Risk factor paradox in wasting diseases

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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

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Abbreviations

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

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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

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 paradoxic association is observed at the individual level, namely better survival in more obese persons. These paradoxic 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 paradoxic 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].

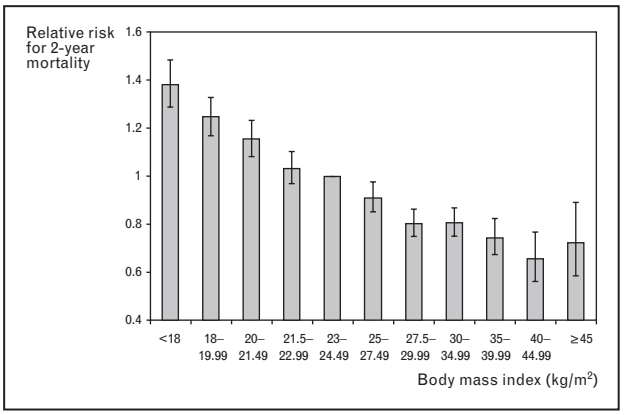
In a recent critical review [16], 11 large studies (including more than 1000 individuals) were identified, each reporting a reverse epidemiology of obesity, that is, obesity paradox, in maintenance hemodialysis patients. Not only is a lower baseline BMI associated with poor survival (Fig. 1), but also 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			

[a]See 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.

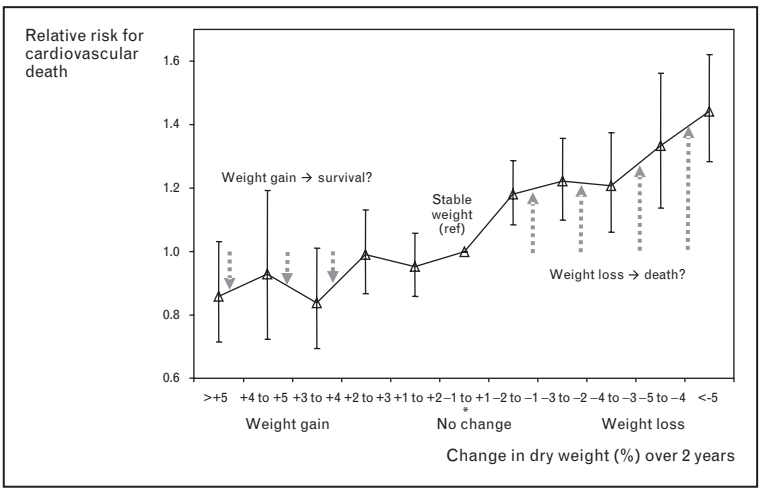
Several studies [20,21,22••] indicate that low, rather than high, serum total cholesterol and low-density lipoprotein are associated with poor survival in dialysis patients. Kilpatrick *et al.* [22••] recently showed that the 'cholesterol paradox' is somewhat universal across most subgroups of dialysis 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 Diabetis 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

