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PERSPECTIVES IN RENAL MEDICINE

Reverse epidemiology of cardiovascular risk factors in maintenance dialysis patients

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Reverse epidemiology of cardiovascular risk factors in maintenance dialysis patients. Conventional risk factors of cardiovascular disease and mortality in the general population such as body mass, serum cholesterol, and blood pressure are also found to relate to outcome in maintenance dialysis patients, but often in an opposite direction. Obesity, hypercholesterolemia, and hypertension appear to be protective features that are associated with a greater survival among dialysis patients. A similar protective role has been described for high serum creatinine and possibly homocysteine levels in end-stage renal disease (ESRD) patients. These findings are in contrast to the well-known association between *over*-nutrition and poor outcome in the general population. The association between *under*-nutrition and adverse cardiovascular outcome in dialysis patients, which stands in contrast to that seen in non-ESRD individuals, has been referred to as "reverse epidemiology." Publication bias may have handicapped or delayed additional reports with such paradoxical findings in ESRD patients. The etiology of this inverse association between conventional risk factors and clinical outcome in dialysis patients is not clear. Several possible causes are hypothesized. First, survival bias may play a role since only a small number of patients with chronic kidney disease (CKD) survive long enough to reach ESRD. Hence, the dialysis patients are probably a distinctively selected population out of CKD patients and may not represent the risk factor constellations of their CKD predecessors. Second, the time discrepancy between competitive risk factors may play a role. For example, the survival disadvantages of under-nutrition, which is frequently present in dialysis patients, may have a major impact on mortality in a shorter period of time, and this overwhelms the long-term negative effects of over-nutrition on survival. Third, the presence of the "malnutrition-inflammation complex syndrome" (MICS) in dialysis patients may also explain the existence of reverse epidemiology in dialysis patients. Both protein-energy malnutrition and inflammation or the combination of the two are much more common in dialysis patients than in the general population and many elements of MICS, such as low weight-for-height, hypocholesterolemia, or hypocreatininemia, are known risk factors of poor outcome in dialysis patients. The existence of reverse epidemiology may have a bearing on the management of dialysis patients. It is possible that new standards or goals for such traditional risk factors as body mass, serum cholesterol, and blood pressure should be considered for these individuals.

Key words: ESRD, dialysis, reverse epidemiology, risk factor paradox, cardiovascular risk factors, malnutrition-inflammation complex syndrome.

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Patients with end-stage renal disease (ESRD) whose life prolongation is dependent on maintenance dialysis experience much poorer outcome as compared to the general population [1–3]. Numerous reports indicate that in contrast to the general population, where markers of *over*-nutrition are associated with increased risk of cardiovascular disease, decreased nutritional measures, such as a low body mass index (BMI) or weight-for-height [4] or a reduced serum cholesterol or creatinine concentration [5], are strongly correlated with increased morbidity and mortality, including a higher risk of cardiovascular events and death in dialysis patients (Fig. 1). Similar findings have been reported concerning blood pressure in that low blood pressure, and not hypertension, appears to be more strongly related to poor outcome in dialysis patients (Table 1). These paradoxic observations have been referred to as "reverse epidemiology" [6, 7] or "risk factor paradox" [8–10]. Such terminologies may not necessarily mean that the principles of vascular pathophysiology are different in ESRD patients but may indicate that there are other superimposed and more dominant factors that cause apparent reversal of the relationships between risk factors and outcome. The phenomenon of an established risk factor in the general population having a markedly different and indeed opposite predictive pattern in ESRD may not be unique to the dialysis population. Elderly individuals in nursing homes [11], hospitalized patients [12], patients with malignancy [13], and possibly other subpopulations may have similar epidemiology. Hence, a better understanding of the causes of reverse epidemiology in ESRD may help improve the poor outcome in this and other similar but distinct populations.

