

UC Irvine

UC Irvine Previously Published Works

Title

Risk factor paradox in wasting diseases

Permalink

<https://escholarship.org/uc/item/24j753cr>

Journal

Current Opinion in Clinical Nutrition & Metabolic Care, 10(4)

ISSN

1363-1950

Authors

Kalantar-Zadeh, Kamyar
Horwich, Tamara B
Oreopoulos, Antigone
[et al.](#)

Publication Date

2007-07-01

DOI

10.1097/mco.0b013e3281a30594

Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at <https://creativecommons.org/licenses/by/4.0/>

Peer reviewed

Risk factor paradox in wasting diseases

Kamyar Kalantar-Zadeh^a, Tamara B. Horwich^b, Antigone Oreopoulos^c,
Csaba P. Kovesdy^d, Houman Younessi^e, Stefan D. Anker^f and John E. Morley^g

Purpose of review

Emerging data indicate that conventional cardiovascular risk factors (e.g. hypercholesterolemia and obesity) are paradoxically associated with better survival in distinct populations with wasting. We identify these populations and review survival paradoxes and common pathophysiologic mechanisms.

Recent findings

A 'reverse epidemiology' of cardiovascular risk is observed in chronic kidney disease, chronic heart failure, chronic obstructive lung disease, cancer, AIDS and rheumatoid arthritis, and in the elderly. These populations apparently have slowly progressive to full-blown wasting and significantly greater short-term mortality than the general population. The survival paradoxes may result from the time differential between the two competing risk factors [i.e. over-nutrition (long-term killer but short-term protective) versus undernutrition (short-term killer)]. Hemodynamic stability of obesity, protective adipokine profile, endotoxin–lipoprotein interaction, toxin sequestration of fat, antioxidation of muscle, reverse causation, and survival selection may also contribute.

Summary

The seemingly counterintuitive risk factor paradox is the hallmark of chronic disease states or conditions associated with wasting disease at the population level. Studying similarities among these populations may help reveal common pathophysiologic mechanisms of wasting disease, leading to a major shift in clinical medicine and public health beyond the conventional Framingham paradigm and to novel therapeutic approaches related to wasting and short-term mortality.

Keywords

chronic disease states, malnutrition–inflammation–cachexia syndrome, paradigm shift, reverse epidemiology, wasting disease

Correspondence to Kamyar Kalantar-Zadeh, MD, PhD, MPH, Associate Professor of Medicine and Pediatrics, Harold Simmons Center for Kidney Disease Research and Epidemiology, David Geffen School of Medicine at UCLA, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, 1000 West Carson Street, Torrance, CA 90509-2910, USA
Tel: +1 310 222 3891; fax: +1 310 782 1837; e-mail: kamkal@ucla.edu

Current Opinion in Clinical Nutrition and Metabolic Care 2007, 10:433–442

Abbreviations

CHF	chronic heart failure
COPD	chronic obstructive pulmonary disease
CKD	chronic kidney disease
HAART	highly active antiretroviral therapy

© 2007 Lippincott Williams & Wilkins
1363-1950

Introduction

Atherosclerotic cardiovascular disease is the leading cause of morbidity and mortality in the general population in most industrialized nations [1]. Based on many ongoing observational investigations, including the Framingham studies, distinct cardiovascular risk factors such as hypercholesterolemia, hypertension, and diabetes mellitus are among the 'causes' of the cardiovascular disease epidemic in the general population [2]. These risk factors may be engendered by – or at least accentuated in the setting of – the metabolic syndrome and obesity. Hence, obesity and over-nutrition are implicated as the epidemiologic origins of the atherosclerotic cardiovascular disease and death of the late 20th and early 21st centuries. Although the roles played by genetic factors in the development of atherosclerosis are instrumental [3[•]], the causative or permissive role of over-nutrition and related cardiovascular risk factors also appears central. According to the Framingham paradigm, longevity can be achieved by reducing the prevalence and severity of such over-nutrition associated cardiovascular risk factors as hypertension, hypercholesterolemia, and obesity [4[•]]. The latter conditions have also been referred to as the conventional or 'traditional' cardiovascular risk factors, even though they have been implicated as causes of death only during the past few decades. More novel cardiovascular risk factors including inflammation, oxidative stress, and hyperhomocysteinemia have been investigated more recently as additional causes of the cardiovascular disease epidemic.

Despite widespread acceptance of the Framingham paradigm and the related detrimental role of over-nutrition

Curr Opin Clin Nutr Metab Care 10:433–442. © 2007 Lippincott Williams & Wilkins.

^aHarold Simmons Center for Kidney Disease Research and Epidemiology, Los Angeles Biomedical Research Center at Harbor-UCLA, Torrance, California, USA, ^bAhmanson UCLA Cardiomyopathy Center, Division of Cardiology, UCLA David Geffen School of Medicine, Los Angeles, California, USA, ^cDepartment of Clinical Epidemiology, School of Public Health, University of Alberta, Edmonton, Alberta, Canada, ^dDepartment Internal Medicine, Veterans Affairs Medical Center, Salem, Virginia, USA, ^eRensselaer Polytechnic Institute, Hartford, Connecticut, USA, ^fApplied Cachexia Research, Department of Cardiology, Charite Campus Virchow-Klinikum, Berlin, Germany and ^gDivision of Geriatric Medicine, and Geriatric Research, Education and Clinical Center, St Louis Veterans Affairs and Saint Louis University Medical Center, St Louis, Missouri, USA

and obesity in contemporary epidemiology of cardiovascular disease, there are observations that cannot be fully explained by this paradigm. For instance, epidemiologic studies that compare populations, the so-called ecologic studies, indicate that obese nations with over-nutrition have a greater life expectancy [5]. Indeed, according to some ecologic studies, there is a trend between the population-averaged BMI and the life expectancy of a given nation [6].

During the past few years, distinct subpopulations have been identified in whom a similar paradoxical association is observed at the individual level, namely better survival in more obese persons. These paradoxical associations have been observed in chronic disease states and advanced age; these are populations with a shorter life expectancy than the general population and with greater likelihood of wasting and cachexia. The terms 'reverse epidemiology' [7,8], 'risk factor paradox' [9,10], and 'altered risk factor pattern' [11] underscore these paradoxical observations. These terms indicate that certain markers such as lower BMI and lower serum cholesterol, which usually predict a low likelihood of cardiovascular events and an improved survival in the general population, become strong risk factors for increased cardiovascular morbidity and death rate; and certain indicators of over-nutrition such as obesity – even morbid obesity – and hypercholesterolemia actually predict improved outcome. This article reviews the unique clinical and epidemiologic features of populations with a reverse epidemiology (Table 1) and the role of wasting disease in engendering such survival paradoxes.

It is important to note that what we call 'reverse epidemiology', that is, the stronger impact of wasting and under-nutrition, may indeed be the natural epidemiology in human beings. The so-called conventional epidemiology, which is based on the overwhelming role of over-nutrition, is indeed a new, unnatural, and counterintuitive phenomenon in our history. In recent decades, excess weight and obesity have become mass

phenomena with a pronounced upward trend in most industrialized nations. Despite the detrimental long-term effects of being overweight, obese populations are living longer than ever [12].