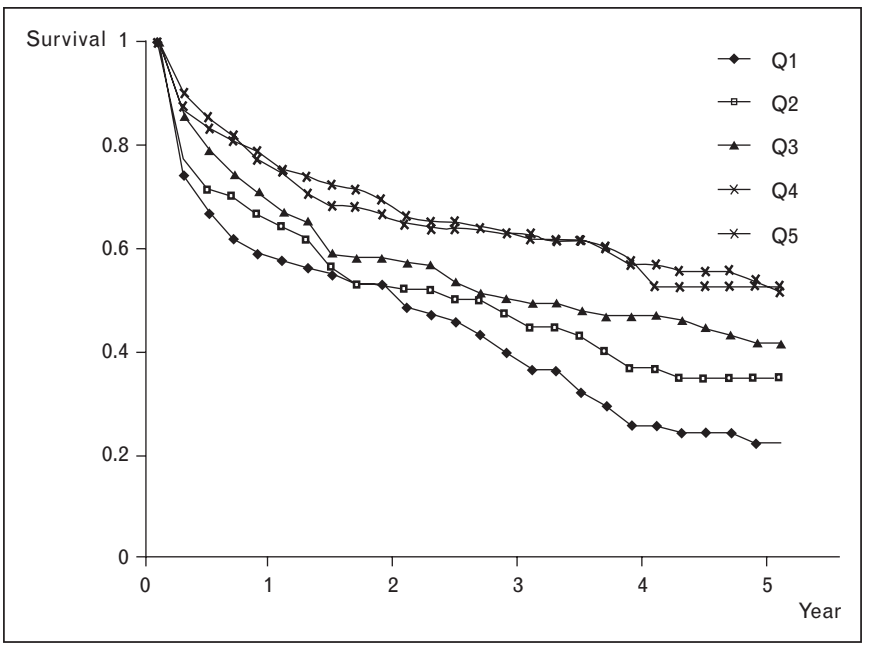
Individuals with chronic heart failure (CHF), currently numbering approximately 5 million in the USA, exhibit striking similarities to CKD patients. Both CKD and CHF populations have a high prevalence of comorbid conditions, a high hospitalization rate, a low self-reported quality of life, and an excessively 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 paradoxic 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-denity lipoprotein cholesterol levels in geriatric populations have been associated with increased mortality [59]. Unlike the paradoxic 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]. Paradoxic 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 ($< 20\,kg/m^2$) as compared with normal BMI ($20–30\,kg/m^2$) 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 $> 30\,kg/m^2$) and extreme obesity (BMI $>35\,kg/m^2$) 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 ($<20\,kg/m^2$) as compared with those with normal BMI (BMI 20–25 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

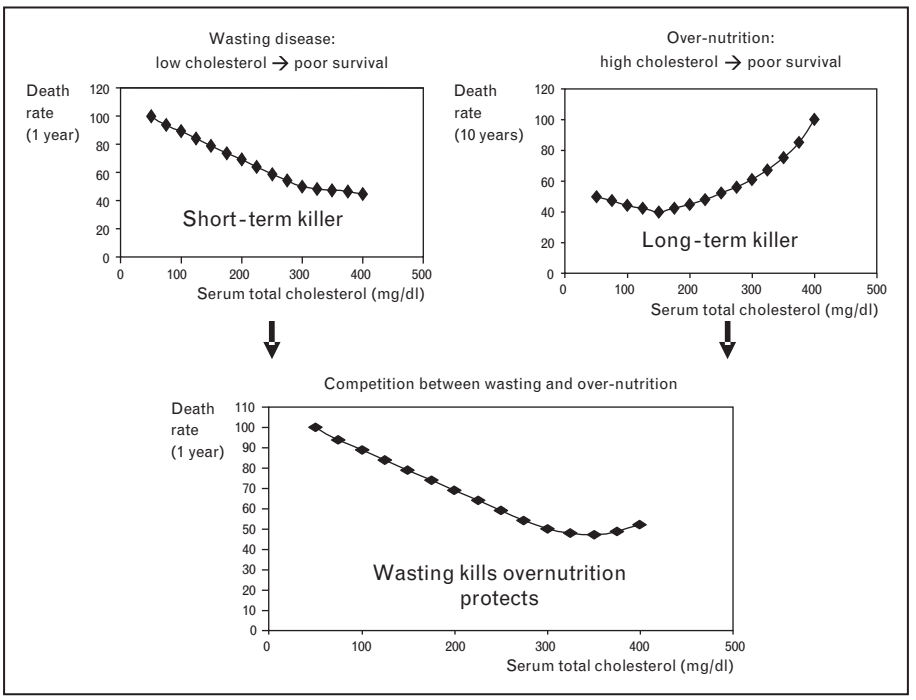
Several hypotheses have been advanced to explain the obesity paradox in chronic disease states such as CHF and CKD that are associated with wasting disease, including the following: time differential of competing risks, hemodynamic stability of obesity, protective adipokine profile, endotoxin–lipoprotein 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 paradoxic 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]. Comoribid 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 cardiovascular 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.

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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).

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