetric screening, she was found to be human immunodeficiency virus (HIV)-seropositive. Except when she received zidovudine intravenously before undergoing a caesarean section that prevented her daughter from becoming HIV infected, she has never received antiretroviral therapy. One year ago, K sought medical attention to initiate treatment with antiretroviral therapy. However, because of the nonnegotiable daily commitments of single motherhood, she could not afford the medication copay. K was 30 years old when I met her.

K doesn't live in desperate poverty, but she stands at the lower end of the social scale with important disadvantages that eventually led her to poor health. Poverty alone does not produce ill health—social inequality does. Unequal and unfair life opportunities are the result of long-term structural imbalances of social systems. Indeed, the distribution of health is directly related to life opportunities and reduced functional capabilities, including conditions of life that matter such as decent housing, adequate nutrition, social support, access to schools and adequate health care, and many other structural factors. Yet amid the increasing entropy of daily life and as the result of social inequities, life went on for K until her illness struck her ability to care for her children.

K was suffering from intracranial hypertension secondary to cryptococcal meningoencephalitis as a manifestation of advanced HIV-associated immunosuppression. Every evening, after work, K would spend time with her children, assisting them in completing their homework and preparing dinner for them. Despite being a single mother of three and facing substantial financial constraints, she never applied for welfare support or requested food stamps support. Who would take care of her children if she died from this life-threatening fungal infection? And if she died, what were the chances of her children remaining trapped in this social vacuum? K was treated with antifungals and underwent placement of a lumbar drain to continuously release cerebrospinal fluid to reduce her intracranial pressure. After a prolonged hospitalization and rehabilitation process, as of this writing she is receiving daily antiretroviral therapy and remains on oral suppressive antifungal therapy. She has returned once again to helping her children complete their homework after school. She is living on food stamps; however, she is planning to return to work as soon as she recovers her strength. Because of her adherence to antiretroviral medications, her plasma level of HIV ribonucleic acid viral load is now undetectable. Her beautiful smile is the most reliable sign of her recovery.

The narrative of health and illness is inexorably linked to societal factors. Unequal distribution of life chances leads to unequally distributed health outcomes.[1] To understand why K became trapped in a position of social disadvantage, there is a need to understand larger societal factors: The immense inequities and vastly complex collective histories of the locations where individuals live and grow up have a direct link to our health outcomes.[1] Inequality disempowered this single mother: She lacked opportunities to achieve control of her life. She did not have the financial means and social support to empower her to seek adequate medical care, to afford expensive medications, to improve her nutrition, and ultimately to have a prospect to transform her life outlook. She became vulnerable to acquiring HIV infection, and once she acquired this infection, a perpetual cycle of social injustices ensued. If K had succumbed to this fungal disease, chances are that the life-opportunities of her children would have been severely impacted. Adverse childhood experiences, including a poor socioeconomic environment[2] when losing a parent, have important implications for adult life functioning. However, K's children have continued to attend school and also care for their mother, ensuring that she continues to improve medically. Despite the obvious societal imbalances in power and personal agency that underlie the social injustices of our times, K's strength and determination provided a far-reaching equilibrium for her family.

CASE 2. THE ETERNAL FAREWELL

One Friday morning, during clinical rounds, I glanced through the window of room 7 of the intensive care unit. Inside, I watched as a thin, elderly woman placed her arms around her husband's dead body

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and lifted him to an almost 45-degree angle, where she continued to embrace for the last time the man with whom she had spent the past 63 years of her life. It became apparent that this moment of farewell reflected a life of happiness, sorrows, and joys that this couple had shared. She recruited strength from an unconscious primeval pool to overcome the pain of losing her life partner, which allowed her to lift his heavy, lifeless body with ease. It was the confluence of all emotions summed up into one final act of love.

Life is maintained by preserving a state of energy imbalance through the movement of molecules. This leads to the generation of action potentials that activate living cells, the building of carbon-based molecules, and the production of the energetic currency that fuels cellular life and helps to maintain vital organic functions against the universal slide toward energetic equilibrium. Human nature emanates from this energetic disequilibrium to produce the harmony of living.

Death is biologically programmed into the matrix of life. The force field around the cell stop as the electrons and protons cease to flux through membranes, creating a state of energetic balance. However, when someone we love becomes severely ill and dies, we cannot simply accept that everything gets lost in the molecular and biological flow: Our destiny manifests through a tapestry of emotions including timeless memories and storytelling that go far beyond our one life. The sum of our life experiences and memories plays an influential role in our human culture and collective history. The quantum forces responsible for shuffling the dimensional grids of time and space are overpowered by the energy flux that bonded this couple.

