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Survival advantages of obesity in dialysis patients¹⁻⁴

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ABSTRACT

In the general population, a high body mass index (BMI; in kg/m²) is associated with increased cardiovascular disease and all-cause mortality. However, the effect of overweight (BMI: 25–30) or obesity (BMI: >30) in patients with chronic kidney disease (CKD) undergoing maintenance hemodialysis (MHD) is paradoxically in the opposite direction; ie, a high BMI is associated with improved survival. Although this “reverse epidemiology” of obesity or dialysis-risk-paradox is relatively consistent in MHD patients, studies in CKD patients undergoing peritoneal dialysis have yielded mixed results. Growing confusion has developed among physicians, some of whom are no longer confident about whether to treat obesity in CKD patients. A similar reverse epidemiology of obesity has been described in geriatric populations and in patients with chronic heart failure (CHF). Possible causes of the reverse epidemiology of obesity include a more stable hemodynamic status, alterations in circulating cytokines, unique neurohormonal constellations, endotoxin-lipoprotein interaction, reverse causation, survival bias, time discrepancies among competitive risk factors, and malnutrition-inflammation complex syndrome. Reverse epidemiology may have significant clinical implications in the management of dialysis, CHF, and geriatric patients, ie, populations with extraordinarily high mortality. Exploring the causes and consequences of the reverse epidemiology of obesity in dialysis patients can enhance our insights into similar paradoxes observed for other conventional risk factors, such as blood pressure and serum cholesterol and homocysteine concentrations, and in other populations such as those with CHF, advanced age, cancer, or AIDS. Weight-gaining interventional studies in dialysis patients are urgently needed to ascertain whether they can improve survival and quality of life. *Am J Clin Nutr* 2005;81:543–54.

KEY WORDS Dialysis, obesity, reverse epidemiology, dialysis-risk-paradox, malnutrition-inflammation complex syndrome

INTRODUCTION

Patients with advanced chronic kidney disease (CKD), who require maintenance dialysis, have a significantly higher mortality rate, primarily because of cardiovascular disease (CVD) (1, 2). Extrapolation of findings from the general population has led to decades of focusing on treating such conventional CVD risk factors in dialysis patients as obesity, hypertension, hypercholesterolemia, and hyperhomocysteinemia. However, survival has not improved substantially in the past 2 decades. Additional efforts targeted other possible correlates of the high mortality

associated with CKD, such as dialysis dose or dialysis membrane. However, several recent multicenter clinical trials, including the HEMO (3) and ADAMEX (4) studies, failed to show any survival advantage of increasing dialysis dose in both maintenance hemodialysis (MHD) (3) and PD patients (4).

An increasing number of epidemiologic studies, based on analyses of large samples of dialysis patients and national databases, have indicated paradoxically inverse associations between classical risk factors of CVD and mortality in dialysis patients (5). Indeed, a worse survival has been observed in dialysis patients with a low rather than with a high body mass index (BMI) (6), blood pressure (7), and serum concentrations of cholesterol (8), homocysteine (9), and creatinine (10). Even more ironically are findings indicating that high values for these risk factors are paradoxically protective and associated with improved survival. This phenomenon has been referred to as “reverse epidemiology” (5) or “dialysis-risk-paradox” (8, 11). Such terms may not necessarily mean that the principles of vascular pathophysiology are different in dialysis patients than in nondialysis patients but may indicate that there are other superimposed and more dominant factors that overwhelm the classic relations between risk factors and outcome as seen in the general population. In general, recent epidemiologic studies have contributed to the growing confusion and have left physicians with the ongoing dilemma as to whether or not to treat obesity, hypercholesterolemia, hypertension, or hyperhomocysteinemia in dialysis patients. Of the abovementioned cardiovascular disease risk factors with an inverse association with mortality, the relation between indexes of body weight or size and clinical outcome in MHD

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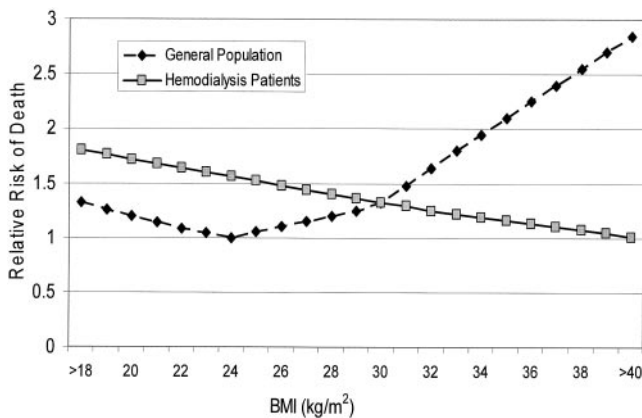


FIGURE 1. Reverse epidemiology of obesity in dialysis patients compared with the general population. Comparison between the effects of BMI on all-cause mortality in the general population and in the maintenance hemodialysis population. The data for the general population (combined data for healthy nonsmoking men and women) are adapted from reference 40. The hemodialysis data (combined US and European data) are adapted from reference 28. Note that each population has a different follow-up period: 14 y for the general population compared with 4 y for the hemodialysis patients (adapted with permission from reference 5).

patients has been the most consistent and most extensively studied (Figure 1).

The reverse epidemiology of obesity is not unique to the dialysis population. Patients with congestive heart failure (CHF) experience a similar risk factor reversal (12). Moreover, geriatric populations (13), including elderly persons living in nursing homes (14), hospitalized patients (15), patients with malignancy (16) or AIDS (17), and possibly other subpopulations, also have paradoxically inverse associations. Hence, a better understanding of the phenomenon of reverse epidemiology in dialysis patients, especially as it pertains to obesity and body size, may help improve the poor outcome in this and other similar but distinct populations. In this article, the inverse mortality predictability of BMI and several hypotheses to that end are reviewed critically.