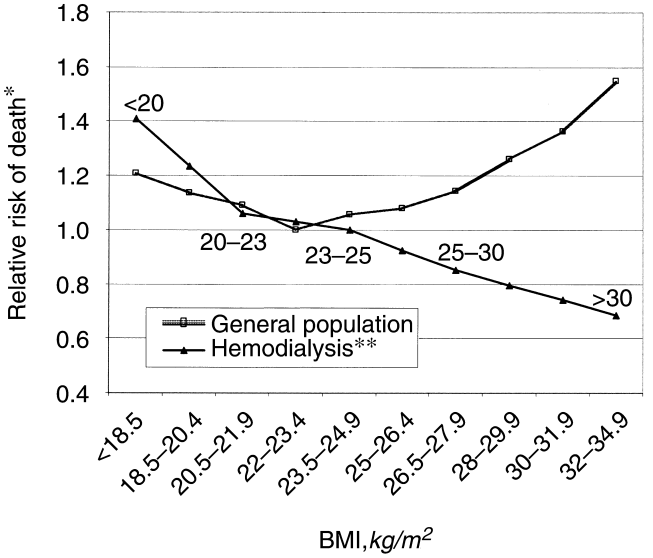

Fig. 1. Reverse epidemiology of mortality risk factors in maintenance dialysis patients. Comparison between the impacts of body mass index (BMI) on all-cause mortality in the general population versus the maintenance hemodialysis population. The general population data are adopted from Calle et al, *N Engl J Med* 341:1097-1105, 1991 (combined men and women, healthy, nonsmoker) [136]. The hemodialysis data are adopted from Leavey et al, *Nephrol Dial Transplant* 16:2386-2394, 2001 (combined data from the United States and Europe) [26]. *Each population has a different follow-up period: 14 years for the general population versus 4 years for hemodialysis patients. **BMI stratifications are different in two populations: X-axis is based on the original graph of the general population and the original hemodialysis BMI subgroup ranges are printed additionally along the hemodialysis curve.

ELEMENTS OF REVERSE EPIDEMIOLOGY

Weight and body mass: Is obesity protective?

The mean body weight in the general population in the United States is on the rise [14]. An appreciable number of epidemiologic studies have shown a strong relationship between obesity and increased risk of cardiovascular disease and mortality in the general population [15–17]. BMI, also known as the Quetelet index [i.e., ratio of weight (kg) to height squared (m^2)] [18], and other adjusted measures of weight (such as for height) [4] are the commonly used parameters to quantify changes in body mass adjusted for height, and the association between body mass and outcome. In some studies of normal adults, a J or U curve effect has been observed in which those individuals with a low BMI also demonstrated an increased mortality, although not as high as obese individuals [16, 17, 19].

Hemodialysis patients have lower BMI values as compared with age- and sex-matched controls from the general population [1, 3]. A lower BMI is consistently found to be a strong predictor of an elevated mortality risk [20–22] (Fig. 1). In contrast, a higher BMI, either mild to moderate overweight or obesity, has generally not been associated with any increase in mortality risk, except in Asian Americans [22]. BMI predicts mortality risk in dialysis patients independently of serum albumin and recorded clinical assessment of nutritional status. The Diaphane Collaborative Study Group in France was one of the first to report that overall mortality risk decreased with increasing BMI [23]. Notably, however, this was reported for a cohort of younger, mostly nondiabetic, French patients treated with hemodialysis during the 1970s, and adjustment was only made for age and sex. Leavy et al [20] described the predictive value for mortality over 5 years of follow-up of a number of risk factors, recorded at baseline, in a national sample of 3607 hemodialysis patients in the 1990s. In hazard regression models, low BMI was independently and significantly predictive of increased mortality; its independent predictive value of mortality risk persisted even 5 years later. No evidence of increasing mortality risk was found for higher values of BMI. Fleischmann et al [21] analyzed the BMI and its relation to 1-year mortality and hospital stay in 1346 predominately African American hemodialysis patients. The 1-year survival rate was significantly higher in the overweight patients and lower in the underweight patients. With a one-unit increase in BMI over 27.5 kg/m^2, the relative risk for dying was reduced by 30% ($P < 0.04$), and with a one-unit decrease in BMI below 20, the relative risk was increased by 1.6-fold ($P < 0.01$). The longer the patients were on dialysis, the lower were the BMI values. The greater duration of dialysis vintage with lower BMI might be a cause of the increased mortality, but it is unlikely that slightly higher dialysis vintage with lower BMI could have accounted for such a substantial impact on mortality [21]. Wolfe et al [24] investigated the role of body size on 2-year mortality risk associated with dialysis dose in 9165 hemodialysis patients and found that body size markers, including body weight and BMI, were independently and inversely related to mortality when adjusted for age and diabetes as well as for Kt/V. Another recent study by Port et al [25], based on data from 45,967 incident hemodialysis patients after adjustment for demographics and 18 comorbid conditions, found that of the three body-size groups, the lowest BMI group had a 42% higher mortality risk than the highest BMI tertile. Kopple et al [3] evaluated approximately 13,000 hemodialysis patients and showed that those hemodialysis patients who had greater weight-for-height percentiles had lower mortality rates.