End-stage chronic kidney disease requiring dialysis

Almost 20 million Americans have chronic kidney disease (CKD), of whom 400 000 individuals have end-stage (stage 5) CKD and must undergo maintenance dialysis to survive [13]. Although dialysis therapy in CKD stage 5 is expected to be life-prolonging, the 5-year survival is currently under 35% [13], because one in every five American dialysis patients dies every year. This 20% annual dialysis mortality rate is worse than that of many cancers in the early 21st century [14^{••}]. Almost half of all deaths in dialysis patients are attributed to cardiovascular disease [13]. The unusually high rate of cardiovascular disease and death in dialysis patients has been attributed to the high prevalence of the cardiovascular risk factors [15]. Numerous recent reports, however, indicate that in marked contrast to the general population – in which cardiovascular risk factors are associated with increased risk for poor outcome – higher BMI, higher serum cholesterol concentration, and higher systolic blood pressure values are paradoxically correlated with decreased morbidity and mortality and better survival in dialysis patients [7]. These apparently counterintuitive associations or survival paradoxes have been referred to as 'reverse epidemiology' [7,11].

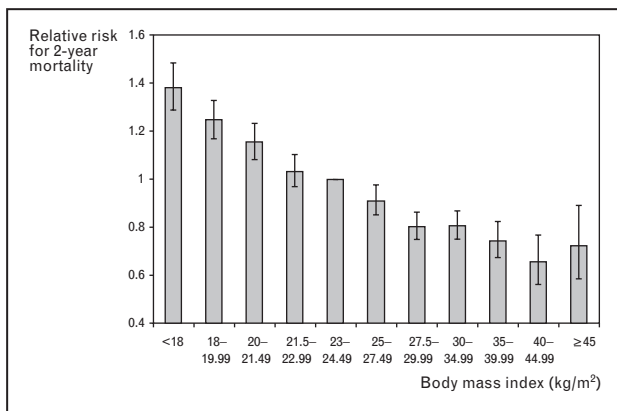
In a recent critical review [16], 11 large studies (including more than 1000 individuals) were identified, each reporting a reverse epidemiology of obesity, that is, obesity paradox, in maintenance hemodialysis patients. Not only is a lower baseline BMI associated with poor survival (Fig. 1), but also losing weight over time is associated with increased risk for death in these patients (Fig. 2) [17]. In a recent observational study [18] greater muscle mass was reported to improve survival in dialysis patients. Another study with repeated body fat measurement in

Table 1 Populations with a reverse epidemiology of cardiovascular risks

Population	Estimated number in the USA (in millions)	Obesity paradox	Lipid paradox	Other survival paradoxes
Maintenance dialysis patients	0.4	+++	++	Hypertension, hyperhomocysteinemia, leptin, creatinine, calcium, iron, AGE ^a
Earlier CKD stages not on dialysis	8–10	++	+	Hypertension, adiponectin ^a
Chronic heart failure	4–5	+++	++	Hypertension, hemoglobin A1c ^a
Advanced age (>80 years)	10–12	+++	+	No data
Malignancy	11–13	++	+	No data
Chronic obstructive pulmonary disease	15–16	++	+	No data
Rheumatoid arthritis	2–3	++	±	No data
Others: AIDS, nursing home residents, acute coronary disease	1–3	+	±	No data
Total	30–40			

^aSee text. ±, mixed or no clear data; +, weak evidence; ++, somewhat consistent data; +++, strong evidence or highly consistent data; AGE, advanced glycation end-products; CKD, chronic kidney disease.

Figure 1 Relative risk for all-cause mortality in a 2-year cohort of 54 535 maintenance hemodialysis patients in the USA



Time-dependent multivariate-adjusted model, based on quarterly (13-week) averaged BMI controlled for case-mix and available time-varying laboratory surrogates of nutritional status and inflammation. Constructed using data presented by Kalantar-Zadeh *et al.* [17].

535 dialysis patients [19] recently showed that a higher level of body fat or an increase in total body fat over time was also associated with greater survival.

Several studies [20,21,22**] indicate that low, rather than high, serum total cholesterol and low-density lipoprotein are associated with poor survival in dialysis patients. Kilpatrick *et al.* [22**] recently showed that the 'cholesterol paradox' is somewhat universal across most subgroups of dialysis patients except for African-Americans, in whom a higher low-density lipoprotein tends to be associated with worse survival – a so-called 'paradox within paradox'. Liu *et al.* [23] showed that the condition termed the 'malnutrition–inflammation–cachexia

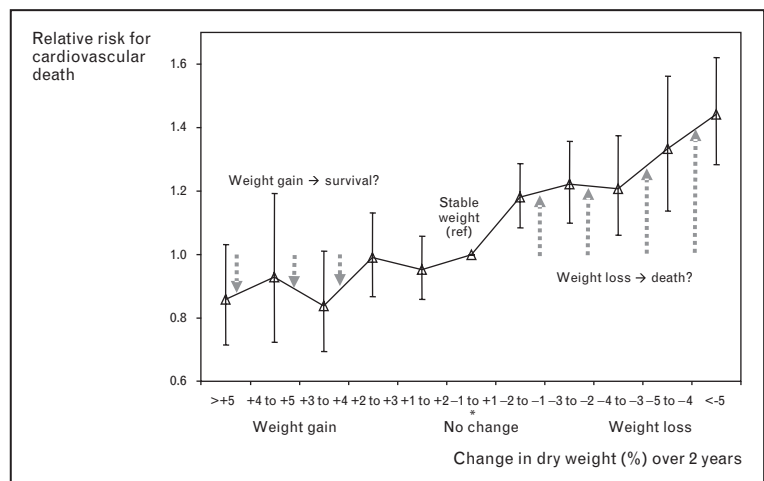
syndrome' [24] leads to the reverse epidemiology of cholesterol in dialysis patients. The randomized, double-blind, placebo-controlled Die Deutsche Diabetes Dialyse Study [25] failed to show an improvement in the composite end-point of death from cardiac causes, nonfatal myocardial infarction, and stroke by lowering cholesterol with statins in diabetic dialysis patients. The latter finding puzzled those who were contending that the reverse epidemiology of cholesterol would be an exclusively statistical phenomenon without any biologic plausibility.

Many observational studies have demonstrated a counterintuitive association between high blood pressure and better survival in dialysis patients, in whom the hypertension prevalence is usually 80% or higher [26]. Some opinion leaders have critically questioned the biologic plausibility of the concept of reverse epidemiology of hypertension, arguing that analytical approaches such as cross-sectional design, inclusion of prevalent patients, and unmeasured comorbidities are at fault [27]. In recent studies, however, even incident dialysis patients exhibited a reverse epidemiology of hypertension [28*].

Several studies have indicated that hyperhomocysteinemia is paradoxically associated with better dialysis survival, a finding that is inconsistent [29]. Interestingly, most folic acid administration trials have not found any survival benefit of reducing homocysteine [30]. Higher levels of serum creatinine [31,32], iron and transferrin saturation ratio [33], calcium [34], leptin [35*,36], and advanced glycation end-products [37] have also been shown to be paradoxically associated with greater survival in dialysis patients.

Figure 2 Changing relative risk for cardiovascular mortality as predicted by changes in weight over time in 46 629 maintenance hemodialysis patients

The regression slope of the change in weight over 2 years indicates that progressively worsening weight loss is associated with poor survival, whereas weight gain exhibits a tendency toward decreased cardiovascular death. The multivariate survival model is controlled for case-mix and available time-varying laboratory surrogates of nutritional status and inflammation, as well as baseline BMI. Ref, reference group for hazard ratio calculation. Constructed using data presented by Kalantar-Zadeh *et al.* [17].