BODY SIZE AND MORTALITY IN THE GENERAL POPULATION

In the United States as well as in most industrialized countries throughout the world, the mean body weight of the population is on the rise (18). Many epidemiologic studies have shown a strong association between obesity and decreased survival, especially that due to an increased risk of CVD in the general population (19–21). BMI, also known as the Quetelet index [ie, ratio of weight (kg) to height squared (m)] (22), is the commonly used variable to quantify changes in body mass adjusted for height to provide a simple marker for body composition that is independent of height. There is a direct relation between BMI and body weight as well as body fat. In some studies of healthy adults, a “J” curve effect has been observed in which those persons with a low BMI also had increased mortality, although not as high as obese persons (20, 21, 23). This J curve effect may disappear when the data are adjusted for smoking status (20).

BODY SIZE AND MORTALITY IN HEMODIALYSIS PATIENTS

MHD patients appear to have a lower BMI than age- and sex-matched control subjects from the general population (24,

25). In a recent matching analyses that compared the lipid profiles of 285 MHD patients with those of 285 outpatients with non-end-stage renal disease evaluated in the same medical center, matched one-to-one on age (± 5 y), sex, race, and diabetes mellitus status, BMI was found to be significantly lower in the MHD patients than in the control subjects (26.2 ± 6.0 compared with 31.5 ± 7.8 ; $P < 0.001$) (26). In MHD patients, in contrast with trends seen in the general population, lower BMI is consistently found to be a strong predictor of an elevated mortality (27–33). Furthermore, a higher BMI, mild-to-moderate overweight, or obesity is generally not associated with an increase in mortality risk in MHD patients, except in Asian Americans, according to at least one study (31). Most studies have shown that the inverse association between BMI and mortality in MHD patients is independent of serum albumin and other markers of nutritional status. These studies are listed in Table 1.

The Diaphane collaborative study group (27) in France was one of the first to report on the paradoxical observation of a lack of increase in mortality with high BMI in dialysis patients. This study included a cohort of 1453 younger, mostly nondiabetic, French MHD patients followed between 1972 and 1978 in 33 French dialysis centers (27). Leavey et al (29), while assessing the influence of many commonly used clinical variables on dialysis survival, confirmed the above lack of association between higher BMI values and increased mortality risk in a national sample of 3607 MHD patients in the United States Renal Data System (USRDS). The mean BMI was 24.4 ± 5.3 in this study. In hazard regression models, low BMI was independently and significantly predictive of increased mortality. With the use of time-dependent models, the greatest predictive value of BMI occurred early during follow-up, but its independent predictive value of mortality risk persisted even 5 y later. All models were adjusted for diabetes as well as for demographic and biochemical variables, ambulatory status, coronary heart disease, peripheral vascular disease, and left ventricular hypertrophy. There were no significant interactions identified between BMI and any of these variables (29).

A study by Fleischmann et al (30) identified for the first time a significantly higher survival rate in overweight and obese MHD patients (BMI: ≥ 27.5) than in those with a normal weight (BMI: 20–27.5) and underweight (BMI: < 20) counterparts (30). The data also showed that for every unit increase in BMI, the relative risk (RR) of mortality was reduced by 10%. In addition to reduced mortality, overweight patients had significantly higher levels of nutritional markers and a lower rate of hospital admissions than did underweight patients. Furthermore, underweight patients had longer hospital stays (30).

Wolfe et al (35) investigated the role of body size on 2-y mortality risk associated with dialysis dose in 9165 MHD patients from a national random sample from the USRD. Body size markers, including body weight, body volume, and BMI, were independently and inversely related to mortality when adjusted for age and diabetes as well as for Kt/V (dialysis dose) ($P < 0.01$ for each measure). A similar study by Port et al (36) was based on data from 45 967 incident MHD patients who started dialysis treatment between April 1997 and December 1998. The data were obtained from the US Federal billing records during months 10 to 15 of MHD therapy. Cox regression models were adjusted for demographics and 18 comorbid conditions. Of the 3 body-size groups, the lowest BMI group had a 42% higher mortality risk than did the highest BMI tertile (36).

TABLE 1Summary of studies with large sample sizes (>1000 subjects) indicating a reverse epidemiology of obesity in maintenance hemodialysis (MHD) patients¹

Reference	Sample size	Follow-up period	Findings and source of data
Degoulet et al, 1982 (27)	1453	y 5	Higher death rate with lower BMI. Younger, mostly nondiabetic, French MHD patients.
Leavey et al, 1998 (29)	3607	5	Higher mortality with lower BMI. USRDS data.
Fleischmann et al, 1999 (30)	1346	1	Better survival with overweight and obesity. Mostly African American MHD patients. Mississippi patients only.
Kopple et al, 1999 (34)	12 965	1	Lower mortality with progressively higher weight-for-height; lowest mortality rates in overweight MHD patients. Data from Fresenius Medical Care.
Wolfe et al, 2000 (35)	9165	2	Better survival in overweight and obese MHD patients. USRDS data.
Leavey et al, 2001 (28)	9417	4	Mortality risk decreased with increasing BMI in both US and European MHD patients in the DOPPS, independent of the degree of sickness.
Port et al, 2002 (36)	45 967	2	The highest BMI tertile had the lowest mortality risk. Data from the US Federal billing records.
Lowrie et al, 2002 (37)	43 334	1	The log of risk decreased linearly for weight, weight-for-height, and BSA and was reverse J-shaped for weight/height and BMI. Data from Fresenius Medical Care.
Glanton et al, 2003 (33)	151 027	2	Paradoxical association between BMI and mortality was stronger in African American MHD patients. USRDS data.
Johansen et al, 2004 (38)	418 055	2	High BMI, adiposity, and fat mass were associated with increased survival in all but Asian American MHD patients. USRDS data.
Kalantar-Zadeh et al, 2004 (39)	54 535	2	Time-varying BMI and weight gain over time were associated with improved survival in all subgroups. Data from DaVita, Inc.

¹ USRDS, US Renal Data System; DOPPS, Dialysis Outcomes and Practice Patterns Study; BSA, body surface area.

Kopple et al (34) evaluated 12 965 MHD patients and found that those patients with greater weight-for-height percentiles had lower mortality rates. After adjustment for clinical characteristics and laboratory measurements, the inverse relation between mortality rates and weight-for-height percentiles was still highly significant, particularly for patients in the lower 50th percentile of body weight-for-height (34). These findings suggest that not only BMI but other measures of body size also correlate inversely with mortality in maintenance dialysis patients, independently of case-mix factors and comorbid conditions.