The prospective Dialysis Outcomes and Practice Patterns Study (DOPPS) [26, 27] has allowed comparison of BMI-mortality relationships in the United States and Europe and among a variety of "healthier," as compared with "sicker" hemodialysis patient subgroups, such as younger patients, never-smokers, and those with less chronic illnesses. The DOPPS study provided baseline demographic, comorbidity, and BMI data on 9714 hemodialysis patients in the United States and Europe from

Table 1. Reverse epidemiology of cardiovascular risk factors in end-stage renal disease (ESRD). Note that the maintenance dialysis patients and the general population have opposite directions

Risk factors of cardiovascular disease	Direction of the associations between risk factors and outcomes		Comments
	General population	Maintenance dialysis patients	
Weight and body mass	High BMI and obesity are deleterious [15–17, 19]	High BMI, weight for height and obesity are protective [3, 20, 21, 23–32]	Elderly, smoking, and hospitalized patients have a similar inverse association as in dialysis patients [11, 12, 34]
Serum cholesterol	Hyperchlesterolemia, high LDL and low HDL are deleterious [55–57]	Hypercholesterolemia (and maybe high LDL) is protective [5, 8, 23, 58–61]	There may be a similar association between low cholesterol and mortality in elderly persons [62–64]
Blood pressure	Hypertension is deleterious [35–37]	Pre-dialysis low BP may indicate a deleterious state [8, 44, 47–49, 51]	Postdialysis hypertension may not be as protective in dialysis patients [47]
Serum creatinine	A mild to moderate increase is an independent risk factor for CVD [65–67]	An increased level is associated with better survival [5, 58, 68–71]	An elevated serum creatinine is essentially a reflection of increased muscle mass and dose of dialysis in ESRD patients [5]
Serum homocysteine	A high level is a risk factor of increased cardiovascular disease in the general population [72, 73] and likely in dialysis patients [74–79]	Two recent studies have found that a low level is associated with increased risk of cardiovascular disease and mortality [81–83]	Dialysis patients essentially have higher levels than non-ESRD population [81–83]. MTRFR gene may have the same deleterious effect in dialysis patients as in the general population [83]
Serum parathyroid hormone	A high serum PTH is associated with increased morbidity [84, 85]	A low serum PTH is associated with poor outcome [86, 87]	
Serum ferritin	A low ferritin is associated with anemia [88]	A high ferritin is more often associated with refractory anemia and EPO hyporesponsiveness [89, 90]	Hyperferritinemia may be associated with increased morbidity and mortality in ESRD patients [60]
Energy (calorie) and/or protein intake	A high energy and food intake may be associated with risk of obesity and increased mortality [90, 91]	Increased protein intake improves survival [93, 94]	Data in dialysis patients are mostly restricted to protein intake estimated based on urea generation and kinetics

Abbreviations are: LDL, low-density lipoprotein; HDL, high-density lipoprotein; EPO, erythropoietin; CVD, cardiovascular disease.