Earlier chronic kidney disease stages not yet requiring dialysis

Until recently it was believed that the counterintuitive phenomenon of reverse epidemiology is restricted to dialysis patients, and that the approximately 10 million individuals with CKD of moderate severity (stages 3 and 4) who are not on dialysis would follow the 'Framingham paradigm'. CKD *per se* is considered a strong and independent predictor of cardiovascular events and death [38]. A recent epidemiologic study [39] showed that death is far more common than progression toward end-stage in CKD. Although obesity can be a risk factor for more rapid progression of CKD [40], recent data indicate that obese individuals with CKD stages 3 and 4 tend to have survival advantages [41^{••}]. Parallel to the foregoing evidence for the obesity paradox in CKD, a cohort study in 986 men with CKD of stages 1–5 not on dialysis identified an inverse association between lipids and survival, hence also indicating that the 'lipid paradox' is at work in earlier stages of CKD [42]. Recently, Kovesdy *et al.* [43] showed that in men with CKD of stages 3–5 and who were not yet on dialysis, lower blood pressure was associated with lower survival rates, especially among those with pre-existing cardiovascular disease. Finally, in another large cohort [44] higher levels of adiponectin, a protective adipokine with survival advantages in the general population, was found to be paradoxically associated with poorer survival.

Survival paradoxes in chronic heart failure

Individuals with chronic heart failure (CHF), currently numbering approximately 5 million in the USA, exhibit

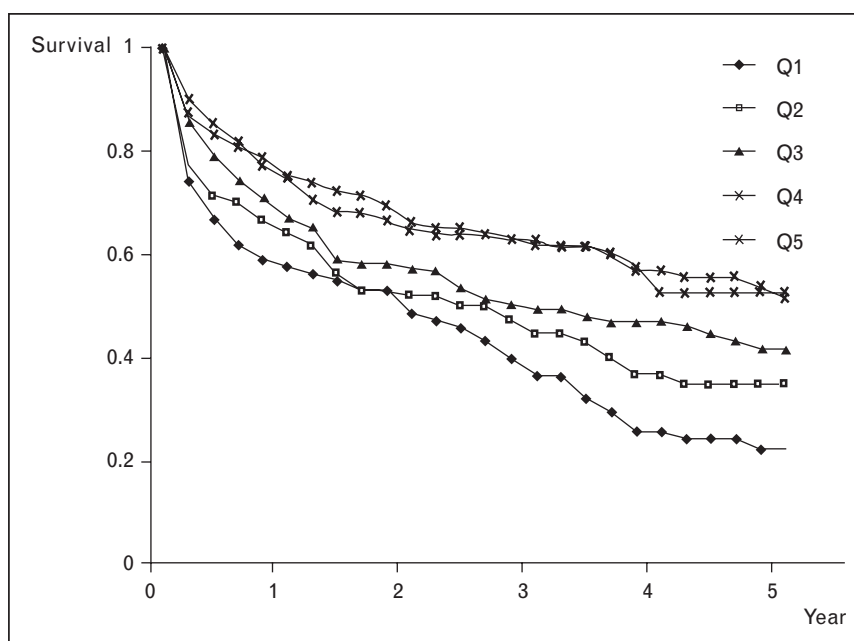
striking similarities to CKD patients. Both CKD and CHF populations have a high prevalence of comorbid conditions, a high hospitalization rate, a low self-reported quality of life, and an excessively high mortality risk, mostly due to cardiovascular causes [14^{••},45]. Like CKD patients, CHF patients with hypercholesterolemia (Fig. 3) [46,47], obesity [48,49], and higher blood pressure [50] have higher rates of survival; whereas low serum cholesterol, BMI, and blood pressure are associated with greater risk for death [14^{••},45]. Finally, although higher hemoglobin A1c in diabetic patients predicts poor outcome and increased risk for CHF development [51] and is associated with mortality in dialysis patients [52], a paradoxical relationship has been observed in patients with pre-existing CHF in that lower hemoglobin A1c ($\leq 7.0\%$) was independently associated with increased mortality [53^{••}].

Geriatric populations

There are currently more than 10 million octogenarians and nonagenarians in the USA, and their proportion is growing [54]. The incidence of cardiovascular disease in the elderly population is high [55]. A reverse epidemiology of traditional cardiovascular risk factors and survival outcomes has, however, been observed in geriatric populations. The relative risk associated with higher BMI decreases substantially in older age groups [56^{••}]. In women older than 75 years or men older than 85 years who participated in the American Cancer Society Prevention Study I [57], BMI was not significantly associated with mortality or cardiovascular death, despite a strong positive association between BMI and mortality in

Figure 3 Probability of death or urgent heart transplant by quintiles low-density lipoprotein

Five-year Kaplan–Meier survival curves for the total study population divided by quintiles of low-density lipoprotein (LDL; <78, 78–99, 100–122, 123–151, >151 mg/dl) in 1134 patients with chronic heart failure. Adapted with permission from Horwich *et al.* [47].



younger cohorts. In the Honolulu Heart Study of elderly Japanese American men aged 71–93 years [58], BMI and skin fold thickness were inversely correlated with mortality. Some but not all studies have also demonstrated a reverse epidemiology with respect to cholesterol levels in the elderly. Low, rather than high, total cholesterol and low-density lipoprotein cholesterol levels in geriatric populations have been associated with increased mortality [59]. Unlike the paradoxical survival trends associated with BMI and cholesterol in the elderly, hypertension and poor glycemic control in diabetic patients remain associated with increased morbidity and mortality in the elderly [60,61].

Rheumatoid arthritis

There are approximately 2.5 million patients with rheumatoid arthritis in the USA alone. Patients with rheumatoid arthritis and those with other similar autoimmune diseases are at elevated risk for atherosclerosis and cardiovascular disease, mainly due to chronic systemic inflammation and other associated risk factors [62–64]. Paradoxical associations between obesity and outcomes in rheumatoid arthritis patients have been described [65]. In a population-based retrospective cohort study of 603 rheumatoid arthritis patients matched to 603 control individuals, low BMI ($<20 \text{ kg/m}^2$) as compared with normal BMI ($20\text{--}30 \text{ kg/m}^2$) in outpatients with rheumatoid arthritis was associated with 3.3-fold increased risk for cardiovascular mortality, even after adjusting for other risk factors including diabetes, hypertension, and smoking [66]. Similarly, a study of 779 patients with rheumatoid arthritis revealed an inverse association between BMI and all-cause mortality. The survival advantages associated with obesity (BMI $>30 \text{ kg/m}^2$) and extreme obesity (BMI $>35 \text{ kg/m}^2$) were independent of age, sex, duration of rheumatoid arthritis, socioeconomic status, smoking status, and medications, but not comorbidity scale or severity of rheumatoid arthritis [67]. No outcome studies have been reported examining the effect of lipid levels or blood pressure levels in rheumatoid arthritis patients.

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) affects approximately 16 million Americans and is the fourth leading cause of death worldwide [68]. Although cardiovascular mortality accounts for roughly 50% of deaths in COPD patients [68], the traditional cardiovascular risk factors of BMI and cholesterol have a 'reverse epidemiology' in this disease entity. Several studies have documented low BMI to be associated with adverse prognosis in COPD patients [69–71]. For example, an analysis of 2132 patients with COPD from the Copenhagen City Heart Study [71] revealed that the relative risks for all-cause mortality in patients with low BMI ($<20 \text{ kg/m}^2$) as compared with those with normal BMI (BMI $20\text{--}25 \text{ kg/}$

m^2) were 1.64 (95% confidence interval 1.20–2.23) in men and 1.42 (95% confidence interval 1.07–1.89) in women. The relationship between BMI and outcomes was strongest in those with severe COPD, with the lowest all-cause and COPD-related mortality in those with BMI of 30 kg/m^2 or greater. Similarly, in chronically hypoxemic COPD patients on long-term oxygen therapy, low BMI was a strong predictor of death and hospitalization rates [69]. Although the data on cholesterol and COPD outcomes is sparse, one large study [72] found a trend toward lower risk for hospitalization in the setting of high cholesterol and a lower risk for death in men with higher cholesterol levels.