The Dialysis Outcomes and Practice Patterns Study (DOPPS) provided baseline demographic, comorbidity and BMI data on 9714 MHD patients in the United States and Western Europe from 1996 to 2000 (28). As expected, an inverse BMI-mortality relation was found in MHD subpopulations defined by continent, race, sex, tertiles of severity of illness (based on a score derived from comorbid conditions and serum albumin concentration), age, smoking, and diabetic status. A BMI < 20 was consistently associated with the highest relative mortality risk. Overall, a lower RR of mortality, as compared with a BMI of 23.0–24.9, was found for overweight (BMI: 25.0–29.9; RR: 0.84, $P = 0.008$), mild obesity (BMI: 30.0–34.9; RR: 0.73; $P = 0.0003$), and moderate obesity (BMI: 35.0–39.9; RR: 0.76; $P = 0.02$). Subanalysis based on overall health status at the start of the study, as defined by severity of illness tertiles, resulted in similar associations. Contrary to the investigator's initial hypothesis that reverse epidemiology may not exist in healthier or younger end-stage renal disease (ESRD) patients, there was a survival benefit for healthy overweight patients (BMI: 25–29.9) that was even greater for the obese patients (BMI: >30), and this was observed for the healthier as well as the sicker groups of HD-treated patients. Even within a cohort of patients < 45-y-old with low comorbidity, overweight and obesity were not associated with

decreased survival (28). The shape of the BMI-mortality relation was unchanged in a sensitivity analysis, which simultaneously adjusted for other measures that reflected fat-free mass. A comparison of the association between BMI and mortality between the general population (40) and dialysis patients, as reported in the DOPPS (28), is presented in Figure 1.

Lowrie et al (37) analyzed survival in 43 334 MHD patients in different Kt and body-size groups (ie, categorized by body weight, weight adjusted statistically for height, body surface area, weight divided by height, and BMI). The log of risk decreased in rough linear fashion for Kt, weight, weight for height, and BSA. The log-risk relations were reverse J-shaped for weight divided by height and BMI. The main-effects models suggested improved survival with increasing Kt and all of the size measures (37). Glanton et al (33) performed a historical cohort study on incident 151 027 maintenance dialysis patients and found that obese patients had a higher unadjusted and case-mix adjusted 2-y survival after control for all comorbidities and risk factors (**Figure 2**); however, the relation was not uniform and was stronger in African Americans. In addition, subgroup analysis suggests that obesity is associated with increased risk of infectious death in females (33).

Johansen et al (38) recently analyzed retrospective data from 418 055 maintenance dialysis patients, who were observed over an average 2-y follow-up time, and found that even an extremely high BMI was associated with increased survival, except in Asian Americans. High BMI was also associated with a reduced risk of hospitalization and a lower rate of mortality in all mortality categories. Other estimates of adiposity and fat mass yielded similar results, whereas adjustments for lean body mass (LBM) did not substantially alter the findings.

Finally, Kalantar-Zadeh et al (39) recently examined the effect of both baseline BMI (classic Cox model) and changes in BMI

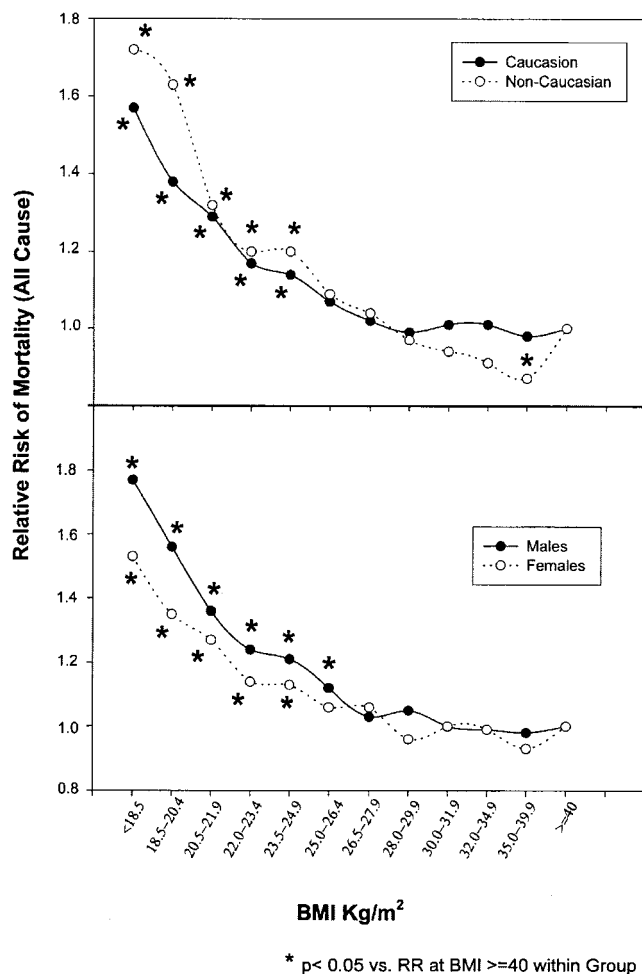


FIGURE 2. Adjusted relative risks (RRs) for all-cause mortality in Caucasians, non-Caucasians, males, and females in the United States with end-stage renal disease, 1995–1998, according to BMI. RRs are compared with risk for BMI > 40. *Statistically significantly different from the RR at BMI > 40 within each group. Reprinted with permission from reference 33.

over time (time-dependent model) on all-cause and cardiovascular mortality in a 2-y nonconcurrent cohort of 54 535 MHD patients in the national database of the second largest dialysis care provider in the United States (DaVita, Inc, El Sagundo, CA). They found that obesity, including morbid obesity (BMI: >35), was associated with survival advantages in virtually all subgroups of age, sex, race, dialysis vintage, serum albumin, and Kt/V. Moreover, they showed for the first time that weight loss is associated with increased mortality, whereas weight gain confers survival advantages (39).