CASE 3. THE EQUILIBRIUM OF DYING WELL

M's mother has cared for him without interruption for almost 2 years, ever since the accident that left him in a persistent vegetative state. A few months after turning 21, M was run over by a car when he stopped on the highway to assist a woman and her child who had been in a car accident in front of him. Since the accident, M has required mechanical ventilatory support through a tracheostomy, a gastrostomy tube for feeding, and 24-hour nursing supportive care. I met M when he presented to the hospital in septic shock precipitated by an episode of ventilator-associated pneumonia. During my initial evaluation, I suggested to M's mother that she consider palliative and compassionate end-of-life care. After listening to this recommendation, she became visibly upset. At her request, we initiated aggressive antimicrobial and supportive intensive care unit management, and he remained in the intensive care unit for many days. Every night, his mother stayed with him and continued to restlessly care for him during the daytime. One morning I glanced through the glass of his room, and M's mother stepped outside the room. That day, her silence said everything: She was ready to let him reach the end of his life. She wanted to remember her son as the hero who offered his assistance, and ultimately his life, to an unknown woman and her baby in need in the middle of a busy highway. An hour later, M died in the company of his mother and his sister. The room was surrounded by an unspeakable harmony. His mother's silence was louder than any word or sound. Her serenity traveled freely through the plumbing of the soul, synchronizing everyone present to an ancestral rhythm.

The narrative of death is as important as the narrative of life. There is sacrifice and dignity in the life of a star: The violent death of an ancient star provided the building elements responsible for our lives. Similarly, M possessed a human spirit capable of courage and sacrifice. In the darkness of reality, his mother's endurance and compassion shed light and warmth into the life of her son up until his last breath.

RESTORING THE HARMONY

Tragedy and despair split human beings into the raw materials that constitute the human spirit. The spectrum of our biological and existential misfortunes manifests in different forms: As social injustices with unfair distribution of health or as illness and death of a loved one. Yet, during these crucial moments we may discover that, against the tyranny of circumstance, acts of compassion and sacrifice restore a natural sense of cosmic equilibrium to our existence that ripples across past and present. ❖

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References

1. Marmot M, Bell R. Social inequalities in health: A proper concern of epidemiology. Ann Epidemiol 2016 Apr;26(4):238-40. DOI: https://doi.org/10.1016/j.annepidem.2016.02.003.
2. Montez JK, Hayward MD. Cumulative childhood adversity, educational attainment, and active life expectancy among US adults. Demography 2014 Apr;51(2):413-35. DOI: https://doi.org/10.1007/s13524-013-0261-x.

Do Not Forsake the Sick

Even in the stage of dying the physician should not forsake the sick, for even then he may become a benefactor, and if he cannot save, may at least relieve departing life.

— Joseph W Freer, MD, 1816-1877, American physician and surgeon

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Section A.

Article 1. (page 35) Real-World Effectiveness of a Medically Supervised Weight Management Program in a Large Integrated Health Care Delivery System: Five-Year Outcomes

In the study of Kaiser Permanente Northern California's medically supervised weight management program, which of the following was not a predictor of weight loss ≥ 5 % at 5 years:

☐ a. percentage difference in weight loss (baseline to 4 months)
☐ b. baseline comorbidity burden
☐ c. female sex, total meal replacement products used
☐ d. frequency of attending weight management behavioral therapy sessions

Among participants with 5-year follow-up, weight loss of ≥ 5.0% from baseline occurred in:

☐ a. 20%-30%
☐ b. 30%-40%
☐ c. 40%-50%
☐ d. 50%-60%

Article 2. (page 43) Impact of Standardizing Management of Atrial Fibrillation with Rapid Heart Rate in the Emergency Department

Which of the following was the conclusion reached by the authors of this article?

☐ a. beta-blockers were shown to be superior to calcium channel blockers for rate control and led to a decrease in the admission rate for primary atrial fibrillation
☐ b. standardizing the treatment of atrial fibrillation, with emphasis on early use of oral rate control medication, was associated with a decrease in hospital admission for atrial fibrillation with rapid ventricular response
☐ c. increased use of direct-current cardioversion in patients with rapid atrial fibrillation did not appear to decrease the hospital admission rate
☐ d. using a standardized approach to atrial fibrillation in the Emergency Department with rapid ventricular response led to worse outcomes and increased length of stay in the Emergency Department

Which of the following atrial fibrillation patients is not a good candidate for the atrial fibrillation guideline discussed in this article?