AIDS

Reverse epidemiologic associations have been described in populations of patients with HIV infection and AIDS. The association between BMI and outcomes in HIV and AIDS is complex because highly active antiretroviral therapy (HAART) can be associated with changes in body composition, including lipodystrophy, whereas HAART *per se* may induce an atherogenic lipid profile [73,74]. HIV infection has been associated with accelerated rates of atherosclerosis and cardiovascular disease [74]. Nevertheless, low BMI, weight loss, and low total cholesterol have all been associated with poor prognosis in AIDS populations [75,76].

Other populations with a reverse epidemiology

Most observations indicate that among the 13 million American survivors of cancer, higher BMI and serum lipid values are associated with better survival [77,78]. Individuals with liver cirrhosis [79,80], hospitalized patients [81,82], and nursing home residents [81,82] also exhibit an obesity paradox. Finally, those with coronary artery disease also may have a reverse epidemiology [83–85], because a recent meta-analysis [86] showed that patients with coronary artery disease who required revascularization procedures had better chances of survival if their BMIs were greater.

Pathophysiology of the reverse epidemiology

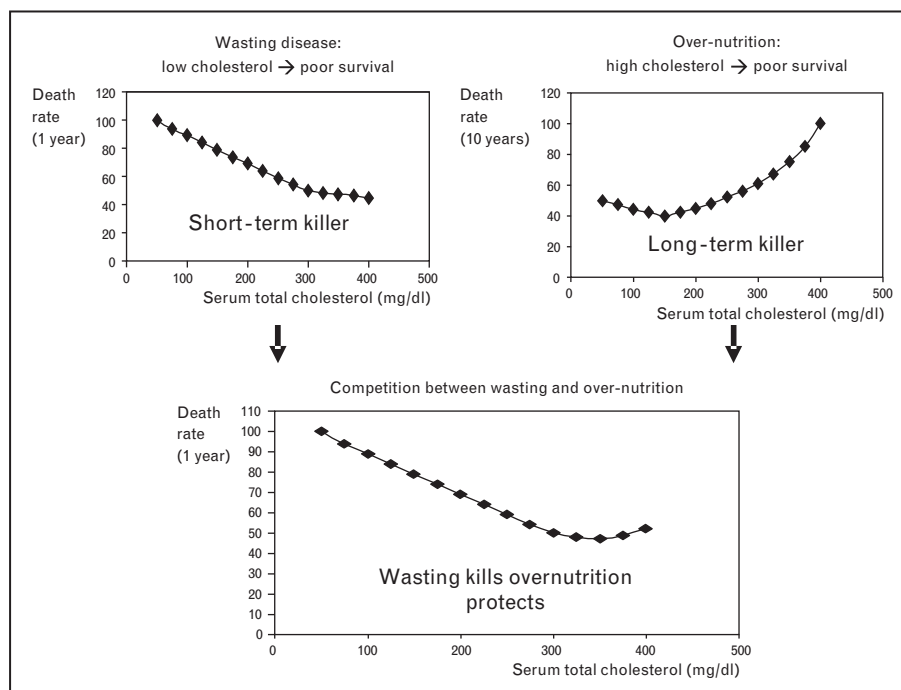
Several hypotheses have been advanced to explain the obesity paradox in chronic disease states such as CHF and CKD that are associated with wasting disease, including the following: time differential of competing risks, hemodynamic stability of obesity, protective adipokine profile, endotoxin–lipoprotein interaction, toxin sequestration of fat tissue, antioxidation of muscle, reverse causation, and survival selection.

Time differential of competing risks

Survival advantages that exist in obese individuals with chronic disease states may, in the short term, outweigh the harmful effects of these risk factors in causing

Figure 4 The temporal discordance hypothesis

Illustrated is the temporal discordance hypothesis – the time differential of two competing risk factors in populations with chronic disease states or wasting disease. The short-term killer (under-nutrition) overwhelms the effect of long-term killer (over-nutrition), which becomes protective over the short-time interval.



cardiovascular disease and death in the long term (Fig. 4) [7]. For example, dialysis patients may not live long enough to die from the adverse effects of over-nutrition, because they are more likely to die much sooner from the consequences of under-nutrition. This so-called 'time discrepancy' between the two sets of competing risk factors – that is, short-term killers (malnutrition–inflammation–cachexia complex) versus long-term killers (obesity and over-nutrition) – can explain why treatment of obesity may be irrelevant, or even harmful, in most dialysis patients if the issue at hand is short-term survival. Currently, two-thirds of all dialysis patients in the USA die within 5 years of commencing dialysis; this 5-year survival is worse than that observed in many cancer patients [14^{••}]. Hence, treatment of malnutrition–inflammation–cachexia syndrome, also known as kidney disease wasting, should be the target of efforts to improve survival in maintenance dialysis patients. Similarly, in most populations with chronic disease states, the short-term death risk is excessively high as a result of the wasting disease. Such individuals will not live long enough to die from obesity or hyperlipidemia – conditions that need years to decades to exert their deleterious impact upon survival.

Hemodynamic stability of obesity

Within the context of a chronic disease state with imminent wasting, obesity and weight gain may be associated with a more stable hemodynamic constellation, including improved hemodynamic tolerance to afterload-reducing

interventions [14^{••},87]. Overweight and obese individuals with chronic diseases are less likely to have cardiovascular instability, especially because they usually have greater systemic blood pressure [48]. Thus, obese patients might better tolerate cardiovascular events or other adverse events that would otherwise occur frequently in the setting of wasting disease. Obesity may also mitigate stress responses and heightened sympathetic and renin–angiotensin activity; the latter would be associated with a poor prognosis in relative fluid overload states such as CHF, CKD and liver disease, among others [88].

Protective adipokine profile

Altered cytokine and neuroendocrine profiles of obese patients may also play a role in conferring survival advantages. Adipose tissue produces adiponectins [89] as well as soluble tumor necrosis factor- α receptors, which may neutralize the adverse biologic effects of tumor necrosis factor- α [90]. The adipokine profile of obesity can effectively mitigate the adverse effects of most chronic disease states and their potential induction of a wasting state.

Endotoxin–lipoprotein hypothesis

Higher concentrations of cholesterol (lipoproteins) may confer a survival advantage in chronic disease states, because lipoproteins can actively bind to and neutralize circulating endotoxins [91]. As a result, having an increased pool of lipoproteins in conditions associated with wasting disease may attenuate the toxicity of circulating endotoxins, which would otherwise cause inflammation and

poor outcome if unbound [92]. This so-called 'endotoxin-lipoprotein' hypothesis was originally advanced to explain the protective role of hypercholesterolemia (lipid paradox) in cardiac cachexia of CHF patients [91].

Toxin sequestration of fat tissue

Higher catabolic rates in cachexia may lead to generation of excessive amounts of toxic metabolites. They can more effectively be sequestered when abundant adipose tissue is present [87]. Indeed, weight loss and reduced adipose tissue reserve is associated with imminent release of, and significant increase in, circulating lipophilic hexachlorobenzene and other chlorinated hydrocarbons [93]. A recent study conducted in dialysis patients [94^{••}] showed that obese patients had a smaller proportion of high metabolic rate compartment, suggesting that dialysis patients with a lower BMI have higher urea generation relative to their body size. These findings may provide an explanation for why loss of body fat was recently found to be associated with increased risk for death in dialysis patients [19].