In a database analysis, Beddhu et al (41) attempted to ascertain whether the survival advantage of BMI in 70 028 incident MHD patients was due to muscle mass or to fat. They used 24-h urine creatinine excretion as a surrogate for muscle mass, even though this information was missing for the absolute majority of eligible dialysis patients. However, the assumption that 24-h urine creatinine represents muscle mass in ESRD patients is questionable because the degree of residual renal function is a strong confounder. Moreover, many reported creatinine clearance values in

ESRD registration forms (Form 2728) are based on serum creatinine values exclusively, ie, are based on Cockcroft-Gault equation (42). Another major problem of Beddhu's study is the contradiction between their findings and their stated conclusions. Their data showed a consistent reverse epidemiology trend among all subgroups of urine creatinine for both all-cause and cardiovascular mortality. However, the authors maintained that the survival advantage of higher BMI was limited to those with a urine creatinine concentration > 0.55 g/d—a statement that is not consistent with the findings presented by Beddhu et al (41).

Very few studies have failed to show survival advantage of obesity in MHD patients. Kaizu et al (43) studied 116 nondiabetic Japanese MHD patients and used Kaplan-Meier survival analysis and proportional hazard model to calculate the RRs of mortality in BMI quintiles. They showed that patients with BMIs <16.9 and >23.0 had lower survival rates than did patients with BMIs of 17.0–18.9. However, even in this very small sample of exclusively Asian subjects, MHD patients with a BMI <16.9 were shown to have the highest risk of mortality, independent of age, sex, smoking, duration of hemodialysis, serum albumin, blood pressure, and urea reduction rate. Moreover, BMI may interact with race and sex to predict long-term survival in dialysis patients. Kutner and Zang (44) investigated the association between BMI and mortality over 11 y of follow-up in 316 prevalent elderly maintenance dialysis patients aged ≥60 y. Black females, black males, and white males with higher BMIs had a reduced risk of death, whereas obesity was associated with reduced survival in white females (44).

BODY SIZE AND MORTALITY IN PERITONEAL DIALYSIS PATIENTS

Most (45–50), but not all (32, 51, 52), studies in PD patients have reported similar inverse weight-mortality relation. In the CANUSA study, a 1% difference in percentage LBM was associated with a 3% change in the RR of death (45, 46). McCusker et al (47) found a significantly lower patient survival rate in patients with lower LBM. Johnson et al (48) studied BMI in a limited number of PD patients and found that obesity conferred a significant survival advantage in the PD population. Chung et al (49) described a similar association between LBM and mortality in Korean PD patients. The largest epidemiologic study included nearly 46 000 PD patients and was conducted by Snyder et al (50), who examined a retrospective cohort of US Medicare patients initiating dialysis between 1995 and 2000 ($n = 418\,021$; 11% PD). Although less likely to initiate PD, the investigators found that overweight and obese PD patients survived longer than did those with lower BMIs, which was not adequately explained by lower transplantation and technique survival rates.

Several studies in PD patients found no survival advantage for obesity or indicated a higher risk of death in obese PD patients. Aslam et al (52) compared 2-y survival in 104 PD patients with a BMI > 27 (high BMI) and in 104 PD patients with a BMI of 20–27 (normal BMI) after matching for age, sex, presence of diabetes, and Charlson comorbidity index. BMI was not a predictor of patient mortality or technique survival when controlled for initial albumin, creatinine kinetics, and initial Kt/V. McDonald et al (51) examined all new adult patients ($n = 9679$) who underwent an episode of PD treatment in Australia or New Zealand over an 11-y interval. In multivariate analyses, obesity was independently associated with death during PD treatment and

technique failure, except among patients of New Zealand Maori/Pacific Islander origin, for whom there was no significant relation between BMI and death during PD treatment. The mortality risk was lowest for BMI values of ≈ 20 . They concluded that obesity at the start of PD is a significant risk factor for death and technique failure (51).

Abbott et al (32) recently performed a retrospective cohort study of the USRDS Dialysis Morbidity and Mortality Wave II Study in 1675 MHD and 1662 PD patients and found that 5-y survival was 39.8% for MHD patients with BMIs ≥ 30 compared with 32.3% for those with lower BMIs ($P < 0.01$ by log-rank test). However, 5-y survival based on a BMI cutoff of 30 was not significantly different in PD patients (32). Finally, very recently, Stack et al (53) examined differences between PD and MHD patients in a cohort of 134 728 ESRD patients from the USRDS who were newly started on dialysis. Cox regression models evaluated the association of BMI in quintiles with mortality over 2 y in both PD and MHD patients separately, whereas time-dependent models evaluated the RR of death by modality for each BMI quintile. In MHD patients, the adjusted death risk was greatest for patients with a BMI ≤ 20.9 and lowest for patients with a BMI > 30.0 compared with the reference group (BMI: 23.5–26.1). For PD patients, the mortality risk was also higher for patients with a BMI < 20.9 , but no survival advantage was associated with higher BMI values. They concluded that the selection of HD over PD was associated with a survival advantage in patients with large body habitus (53).

ARE THERE OTHER POPULATIONS WITH A REVERSE EPIDEMIOLOGY?

Are dialysis patients the only ones with a reverse epidemiology of obesity, or are there other populations with a similar risk factor paradox? Indeed, the reverse epidemiology of obesity is not unique to the dialysis population. Patients with chronic heart failure (12), geriatric populations (13), and patients with malignancy (14) or AIDS (54) also exhibit a risk factor reversal. Studying these populations may confer better insight into understanding the pathophysiology of reverse epidemiology in dialysis patients.

Body size and mortality in the elderly

An increasing number of studies suggest that a higher BMI in certain age groups may not necessarily be associated with higher morbidity and mortality (13, 15, 55). As was shown for dialysis patients, Grabowski and Ellis (55) showed that a high BMI does not predict mortality in older people. In their Longitudinal Study of Aging that involved 7527 participants aged ≥ 70 y, they used Cox regression to calculate proportional hazards ratios for mortality over 96 mo after adjustment for demographic factors, health services utilization, and functional status. They showed reduced mortality in obese older people and showed that thin older people remained more likely to die than did normal-weight, older people (55).