☐ a. a 60-year-old patient presents to the Emergency Department with palpitations and an irregular heart rate of 160 beats/min after drinking a cappuccino at a local coffee house
☐ b. a 69-year-old patient with chronic atrial fibrillation experiences some chest tightness and mild shortness of breath. On arrival to the Emergency Department his pulse is found to be 140 beats/min
☐ c. a 70-year-old patient arrives at the Emergency Department via ambulance from home with a complaint by family members of altered mental status. The patient has a blood pressure of 70 systolic and a heart rate of 180 beats/min
☐ d. an 80-year-old patient is sent to the Emergency Department by her physician because of new-onset atrial fibrillation with a heart rate of 136 beats/min found during her annual physical

Article 3. (page 49) Lifestyle Medicine: A Brief Review of Its Dramatic Impact on Health and Survival

Limitations to physicians addressing lifestyle issues in the management of chronic diseases include the following except

☐ a. inadequate amount of time for patient visits
☐ b. inadequate practitioner education to present information addressing the effectiveness of lifestyle interventions in the management of chronic diseases
☐ c. patients' perception that they need a prescription for every complaint
☐ d. easily accessible and accurate information for physicians and patients regarding a healthy lifestyle

Western nations spend more money per capita and yet have poorer outcomes than less advanced countries because there is

☐ a. a lack of a proactive approach to disease management
☐ b. a lack of concern and care by health care practitioners
☐ c. adequate lifestyle medicine education of health care professionals to address chronic conditions
☐ d. a clear understanding of the importance and value of nutritious foods

Article 4. (page 71) Current Epidemiology and Management of Radiocontrast-Associated Acute- and Delayed-Onset Hypersensitivity: A Review of the Literature

A 70-year-old woman with type 2 diabetes presents to the emergency room with evidence for an acute myocardial infarction. Angioplasty is now pending, but she has a history, in 1975, of anaphylaxis associated with radiocontrast use. She has also avoided shellfish since 1975, but she had tolerated shrimp many times before 1975. The safest way to proceed is to

☐ a. use iohexol
☐ b. premedicate with prednisone 40 mg at least 6 hours before the angioplasty and diphenhydramine 50 mg 1 hour before the angioplasty
☐ c. continue to avoid shrimp
☐ d. all of the above

A 50-year-old man had a benign, mild, delayed-onset total-body macular-papular rash that started 2 days after receiving iohexol for an abdominal computed tomography scan. Concurrent with the scan, he had also been exposed to povidone iodine as a skin prep before the suturing of a cut on his right arm. He now needs a head computed tomography scan with contrast. The safest way to proceed is to

☐ a. avoid all future radiocontrast exposure
☐ b. avoid all iodine-containing products
☐ c. use iodixanol without any premedication
☐ d. use iohexol and premedicate with prednisone 40 mg 24 hours before imaging and diphenhydramine 50 mg 1 hour before imaging

Section B.

Referring to the CME articles, how likely is it that you will implement this learning to improve your practice within the next 3 months?

Key
5 = highly likely
4 = likely
3 = unsure
2 = unlikely
1 = highly unlikely
0 = I already did this

	Objective 1 Integrate learned knowledge and increase competence/ confidence to support improvement and change in specific practices, behaviors, and performance.	**Objective 2** Lead in further developing "Patient-Centered Care" activities by acquiring new skills and methods to overcome barriers, improve physician/patient relationships, better identify diagnosis and treatment of clinical conditions, as well as, efficiently stratify health needs of varying patient populations.	**Objective 3** Implement changes and apply updates in services and practice/policy guidelines, incorporate systems and quality improvements, and effectively utilize evidence-based medicine to produce better patient outcomes.
Article 1	5 4 3 2 1 0	5 4 3 2 1 0	5 4 3 2 1 0
Article 2	5 4 3 2 1 0	5 4 3 2 1 0	5 4 3 2 1 0
Article 3	5 4 3 2 1 0	5 4 3 2 1 0	5 4 3 2 1 0
Article 4	5 4 3 2 1 0	5 4 3 2 1 0	5 4 3 2 1 0

Section C.

What other changes, if any, do you plan to make in your practice as a result of reading these articles?

_____

_____

_____

Section D. (Please print)

Name _____

☐ Physician ☐ Non-Physician

Title _____

E-mail _____

Address _____

_____

Signature _____

Date _____

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