Antioxidative muscle

Weight loss may also be associated with reduced skeletal muscle oxidative metabolism, leading to weakened antioxidant defense [95]. Hence, in wasting disease associated with sarcopenia, oxidative stress may lead to inflammation and poor outcome.

Reverse causation

It is possible that BMI is not a cause but a consequence of conditions that lead to poor outcome in dialysis patients or in similar populations with a paradoxical risk factor profile. Hence, a 'reverse causation', rather than reverse epidemiology, may be the reason why survival paradoxes such as the obesity paradox are observed. Reverse causation is a known possible source of bias in epidemiologic studies that examine associations without knowledge of the direction of the causal pathway [96]. Comorbid states may lead to kidney disease wasting or cardiac cachexia, and to higher mortality rate. Reverse causation alone, however, fails to explain why obesity, including morbid obesity, is associated with better outcome in the populations listed in Table 1.

Survival selection

Out of 300 million Americans, only 10–11 million are older than 80 years. Hence, the 'unlucky lucky' octogenarians or nonagenarians represent less than 5% of the US population. This may indicate a significant 'survival selection', resulting in genetic constellations in the surviving geriatric population that make them significantly different from their younger predecessors. According to this theory, those few individuals who have distinct survival advantages to reach such an advanced age may be genetically protected against the ravages of cardiovas-

cular disease and other fatal conditions. A similar explanation can be applied to dialysis patients, who represent the 5% survivors of the entire spectrum of CKD, and to CHF patients, who are the survivors of a large population with cardiovascular disease [19,97]. Hence, geriatric populations, or dialysis or CHF patients could be genetically or phenotypically dissimilar to their peers who did not survive. The 'survival selection' hypothesis, however, cannot explain the survival paradoxes observed in other chronic disease states such as rheumatoid arthritis, and neither can it explain why the reverse epidemiology 'reverses' in dialysis or CHF patients after successful kidney or heart transplantation, respectively [14^{••},98^{••}].

Clinical and public health implications of reverse epidemiology

The survival paradoxes in populations with chronic disease states and wasting have contributed to growing confusion. They have left physicians, public health advocates, and many patients with the dilemma of whether to treat obesity, hypercholesterolemia or hypertension in elderly individuals or those with CKD, CHF, COPD, rheumatoid arthritis, AIDS and cancer, among others. The wisdom of recommending weight loss to transplant wait-listed CKD and CHF patients has been questioned even though obesity is associated with greater surgical risk, making this conundrum quite complex [14^{••},98^{••},99]. It is not clear whether muscle [18] or fat [19] confers survival advantages in these individuals. Treatment of hyperlipidemia with statins [100^{••}] may be revisited in dialysis patients. There is even confusion about the treatment of hypertension in some stages of CKD [27,43]. Whereas the concept of reverse epidemiology was at the top of the list of the Clinical Medicine section of Emerging Research Fronts in early 2006 [101], more generalizable models are still sought. Studying half a million dialysis patients as the archetypal population in which such paradoxes manifest may be the key to elucidating the clinical and public health implications of this interesting phenomenon.

Studying the nature and potential pathophysiologic mechanisms of reverse epidemiology raises a number of questions. Does reverse epidemiology have biologic plausibility and, hence, clinical and public health implications in millions of individuals with CKD, CHF, advanced age, malignancy, COPD and AIDS, among other conditions? Alternatively, is it a statistical fallacy or anomaly that needs to be 'controlled away' [23]? In which chronic disease or wasting associated condition is the reverse epidemiology more prominent and robust, or more weak and inconsistent? Is reverse epidemiology the hallmark of wasting disease at the population level, or do such populations exhibit a different type of wasting disease that is slower and more

indolent than the classic cachexia—the so-called ‘cachexia in slow motion’? Can the so-called ‘reversal of the reverse epidemiology’ (or ‘back to normal’) phenomenon upon successful kidney or heart transplantation of dialysis or CHF patients, respectively, or upon HAART in AIDS patients be indicative of effective treatment of the wasting disease in these conditions? Should the therapeutic targets for serum cholesterol, BMI, and blood pressure be different in the 20–30 million Americans who belong to any of the reverse epidemiology populations as listed in Table 1? Should we revise the current guidelines that recommend that obese dialysis or CHF patients on transplant waiting lists lose weight as a prerequisite for transplantation [99]? Is the evidence for reverse epidemiology sufficiently established to justify proposing to research granting agencies the funding of randomized, prospective interventional trials to examine the appropriate therapeutic targets for BMI or some of these other clinical targets in chronic disease states?

The field of reverse epidemiology is in its infancy, but it appears to be evolving quickly. The concept of reverse epidemiology challenges traditional paradigms and remains controversial. The poor clinical outcomes in dialysis, CHF, COPD, and cancer patients do not appear to be amenable to interventions that target traditional cardiovascular risk factors. If our hypothesis is true that a complex set of conditions that are related to malnutrition and inflammation (called herewith ‘wasting disease’) represents the etiology of this risk factor reversal and high death rate, and if the short-term death risk due to wasting overwhelms the long-term effects of over-nutrition, then the key to improving survival in 30 million Americans with a reverse epidemiology may be interventions that can correct wasting disease. If weight loss over time is associated with poor outcome and if weight gain confers improved survival, then nutritional interventions and anti-inflammatory strategies, rather than lipid lowering and weight-reducing interventions, may be the most promising alternatives in these patients. Integrated interventions that target several aspects of the wasting disease in form of combined nutritional treatment strategies with novel micronutrient components that have antioxidant and anti-inflammatory properties may be a solution and need to be tested [102]. Dietary restriction in dialysis and CHF patients in the name of reducing salt, potassium, and cholesterol intake may have unintended deleterious consequences.

Conclusion

Ongoing focus on treating so-called conventional risk factors such as hypercholesterolemia, obesity and hypertension, utilizing treatment targets derived from healthy community cohorts, is unlikely to lead to

an immediate improvement in high mortality rates in geriatric populations and those with chronic disease states, as long as the short-term survival is the issue at hand. Such practices as imposing ‘ideal’ BMI ranges based on general population norms or mandatory weight loss programs for kidney or heart transplant wait-listed dialysis or CHF patients may need to be re-evaluated. Dismissing the theory of reverse epidemiology as counterintuitive and harmful may not be the most scientifically rigorous approach to dealing with this emerging conundrum [101]. The characteristics of a surviving nonagenarian or a dialysis, CHF, or COPD patient with terminal kidney, heart, or lung disease may indeed stand in a clear contradistinction to those predicted by traditional cardiovascular risk factors. Focusing on detection and management of such conventional cardiovascular risk factors as hypercholesterolemia and obesity in these populations would be similar to screening for cancer among patients who already have metastatic cancer. For the 30 million Americans included in the reverse epidemiology populations, it may be time to go beyond the Framingham risk factors and try to explore new paradigms and modalities that can correct their main risk factor, namely the wasting disease.

Acknowledgement

KKZ was supported by research grants from the American Heart Association (#0655776Y), the National Institute of Diabetes, Digestive and Kidney Disease grant # DK61162, and philanthropist Mr Harold Simmons. TBH was funded by NIH training grant 401357J130608.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 552–553).