Stevens et al (13) examined mortality over 12 y among white men and women who participated in the American Cancer Society's Cancer Prevention Study I (from 1960 through 1972). Of 62 116 men and 262 019 women included in this analysis who had no history of recent unintentional weight loss, had never smoked cigarettes, and had no history of heart disease, stroke, or cancer (other than skin cancer) at baseline (1959–1960), the

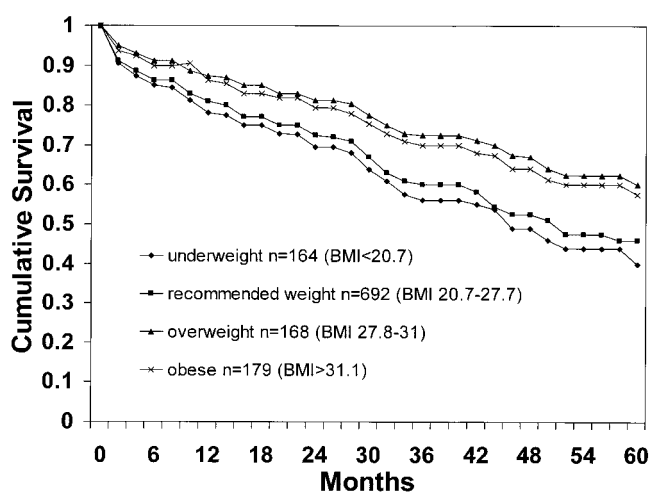


FIGURE 3. Risk-adjusted survival curves for the 4 BMI (in kg/m^2) categories at 5 y. The variables entered into the equation were age, sex, hypertension, diabetes mellitus, left ventricular ejection fraction, hemodynamic variables, peak oxygen, mitral regurgitation, tricuspid regurgitation, medications, and serum sodium, creatinine, and lipid concentrations. Survival was significantly better for persons in the overweight and obese BMI categories. Reprinted with permission from reference 63.

associations between BMI and mortality were examined for 6 age groups adjusted for age, educational level, physical activity, and alcohol consumption. Greater BMI was associated with higher mortality from all causes and from CVD in men and women up to 75 y of age. However, the RR associated with greater BMI decreased and even reversed with age (13). In another study of 18 316 hospitalized Italian patients who were consecutively admitted to 79 clinical centers between 1991 and 1998 (15), the graphed relation between BMI and mortality in younger patients was hyperbolic and death rates increased at the lowest and highest BMI rankings. However, the older patients had an increased death rate at the lowest BMIs with only a slight elevation at the highest BMIs (> 35) (15).

Body size and mortality in patients with chronic heart failure

Higher BMI is associated with an increased risk of heart failure (56, 57). Paradoxically, however, patients with more severe CHF tend to have lower BMI values compared with age- and sex-matched control subjects from the general population (58–60). A study of prognostic variables in 401 patients with CHF did not find overweight status to be a risk factor for mortality, despite inclusion of $> 40\%$ overweight patients with a BMI > 26 (61). In the Systolic Hypertension in the Elderly Program Study, overweight status was associated with an improved stroke risk and decreased total mortality compared with lean subjects with CHF (62). Horwich et al (63) studied 1203 persons with moderate-to-severe CHF ($> 60\%$ with NY Heart Association class IV) who were followed for up to 5 y. Higher BMI was associated with a better 2-y survival. One-year and 5-y survival showed the same trend, although the association was not statistically significant. Multivariate analysis showed an inverse association between the BMI and mortality rate. In their cohort, obese patients who had survival advantages also had a higher prevalence of hypertension and hypercholesterolemia (Figure 3) (63).

TABLE 2

Possible mechanisms leading to the observed associations between obesity and improved survival in dialysis patients

Possible mechanisms of reverse epidemiology of obesity
Malnutrition-inflammation complex syndrome (cachexia in slow motion)
Time discrepancies among competitive risk factors: overnutrition compared with undernutrition
Endotoxin-lipoprotein hypothesis
More stable hemodynamic status in obese patients
Tumor necrosis factor α receptors in obesity
Neurohormonal alterations in obesity
Reverse causation
Survival bias
Alteration of conventional risk factors in uremic milieu
Predominance of reverse epidemiology in the history of mankind

Mosterd et al (64) examined the survival predictors in all patients with CHF within the Rotterdam Study cohort; 181 of 5255 patients were identified to have CHF. A higher BMI was an independent predictor of a more favorable prognosis in 4-y follow-up. Both cardiac death and all-cause mortality were lower in obese CHF patients (64). Davos et al (65) examined the effect of BMI in 589 patients with CHF who did not have cachexia, as defined by a weight loss $>7.5\%$ over ≥ 6 mo. After the patients were divided into 5 equally sized quintiles (Q1 to Q5), survival was significantly better in mildly to moderately obese patients (Q4) but not in most obese patients (Q5). However, in multivariate analyses, higher BMI (as a continuous variable) conferred better survival (65). Lissin et al (66) reported a similar finding in 522 veteran patients with CHF. BMI was significantly lower in deceased (compared with surviving) patients. Patients with a BMI < 22 had worse and patients with a BMI > 30 had the best survival. Finally, Lavie et al (67) also described the obesity paradox; in their study of 209 ambulatory patients with New York Heart Association classes I–III heart failure, a better event-free survival was observed with higher body composition. For every 1% decrease in body fat, unfavorable clinical events increased by $\geq 13\%$. In this study, BMI and percentage body fat associated with adverse outcome were at levels generally considered to be “healthy” and not at levels consistent with a cachectic state (67).

POSSIBLE EXPLANATIONS FOR REVERSE EPIDEMIOLOGY

The concept of reverse epidemiology may appear counterintuitive, especially because obesity is an established risk factor for CVD and poor outcome in the general population. Indeed, it is not a question of the existence or lack of an association between obesity and mortality, but the complete reversal and the opposite direction of this relation. Hence, there must be prevailing conditions that are uniquely and characteristically present in maintenance dialysis patients, as well as in similar populations with a similar risk factor reversal, that render them more susceptible to a poor outcome when low BMI is present, and in whom obesity has a favorable effect on their future well-being. Several hypothetical explanations are offered here for the reverse epidemiology of obesity (Table 2).

More stable hemodynamic status in obese patients

Many dialysis patients have some degree of heart failure or are in some relative state of fluid overload. Despite having similar pulmonary capillary wedge pressure and cardiac indexes, overweight and obese patients with heart failure tend to have higher systemic blood pressure values (63). Hence, there appears to be an improved hemodynamic tolerance to after load–reducing agents. This may explain why a larger proportion of obese and overweight patients take angiotensin-converting enzyme inhibitors, which are known to prolong the lives of patients with advanced heart failure (68) and that may also confer survival advantages to maintenance dialysis patients.

Tumor necrosis factor α receptors in obesity

Altered cytokine and neuroendocrine profiles of obese patients may play a role in conferring survival advantages to obese patients (63). Tumor necrosis factor α (TNF- α) is elevated in heart failure (69) and in dialysis patients (70), especially those with intermittent bouts of fluid overload. TNF- α may contribute to cardiac injury through its pro-apoptotic and negative inotropic effects (69). However, favorable alteration in the TNF- α system is observed in obese patients. Adipose tissue produces soluble TNF- α receptors, resulting in higher circulating concentrations of both type I and II receptors in obese subjects (71). Soluble TNF- α receptors may hence play a cardioprotective role, because they neutralize the adverse biologic effects of TNF- α . It is important to note that obesity per se may contribute to increased inflammatory processes (72); however, in “sick” patients, any salutary effects attributable to obesity may outweigh the risk of any plausible inflammation.

Neurohormonal alterations in obesity

Obesity is also associated with alterations in the sympathetic nervous system and renin-angiotensin system. A study that compared exercise responses in obese and lean subjects found that the lean subjects had significantly higher increases in plasma adrenaline and renin concentrations during treadmill testing, despite similar baseline values and a history of hypertension (73). Because heightened sympathetic and renin-angiotensin activities are associated with a poor prognosis in heart failure and fluid overload states (such as those seen in dialysis patients) (74), diminished stress responses of these neurohormonal systems may provide insight into the favorable prognosis seen in obese CHF and MHD patients. However, it is important to note that one of the coauthors of this manuscript showed that obesity in MHD patients is associated with lower blood pressure values compared with underweight MHD patients (75).

Endotoxin-lipoprotein hypothesis

Obese patients generally have higher lipid and lipoprotein concentrations. Lower serum total cholesterol and lipoprotein concentrations are strongly and independently associated with impaired survival in dialysis (8) and CHF patients (76). Inflammation is quite common in dialysis patients (77). Greater lipopolysaccharide concentrations have been shown in persons with fluid overload than in the general population (76, 78). It has been postulated that higher concentrations of total cholesterol are beneficial in these patients, because they reflect a richer pool of internal lipoproteins that can actively bind to and remove circulating endotoxins, which effectively retards their deleterious effects, ie, inflammation and subsequent atherosclerosis (78). This

is potentially attributable to the property of lipoproteins to bind lipopolysaccharide, thereby preventing its deleterious effects. Plasma concentrations of lipopolysaccharides are elevated in edematous patients who also show substantial immune activation (78). The findings of higher lipopolysaccharide concentrations in patients with fluid overload (78) and abnormal monocyte responsiveness to lipopolysaccharide (79, 80) indicate a strong possibility that mononuclear cells contribute to the generation of inflammatory cytokines in CHF and dialysis patients. Rauchhaus et al (76, 81) hypothesized that there is an optimum lipoprotein concentration below which lipid reduction would be detrimental. Hence, it is possible that obese dialysis patients whose serum cholesterol concentrations generally tend to be higher have a superior survival because of their ability to better neutralize circulating lipopolysaccharides (82).

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 reverse epidemiology. Reverse causation is a known possible source of bias in epidemiologic studies that examine associations without the direction of the causal pathway (83). Comorbid states may lead to wasting syndrome (such as cardiac cachexia) and also to a higher rate of mortality. However, even if the reverse causation is a cause of the reverse epidemiology, it does not explain why obesity, including morbid obesity, is associated with better outcome in dialysis patients. Moreover, it is quite possible that interventions leading to weight gain in dialysis patients result in improved survival, irrespective of the direction of the causal pathway.

Survival bias

Dialysis patients are a very small proportion of the general population, who have undergone specific processes of selection and survival; hence, they may not represent the general population. The same can be stated for CHF patients, geriatric populations, and patients with AIDS and cancer. If this is true, the relation between the risk factors and outcomes may have been modified through this process. Secondary analyses of data from the National Health and Nutrition Examination Survey (NHANES) (84) have shown that there are >20 million patients with CKD in the United States, ie, those with an irreversible and progressive damage to the kidney who are destined to advance to ESRD. However, there are only 250 000–300 000 maintenance dialysis patients in the United States (24). This constitutes only <5% of the large pool of CKD patients. It has been shown that the vast majority of CKD patients will not live long enough to reach ESRD to commence maintenance dialysis (85). CKD patients have a high mortality rate, because many of them have severe and complex comorbid conditions, such as diabetes mellitus, hypertension, and atherosclerotic vascular disease (85). Indeed, renal disease with or without proteinuria or an increased serum creatinine concentration itself is an independent risk factor for greater morbidity and mortality, particularly from cardiovascular and cerebrovascular diseases (85–87). This explains why only a small proportion of CKD patients develop ESRD. It is not clear what specific characteristics of this relatively small percentage of CKD patients give them a greater survival chance to reach ESRD status. An alternative explanation would be that those CKD patients who develop ESRD simply have a more accelerated rate of

progression of their chronic renal failure. But whatever the survival features are, these “unfortunately lucky” persons may be considered “specifically selected” people, who are not necessarily genetically or phenotypically similar to their CKD predecessors and may not have the survival characteristics and epidemiologic features of their progenitors. Some of those who have survived to make up the ESRD population might be “exceptional individuals” who successfully survived the conventional (traditional) risk factors such as obesity, hypertension, hypercholesterolemia, hypercreatininemia, and hyperhomocysteinemia, which are often strongly present in CKD patients. Hence, the assumption that the epidemiology of cardiovascular disease risk factors is the same in dialysis-dependent populations as in the general population may be flawed, because a survival bias—a form of selection bias—may heavily influence the epidemiologic constellations in this small proportion of CKD survivors, ie, the maintenance dialysis patients.