- 1 Yusuf S. The global problem of cardiovascular disease. *Int J Clin Prac* 1998; 94 (Suppl):3–6.
- 2 Grundy S. Age as a risk factor: you are as old as your arteries. *Am J Cardiol* 1999; 83:1455–1457.
- 3 Mani A, Radhakrishnan J, Wang H, *et al.* LRP6 mutation in a family with early coronary disease and metabolic risk factors. *Science* 2007; 315:1278–1282. This is the first report linking a single gene defect in Wnt signaling to coronary artery disease and multiple cardiovascular risk factors.
- 4 Pardo Silva MC, De Laet C, Nusselder WJ, *et al.* Adult obesity and number of years lived with and without cardiovascular disease. *Obesity (Silver Spring)* 2006; 14:1264–1273. This Framingham cohort based analysis indicates that obesity before middle age is associated with a reduction in life expectancy and number of years lived free from cardiovascular disease.
- 5 Darnton-Hill I, Coyne ET. Feast and famine: socioeconomic disparities in global nutrition and health. *Public Health Nutr* 1998; 1:23–31.
- 6 Menotti A, Blackburn H, Kromhout D, *et al.* Cardiovascular risk factors as determinants of 25-year all-cause mortality in the seven countries study. *Eur J Epidemiol* 2001; 17:337–346.
- 7 Kalantar-Zadeh K, Block G, Humphreys MH, Kopple JD. Reverse epidemiology of cardiovascular risk factors in maintenance dialysis patients. *Kidney Int* 2003; 63:793–808.
- 8 Kalantar-Zadeh K, Kilpatrick RD, Kuwae N, Wu DY. Reverse epidemiology: a spurious hypothesis or a hardcore reality? *Blood Purif* 2005; 23:57–63.
- 9 Fleischmann EH, Bower JD, Salahudeen AK. Risk factor paradox in hemodialysis: better nutrition as a partial explanation. *ASAIO J* 2001; 47:74–81.

- 10 Nishizawa Y, Shoji T, Ishimura E, *et al.* Paradox of risk factors for cardiovascular mortality in uremia: is a higher cholesterol level better for atherosclerosis in uremia? *Am J Kidney Dis* 2001; 38 (4 Suppl 1):S4–S7.
- 11 Kopple JD. The phenomenon of altered risk factor patterns or reverse epidemiology in persons with advanced chronic kidney failure. *Am J Clin Nutr* 2005; 81:1257–1266.
- 12 Lev-Ran A. Human obesity: an evolutionary approach to understanding our bulging waistline. *Diabetes Metab Res Rev* 2001; 17:347–362.
- 13 United States Renal Data System. Excerpts from the USRDS 2005 Annual Data Report: Atlas of End-Stage Renal Disease in the United States; National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. *Am J Kidney Dis* 2006; 47 (Suppl 1):1–286.
- 14 Kalantar-Zadeh K, Abbott KC, Kronenberg F, *et al.* Epidemiology of dialysis patients and heart failure patients. *Semin Nephrol* 2006; 26:118–133.
- This inclusive review compares survival paradoxes between dialysis and heart failure patients, the conundrum of hyperhomocysteinemia in kidney failure, and the reversal of reverse epidemiology after kidney transplantation.
- 15 Vlagopoulos PT, Sarnak MJ. Traditional and nontraditional cardiovascular risk factors in chronic kidney disease. *Med Clin North Am* 2005; 89:587–611.
- 16 Kalantar-Zadeh K, Abbott KC, Salahudeen AK, *et al.* Survival advantages of obesity in dialysis patients. *Am J Clin Nutr* 2005; 81:543–554.
- 17 Kalantar-Zadeh K, Kopple JD, Kilpatrick RD, *et al.* Association of morbid obesity and weight change over time with cardiovascular survival in hemodialysis population. *Am J Kidney Dis* 2005; 46:489–500.
- 18 Beddhu S, Pappas LM, Ramkumar N, Samore M. Effects of body size and body composition on survival in hemodialysis patients. *J Am Soc Nephrol* 2003; 14:2366–2372.
- 19 Kalantar-Zadeh K, Kuwae N, Wu DY, *et al.* Associations of body fat and its changes over time with quality of life and prospective mortality in hemodialysis patients. *Am J Clin Nutr* 2006; 83:202–210.
- 20 Iseki K, Yamazato M, Tozawa M, Takishita S. Hypocholesterolemia is a significant predictor of death in a cohort of chronic hemodialysis patients. *Kidney Int* 2002; 61:1887–1893.
- 21 Habib AN, Baird BC, Leypoldt JK, *et al.* The association of lipid levels with mortality in patients on chronic peritoneal dialysis. *Nephrol Dial Transplant* 2006; 21:2881–2892.
- 22 Kilpatrick RD, McAllister CJ, Kovesdy CP, *et al.* Association between Serum Lipids and Survival in Hemodialysis Patients and Impact of Race. *J Am Soc Nephrol* 2007; 18:293–303.
- This large epidemiologic study conducted in 15 859 hemodialysis patients found that high levels of both total and low-density lipoprotein cholesterol levels have paradoxical associations with greater survival.
- 23 Liu Y, Coresh J, Eustace JA, *et al.* Association between cholesterol level and mortality in dialysis patients: role of inflammation and malnutrition. *JAMA* 2004; 291:451–459.
- 24 Kalantar-Zadeh K. Recent Advances in Understanding the Malnutrition-Inflammation-Cachexia Syndrome in Chronic Kidney Disease Patients: What is Next? *Semin Dial* 2005; 18:365–369.
- 25 Wanner C, Krane V, Marz W, *et al.* Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* 2005; 353:238–248.
- 26 Kalantar-Zadeh K, Kilpatrick RD, McAllister CJ, *et al.* Reverse epidemiology of hypertension and cardiovascular death in the hemodialysis population: the 58th annual fall conference and scientific sessions. *Hypertension* 2005; 45:811–817.
- 27 Foley RN. Cardiac disease in chronic uremia: can it explain the reverse epidemiology of hypertension and survival in dialysis patients? *Semin Dial* 2004; 17:275–278.
- 28 Li Z, Lacson E Jr, Lowrie EG, *et al.* The epidemiology of systolic blood pressure and death risk in hemodialysis patients. *Am J Kidney Dis* 2006; 48:606–615.