Time discrepancies among competitive risk factors: overcompared with undernutrition

In the general US population as well as in the populations of most industrialized countries, milestones of overnutrition, such as obesity and hypercholesterolemia, are major risk factors for long-term cardiovascular mortality (19–23, 88, 89). These are areas in the world where people have a greater life expectancy than do those in other parts of the world; hence, such populations are relatively healthy and live long enough to die of consequences of conventional risk factors. Studies of risk factors for cardiovascular mortality are essentially based on these long-living populations. In contrast, in developing countries, which represent most of the world’s population, undernutrition is still a powerful determinant of poor clinical outcome and morbidity and mortality, which leads to a shorter life expectancy (90–92). Similarly, survival advantages that exist in obese dialysis patients may, in the short term, outweigh the harmful effects of these risk factors on CVD in the long term. Because most maintenance dialysis patients die within 5 y of commencing dialysis treatment (1, 2), the long-term effects of conventional risk factors on future mortality must be overwhelmed by the short-term effects of other risk factors intrinsic to dialysis populations such as undernutrition and inflammation (*see* below). Indeed, it may be difficult, if not impossible, to observe a significantly greater life expectancy with reduction of the traditional risk factors in maintenance dialysis patients, who have a short life expectancy, even when such a risk factor reduction is beneficial in the general population, who have a normal life expectancy. Hence, dialysis patients, ironically, do not live long enough to die of the consequences of overnutrition!

Malnutrition-inflammation complex syndrome

If overweight patients who have an increase in adipose tissue develop a deficiency in energy or protein intake, they would be less likely to develop frank protein-energy malnutrition (PEM). Arguably, for this reason, underweight elderly patients or those with CHF or renal failure undergoing maintenance dialysis are more likely to become ill or tend to recover more slowly from illness compared with patients who have normal weight or who are overweight (15). Moreover, many studies have indicated that measures of PEM and inflammation are major predictors of clinical outcome in maintenance dialysis patients (93–101). Similarly, dialysis patients with CVD have a higher prevalence of

hypoalbuminemia, elevated concentrations of inflammatory markers and cytokines, and lower protein and energy intakes than did those without CVD (97, 100, 102). Several factors, separately or working together, may engender PEM, inflammation, or both in ESRD patients (103).

Many studies report a strong association between hypoalbuminemia and CVD in maintenance dialysis patients (104–107). Cardiac diseases such as heart failure or other comorbid conditions may engender anorexia and, if sufficiently severe, may independently induce protein and muscle wasting, which is also known as cardiac cachexia (12, 108). A major mechanism for the development of CVD and PEM in dialysis patients may be cytokine activation associated with reduced renal function or other pro-inflammatory comorbid conditions (77). Increased release or activation of inflammatory cytokines, such as interleukin 6 or TNF- α , may suppress appetite (109), may cause muscle proteolysis and hypoalbuminemia, and may be involved in the processes that lead to atherosclerosis. Because both PEM and inflammation are strongly associated with each other and can change many nutritional measures in the same direction, and because the relative contributions of measures of these 2 conditions to each other and to outcomes in maintenance dialysis patients are not yet well defined, the term “malnutrition-inflammation complex syndrome” (MICS) has been suggested to denote the important contribution of both of these conditions to ESRD outcome (103). Because a gradual but significant decline in all measured nutritional markers is observed with the increasing number of years on dialysis (110), the unique wasting syndrome in these patients can also be referred to as “cachexia in slow motion.”

The reverse epidemiology in dialysis and CHF patients may indeed be due to MICS and its interplay with traditional CVD risk factors, possibly in several ways (5). First, patients who are underweight or who have a low serum cholesterol, creatinine, or homocysteine concentration may have the MICS. Thus, MICS may both cause these alterations and be associated with increased mortality, either caused by the illnesses that engender the MICS or the CVD that seems to be promoted by the MICS (103, 111, 112). Second, the above paradoxical factors may indicate a state of undernutrition, which may predispose to infection or other inflammatory processes (77). Finally, it may be that when persons are malnourished, they are more susceptible to the ravages of inflammatory diseases (77, 103, 113). Hence, any condition, such as obesity, that potentially attenuates the magnitude of PEM or inflammation should be favorable to dialysis and CHF patients. Because almost all the so-called conventional CVD risk factors, such as obesity, hypercholesterolemia, and hyperhomocysteinemia, are related to supraoptimal nutrition, it may explain why there is a reverse epidemiology in such vulnerable populations as dialysis and CHF patients or the elderly. The nutritional hypothesis may also explain why, in PD patients, reverse epidemiology is less evident or even inverted, ie, the so-called “paradox-in-paradox” (114). In general, all PD patients—obese or nonobese—use 1.5–4.25% of dextrose in their peritoneal dialysate (often around the clock), which is estimated to be absorbed at 45% (115). In contrast, HD patients are exposed to 1% of dextrose in their dialysate during the 4-h, thrice-weekly dialysis. Therefore, a higher caloric intake by PD patients for many conceivable reasons may contribute to longer survival (114).

It is important to note that, in the study by Fleischmann et al (30), MHD patients who were obese and had better survival also

had higher biochemical markers of improved nutrition. However, in the same study, higher BMI retained its positive influence on survival even after adjustment for the markers of better nutrition. This finding implies that higher BMI, through mechanisms beyond better nutrition, may offset part of the toxic effects of uremia in uremic patients. Consistent with the view that the survival advantage of higher BMI may not be due solely to nutrition is the finding of Leavey et al (28), ie, biochemical markers of better nutrition were not significantly greater in overweight and obese patients than in normal-weight patients in DOPPS, although a trend existed for such.