- In a national cohort of dialysis patients lower blood pressure was independently associated with poorer survival in most subgroups.
- 29 Suliman ME, Barany P, Kalantar-Zadeh K, *et al.* Homocysteine in uraemia: a puzzling and conflicting story. *Nephrol Dial Transplant* 2005; 20:16–21.
- 30 Wronc EM, Hornberger JM, Zehnder JL, *et al.* Randomized trial of folic acid for prevention of cardiovascular events in end-stage renal disease. *J Am Soc Nephrol* 2004; 15:420–426.
- 31 Lowrie EG, Lew NL. Death risk in hemodialysis patients: the predictive value of commonly measured variables and an evaluation of death rate differences between facilities. *Am J Kidney Dis* 1990; 15:458–482.
- 32 Combe C, McCullough KP, Asano Y, *et al.* Kidney Disease Outcomes Quality Initiative (K/DOQI) and the Dialysis Outcomes and Practice Patterns Study (DOPPS): nutrition guidelines, indicators, and practices. *Am J Kidney Dis* 2004; 44 (5 Suppl 3):39–46.
- 33 Kalantar-Zadeh K, McAllister CJ, Lehn RS, *et al.* A low serum iron level is a predictor of poor outcome in hemodialysis patients. *Am J Kidney Dis* 2004; 43:671–684.
- 34 Kalantar-Zadeh K, Kuwae N, Regidor DL, *et al.* Survival predictability of time-varying indicators of bone disease in maintenance hemodialysis patients. *Kidney Int* 2006; 70:771–780.
- 35 Scholze A, Rattensperger D, Zidek W, Tepel M. Low serum leptin concentration predicts mortality in patients with chronic kidney disease stage 5 on hemodialysis therapy. *Obesity* 2007 (in press).
- In 71 hemodialysis patients who were followed for 7 years, there was 3.8 times higher risk for death in patients with a serum leptin concentration below the median.
- 36 Kalantar-Zadeh K. So, is leptin good or bad in chronic kidney disease? *Obesity* 2007 (in press).
- 37 Schwedler SB, Metzger T, Schinzel R, Wanner C. Advanced glycation end products and mortality in hemodialysis patients. *Kidney Int* 2002; 62:301–310.
- 38 Kovesdy CP, Trivedi BK, Anderson JE. Association of kidney function with mortality in patients with chronic kidney disease not yet on dialysis: a historical prospective cohort study. *Adv Chronic Kidney Dis* 2006; 13:183–188.
- 39 Keith DS, Nichols GA, Gullion CM, *et al.* Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med* 2004; 164:659–663.
- 40 Ejerblad E, Forel CM, Lindblad P, *et al.* Obesity and risk for chronic renal failure. *J Am Soc Nephrol* 2006; 17:1695–1702.
- 41 Kovesdy CP, Anderson JE, Kalantar-Zadeh K. Paradoxical association between body mass index and mortality in men with chronic kidney disease not yet on dialysis. *Am J Kidney Dis* 2007 [Epub ahead of print].
- This pioneering study demonstrates the obesity paradox for the first time in earlier stages of CKD.
- 42 Kovesdy CP, Anderson JE, Kalantar-Zadeh K. Inverse association between lipid levels and mortality in men with chronic kidney disease who are not yet on dialysis: effects of case mix and the malnutrition–inflammation–cachexia syndrome. *J Am Soc Nephrol* 2007; 18:304–311.
- 43 Kovesdy CP, Trivedi BK, Kalantar-Zadeh K, Anderson JE. Association of low blood pressure with increased mortality in patients with moderate to severe chronic kidney disease. *Nephrol Dial Transplant* 2006; 21:1257–1262.
- 44 Menon V, Li L, Wang X, *et al.* Adiponectin and mortality in patients with chronic kidney disease. *J Am Soc Nephrol* 2006; 17:2599–2606.
- 45 Kalantar-Zadeh K, Block G, Horwich T, Fonarow GC. Reverse epidemiology of conventional cardiovascular risk factors in patients with chronic heart failure. *J Am Coll Cardiol* 2004; 43:1439–1444.
- 46 Rauchhaus M, Clark AL, Doehner W, *et al.* The relationship between cholesterol and survival in patients with chronic heart failure. *J Am Coll Cardiol* 2003; 42:1933–1940.
- 47 Horwich TB, Hamilton MA, MacLellan WR, Fonarow GC. Low serum total cholesterol is associated with marked increase in mortality in advanced heart failure. *J Card Fail* 2002; 8:216–224.
- 48 Horwich TB, Fonarow GC, Hamilton MA, *et al.* The relationship between obesity and mortality in patients with heart failure. *J Am Coll Cardiol* 2001; 38:789–795.
- 49 Davos CH, Doehner W, Rauchhaus M, *et al.* Body mass and survival in patients with chronic heart failure without cachexia: the importance of obesity. *J Card Fail* 2003; 9:29–35.
- 50 Horwich TB, Hamilton MA, Fonarow GC. B-type natriuretic peptide levels in obese patients with advanced heart failure. *J Am Coll Cardiol* 2006; 47:85–90.
- 51 Iribarren C, Karter AJ, Go AS, *et al.* Glycemic control and heart failure among adult patients with diabetes. *Circulation* 2001; 103:2668–2673.
- 52 Kalantar-Zadeh K, Kopple JD, Regidor DL, *et al.* Hemoglobin A1c and survival in maintenance hemodialysis patients. *Diabetes Care* 2007 [Epub ahead of print].
- 53 Eshaghian S, Horwich TB, Fonarow GC. An unexpected inverse relationship between HbA1c levels and mortality in patients with diabetes and advanced systolic heart failure. *Am Heart J* 2006; 151:91.
- In a cohort of 123 patients with diabetes and advanced systolic heart failure, elevated hemoglobin A1c levels were paradoxically associated with improved survival.
- 54 Morley JE. Anorexia and weight loss in older persons. *J Gerontol A Biol Sci Med Sci* 2003; 58:131–137.
- 55 Arnold AM, Psaty BM, Kuller LH, *et al.* Incidence of cardiovascular disease in older Americans: the Cardiovascular Health Study. *J Am Geriatr Soc* 2005; 53:211–218.

- 56 Morley JE, Thomas DR, Wilson MM. Cachexia: pathophysiology and clinical relevance. *Am J Clin Nutr* 2006; 83:735–743.
This is an inclusive and updated review of cachexia and wasting disease in geriatric and other populations, along with an introduction to novel and conceptual therapeutic approaches.
- 57 Stevens J, Cai J, Pamuk ER, *et al.* The effect of age on the association between body-mass index and mortality. *N Engl J Med* 1998; 338:1–7.
- 58 Kalmijn S, Curb JD, Rodriguez BL, *et al.* The association of body weight and anthropometry with mortality in elderly men: the Honolulu Heart Program. *Int J Obes Relat Metab Disord* 1999; 23:395–402.
- 59 Tikhonoff V, Casiglia E, Mazza A, *et al.* Low-density lipoprotein cholesterol and mortality in older people. *J Am Geriatr Soc* 2005; 53:2159–2164.
- 60 Fried LP, Kronmal RA, Newman AB, *et al.*, for the Cardiovascular Health Study Collaborative Research Group. Risk factors for 5-year mortality in older adults: the Cardiovascular Health Study. *JAMA* 1998; 279:585–592.
- 61 Aronow WS. Guest editorial: what is the appropriate treatment of hypertension in elders? *J Gerontol A Biol Sci Med Sci* 2002; 57:M483–M486.
- 62 Frostegard J. Atherosclerosis in patients with autoimmune disorders. *Arterioscler Thromb Vasc Biol* 2005; 25:1776–1785.
- 63 Del Rincon I, O'Leary DH, Freeman GL, Escalante A. Acceleration of atherosclerosis during the course of rheumatoid arthritis. *Atherosclerosis* 2006 [Epub ahead of print].
- 64 Solomon DH, Avorn J, Katz JN, *et al.* Immunosuppressive medications and hospitalization for cardiovascular events in patients with rheumatoid arthritis. *Arthritis Rheum* 2006; 54:3790–3798.
- 65 Horwich TB, Fonarow GC. Reverse epidemiology beyond dialysis patients: chronic heart failure, geriatrics, rheumatoid arthritis, COPD, and AIDS. *Semin Dial* 2007 (in press).
- 66 Kremers HM, Nicola PJ, Crowson CS, *et al.* Prognostic importance of low body mass index in relation to cardiovascular mortality in rheumatoid arthritis. *Arthritis Rheum* 2004; 50:3450–3457.
- 67 Escalante A, Haas RW, del Rincon I. Paradoxical effect of body mass index on survival in rheumatoid arthritis: role of comorbidity and systemic inflammation. *Arch Intern Med* 2005; 165:1624–1629.
- 68 Sin DD, Man SF. Chronic obstructive pulmonary disease as a risk factor for cardiovascular morbidity and mortality. *Proc Am Thorac Soc* 2005; 2: 8–11.
- 69 Chailleux E, Laaban JP, Veale D. Prognostic value of nutritional depletion in patients with COPD treated by long-term oxygen therapy: data from the ANTADIR observatory. *Chest* 2003; 123:1460–1466.
- 70 Marti S, Munoz X, Rios J, *et al.* Body weight and comorbidity predict mortality in COPD patients treated with oxygen therapy. *Eur Respir J* 2006; 27:689–696.
- 71 Landbo C, Prescott E, Lange P, *et al.* Prognostic value of nutritional status in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; 160:1856–1861.
- 72 Iribarren C, Jacobs DR Jr, Sidney S, *et al.* Serum total cholesterol and risk of hospitalization, and death from respiratory disease. *Int J Epidemiol* 1997; 26:1191–1202.
- 73 Brown T, Wang Z, Chu H, *et al.* Longitudinal anthropometric changes in HIV-infected and HIV-uninfected men. *J Acquir Immune Defic Syndr* 2006; 43:356–362.
This prospective study examined changes in nutritional and anthropometric markers over time in patients with HIV and compared them with those in individuals without this infection.
- 74 Hsue PY, Waters DD. What a cardiologist needs to know about patients with human immunodeficiency virus infection. *Circulation* 2005; 112:3947–3957.
- 75 Thiebaut R, Malvy D, Marimoutou C, Davis F. Anthropometric indices as predictors of survival in AIDS adults. Aquitaine Cohort, France, 1985–1997. Groupe d'Epidemiologie Clinique du Sida en Aquitaine (GECSA). *Eur J Epidemiol* 2000; 16:633–639.
- 76 Chlebowski RT, Grosvenor M, Lillington L, *et al.* Dietary intake and counseling, weight maintenance, and the course of HIV infection. *J Am Diet Assoc* 1995; 95:428–432; quiz 433–435.
- 77 Chao FC, Efron B, Wolf P. The possible prognostic usefulness of assessing serum proteins and cholesterol in malignancy. *Cancer* 1975; 35:1223–1229.
- 78 Halabi S, Small EJ, Vogelzang NJ. Elevated body mass index predicts for longer overall survival duration in men with metastatic hormone-refractory prostate cancer. *J Clin Oncol* 2005; 23:2434–2435; author reply 2435.
- 79 Matos C, Porayko MK, Francisco-Ziller N, DiCecco S. Nutrition and chronic liver disease. *J Clin Gastroenterol* 2002; 35:391–397.
- 80 Alberino F, Gatta A, Amodio P, *et al.* Nutrition and survival in patients with liver cirrhosis. *Nutrition* 2001; 17:445–450.
- 81 Landi F, Onder G, Gambassi G, *et al.* Body mass index and mortality among hospitalized patients. *Arch Intern Med* 2000; 160:2641–2644.
- 82 O'Brien JM Jr, Phillips GS, Ali NA, *et al.* Body mass index is independently associated with hospital mortality in mechanically ventilated adults with acute lung injury. *Crit Care Med* 2006; 34:738–744.
- 83 Gruberg L, Weissman NJ, Waksman R, *et al.* The impact of obesity on the short-term and long-term outcomes after percutaneous coronary intervention: the obesity paradox? *J Am Coll Cardiol* 2002; 39:578–584.
- 84 Gurm HS, Brennan DM, Booth J, *et al.* Impact of body mass index on outcome after percutaneous coronary intervention (the obesity paradox). *Am J Cardiol* 2002; 90:42–45.
- 85 Lavie CJ, Milani RV. Obesity and cardiovascular disease: the Hippocrates paradox? *J Am Coll Cardiol* 2003; 42:677–679.
- 86 Oreopoulos A, Padwal R, Norris C, *et al.* The relationship between different degrees of obesity and short and long-term mortality postcoronary revascularization: a meta-analysis. *Obesity Res* 2007 (in press).
- 87 Kalantar-Zadeh K, Kopple JD. Obesity paradox in patients on maintenance dialysis. *Contrib Nephrol* 2006; 151:57–69.
- 88 Schrier RW, Abraham WT. Hormones and hemodynamics in heart failure. *N Engl J Med* 1999; 341:577–585.
- 89 Stenvinkel P, Marchlewska A, Pecoits-Filho R, *et al.* Adiponectin in renal disease: relationship to phenotype and genetic variation in the gene encoding adiponectin. *Kidney Int* 2004; 65:274–281.
- 90 Mohamed-Ali V, Goodrick S, Bulmer K, *et al.* Production of soluble tumor necrosis factor receptors by human subcutaneous adipose tissue in vivo. *Am J Physiol* 1999; 277 (6 Pt 1):E971–E975.
- 91 Rauchhaus M, Coats AJ, Anker SD. The endotoxin-lipoprotein hypothesis. *Lancet* 2000; 356:930–933.
- 92 Niebauer J, Volk HD, Kemp M, *et al.* Endotoxin and immune activation in chronic heart failure: a prospective cohort study. *Lancet* 1999; 353:1838–1842.
- 93 Jandacek RJ, Anderson N, Liu M, *et al.* Effects of yo-yo diet, caloric restriction, and olestra on tissue distribution of hexachlorobenzene. *Am J Physiol Gastrointest Liver Physiol* 2005; 288:G292–G299.
- 94 Sarkar SR, Kuhlmann MK, Kotanko P, *et al.* Metabolic consequences of body size and body composition in hemodialysis patients. *Kidney Int* 2006; 70:1832–1839.
This is the most recent and updated review article on the obesity paradox in dialysis patients, including recently advanced pathophysiologic mechanisms and conceptual therapeutic approaches to the conundrum.
- 95 Imbeault P, Tremblay A, Simoneau JA, Joanisse DR. Weight loss-induced rise in plasma pollutant is associated with reduced skeletal muscle oxidative capacity. *Am J Physiol Endocrinol Metab* 2002; 282:E574–E579.
- 96 Macleod J, Davey Smith G. Psychosocial factors and public health: a suitable case for treatment? *J Epidemiol Commun Health* 2003; 57:565–570.
- 97 Kalantar-Zadeh K, Balakrishnan VS. The kidney disease wasting: inflammation, oxidative stress, and diet-gene interaction. *Hemodial Int* 2006; 10: 315–325.
- 98 Schold JD, Srinivas TR, Guerra G, *et al.* A 'weight-listing' paradox for candidates of renal transplantation? *Am J Transplant* 2007; 7:550–559.
This epidemiologic analysis of body weight in renal transplant recipients shows that higher BMI is associated with poor survival, hence it identifies a reversal in reverse epidemiology post-transplantation.
- 99 Johansen KL, Young B, Kaysen GA, Chertow GM. Association of body size with outcomes among patients beginning dialysis. *Am J Clin Nutr* 2004; 80:324–332.
- 100 Krane V, Wanner C. At which stage of chronic kidney disease should dyslipidemia be treated? *Nature Clin Practice Nephrol* 2006; 2:176–177.
This article presents a clinically relevant discussion about the approach to dyslipidemia in CKD and dialysis patients, given the recent negative findings of clinical trials on lipid-lowering interventions.
- 101 Essential Science Indicators. Emerging Research Fronts in Feb 2006. Thomson Scientific Solutions; 2006. <http://www.esi-topics.com/erf/february2006.html> (Accessed 19 April 2007).
- 102 Kalantar-Zadeh K, Stenvinkel P, Bross R, *et al.* Kidney insufficiency and nutrient-based modulation of inflammation. *Curr Opin Clin Nutr Metab Care* 2005; 8:388–396.