Finally, another explanation similar to the nutritional-inflammatory hypothesis has been put forward by Lowrie et al (116): during inflammatory conditions or malnutrition, body protein stores are diverted to defend against inflammation and to repair injury. Thus, the increased body mass of overweight dialysis patients does offer protection against or resources for responding to inflammation, infection, and subsequent CVD. This theory may explain the survival benefit of a high BMI or elevated serum cholesterol or creatinine concentrations in maintenance dialysis patients who have low nutritional reserves and cannot survive further worsening of their inflammatory or nutritional status (116).

Other hypotheses

As described above, the malnutrition-inflammation complex appears to be the most plausible explanation for the reverse epidemiology phenomenon. However, 2 additional hypotheses that are also related to nutritional state deserve mention. Goldberg et al (117) suggested that the paradigm of coronary artery disease in ESRD shifts from solely traditional risk factors such as age, diabetes, hyperlipidemia, and hypertension to many additional factors that may regulate coronary event rates in ESRD in a different way (117). Theoretically, hypotension and undernutrition can contribute to the increased RR of death by several mechanisms, such as acute coronary syndrome, autoregulation dysfunction, ischemia, and arrhythmia genesis (118). Currently, there is a renewed emphasis on the contribution of endothelial abnormalities, alterations in arterial function, cellular activation (platelets, macrophages, smooth muscle cells, and white blood cells), increases in procoagulant activity, and the subsequent development of occlusive thrombosis cap (118). These factors, if indeed altered or exaggerated in the uremic milieu, may provide an environment, in maintenance dialysis patients, in which hypotension and undernutrition may become more influential than the traditional risk factors in the development of CVD. Hence, it is possible that other unknown causes of accelerated atherosclerosis that may exclusively be characteristic of the uremic milieu drive vascular disease in maintenance dialysis patients differently, rendering the traditional risk factors such as obesity and hypertension relatively less important.

Finally, another hypothesis represents the notion that what we consider to be reverse epidemiology (the stronger effect of undernutrition) may indeed be the natural epidemiology in human beings and that the so-called conventional epidemiology (overnutrition) is a new, unusual, and counterintuitive phenomenon in the history of mankind (119). In recent decades, excess weight and obesity have become mass phenomena with a pronounced upward trend in most industrialized nations. However, despite the detrimental effects of being overweight, the populations of these nations indeed live longer than ever. Moreover, with aging,

the detrimental effects of obesity, overnutrition, and hypertension may diminish if not disappear (*see above*), a similar trend that can be observed in the ESRD population as well.

CONCLUSIONS AND FUTURE STEPS

The reversal of the effect of such a key cardiovascular disease risk factor as obesity in dialysis patients and other similar populations, including the elderly and patients with CHF, AIDS, or malignancies, may have major and indeed serious clinical and public health implications. Are the survival advantages of obesity in dialysis and CHF patients and in geriatric populations a clinically valid characteristic? Do overnutrition, obesity, and hypercholesterolemia—which promote atherosclerosis and mortality in the general population—prevent cardiovascular death in maintenance dialysis patients and, if so, how? Do clinical characteristics that stand in contrast with undernutrition, such as a high BMI or an elevated serum cholesterol or homocysteine concentration, predict opposite effects in dialysis and CHF patients or in the elderly than in the general population? Should dialysis patients be advised to increase their nutrient intake to gain weight and to increase their serum cholesterol and homocysteine concentrations?


Is the reverse epidemiology a true entity with clinical and public health implications in millions of patients with ESRD, CHF, advanced age, malignancy, AIDS, liver disease, chronic pulmonary disease, etc? Or, is the reverse epidemiology a flawed hypothesis without any clinical significance? At which stage of CKD does the reverse epidemiology start to emerge? In which subgroups of CKD patients is obesity more protective than in others? Why do those ESRD patients who undergo kidney transplantation not show any evidence of reverse epidemiology? What implications does the provocative doctrine of reverse epidemiology of obesity have for the clinical and public health management of 20–30 million Americans with ESRD, CHF, AIDS, or malignancies or who merely have an advanced age?

Studies presented in this critical review indicate that a higher BMI is associated with reduced mortality in these vulnerable populations. However, it is possible that, in the long run, overweight patients—if they survive long enough—suffer from more cardiovascular consequences. But, do most dialysis patients survive that long? Currently, >60% of dialysis patients die within 5 y of commencing dialysis treatment. Extended observational studies that sequentially measure BMI and other relevant markers should be conducted to identify different subgroups of dialysis patients, with a traditional epidemiology or a reverse epidemiology, who may live exceptionally long. Such a study, of the reverse epidemiology of serum cholesterol in dialysis patients, was recently conducted by Liu et al (120).

As more effective treatments for dialysis patients become available, it is possible that they live longer and longer so that a “reversal” of the reverse epidemiology back to a traditional epidemiology is observed, as is currently found in kidney-transplant patients. The fundamental question of what indeed is “normal” epidemiology and what is “reverse” epidemiology may remain unanswered. Which epidemiology is natural and which is counterintuitive?

Efforts to obtain a better understanding of the existence, etiology, and components of the reverse epidemiology and the role

of MICS in its development in MHD patients remain of paramount importance, because the annual mortality and hospitalization rate among MHD patients remain high (5). Moreover, such extremely costly clinical trials as the HEMO and AMADEX studies have failed to show improved survival in dialysis patients by means of a higher dialysis dose or the use of high flux dialysis membranes (3, 4). Hence, revisiting other risk factors of poor dialysis outcome, especially markers of PEM and inflammation, is urgently needed.

Certain nutritional markers or inflammatory states may be potentially modifiable, and there is a possibility that altering these nutritional and inflammatory markers may improve outcome; this possibility has not yet been tested in randomized prospective clinical trials. However, before testing whether such alterations would improve outcomes and before launching such extremely expensive trials, it is important to know how MICS is engendered and through which mechanism it is associated with poor outcome in MHD patients. This may be achieved by conducting less expensive studies, ie, well-designed epidemiologic studies. 

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