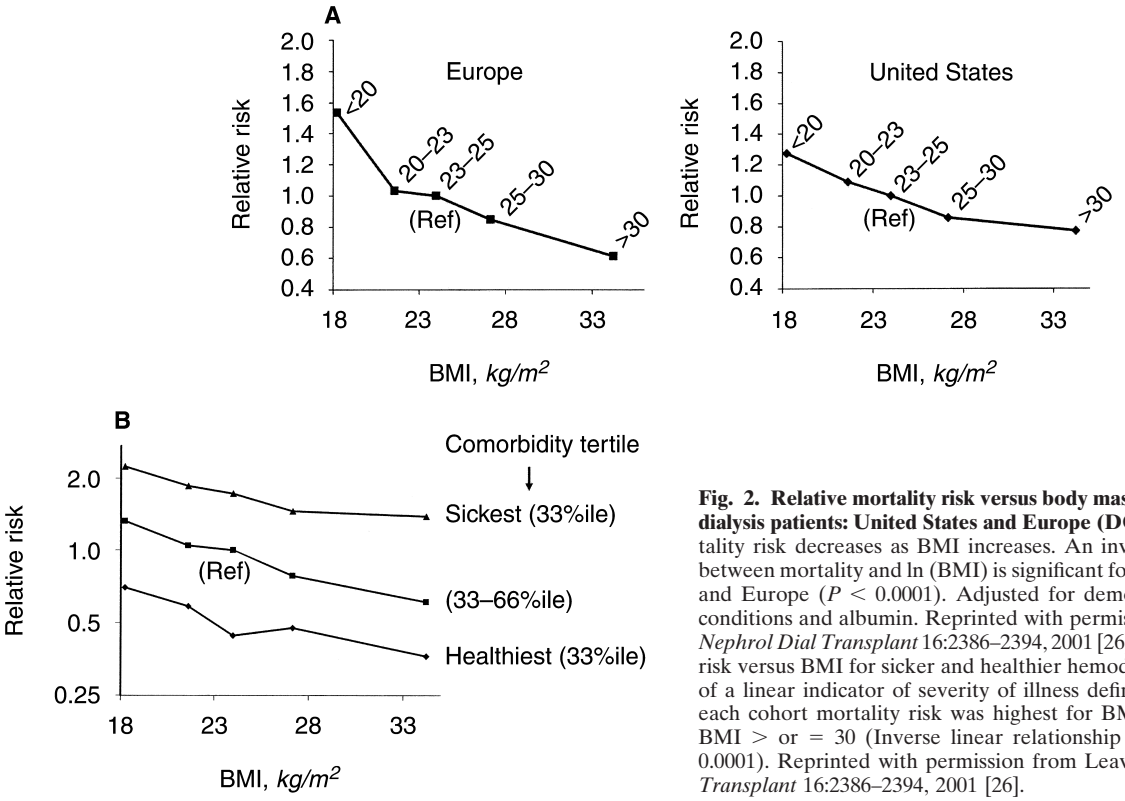

Fig. 2. Relative mortality risk versus body mass index (BMI) in hemodialysis patients: United States and Europe (DOPPS Study). (*A*) Mortality risk decreases as BMI increases. An inverse linear relationship between mortality and ln (BMI) is significant for both the United States and Europe ($P < 0.0001$). Adjusted for demographics, all comorbid conditions and albumin. Reprinted with permission from Leavey et al, *Nephrol Dial Transplant* 16:2386–2394, 2001 [26]. (*B*) Relative mortality risk versus BMI for sicker and healthier hemodialysis patients. Tertiles of a linear indicator of severity of illness define the three cohorts. In each cohort mortality risk was highest for BMI < 20 and lowest for BMI > or = 30 (Inverse linear relationship with lane (BMI), $P < 0.0001$). Reprinted with permission from Leavey et al, *Nephrol Dial Transplant* 16:2386–2394, 2001 [26].

1996 to 2000. Relative mortality risk decreased with increasing BMI. A BMI <20 kg/m^2 was consistently associated with the highest relative mortality risk. Overall, a lower relative risk (RR) of mortality as compared with a BMI of 23 to 24.9 kg/m^2, was found for overweight (BMI 25 to 29.9 kg/m^2; RR 0.84; $P = 0.008$), for mild obesity (BMI 30 to 34.9 kg/m^2; RR 0.73; $P = 0.0003$), and for moderate obesity (BMI 35 to 39.9 kg/m^2; RR 0.76; $P = 0.02$) (Fig. 2A). Most intriguingly, subanalysis of categories of patients defined by overall health status at the beginning of the study and indicated by severity of illness tertiles were performed and resulted in similar associations (Fig. 2B), contrary to the initial hypothesis of the investigators that reverse epidemiology may not exist in healthier or younger ESRD patients. There was a survival benefit for healthy overweight patients (BMI 25 to 29.9 kg/m^2) that was even greater for the obese patients (BMI ≥30 kg/m^2), and this was observed for the healthier as well as the sicker groups of hemodialysis-treated patients. Even within a cohort of patients younger than 45 years old with low comorbidity, overweight/obesity was not associated with decreased survival [26, 27].

Finally, a similar inverse weight-mortality relationship has been reported among chronic peritoneal dialysis patients. In the CANUSA study, a 1% difference in percent lean body mass was associated with a 3% change in the RR of death [28, 29]. McCusker et al [30] found a significantly lower survival rate in patients with lower lean body mass. For those with an initial lean body mass >73%, 63% to 73%, and <63%, the 2-year survival probabilities were 88.3%, 81.2%, and 65.2%, respectively. Johnson et al [31] studied the BMI in a limited number of peritoneal dialysis patients and found that obesity conferred a significant survival advantage in the peritoneal dialysis population. Chung, Lindholm, and Lee [32] performed a similar study in Korean peritoneal dialysis patients and found that lean body mass was an independent predictor of death in peritoneal dialysis patients.

There are very few studies that have shown a deleterious effect of a high BMI in ESRD patients. These are usually based on small sample sizes or different subgroups of dialysis patients. For instance, Kaizu et al [33] studied 116 nondiabetic hemodialysis patients and used Kaplan-Meier survival analysis and proportional hazard models to calculate the RR of mortality in BMI quintiles. They showed that patients with BMI of less than 16.9 kg/m^2 and higher than 23.0 kg/m^2 showed lowered survival relative to the patients with BMI of 17.0 to 18.9 kg/m^2. However, even in this study, patients with a BMI <16.9 kg/m^2 were shown to have the highest risk of mortality independent of other factors.

Although high BMI has been emphasized as a strong risk factor for morbidity and mortality in the general population, a recent study suggests that a higher BMI

in certain age groups in normal or nonuremic individuals may not necessarily be associated with higher morbidity and mortality [11]. Similar to ESRD patients, Grabowski and Ellis [34] showed that a high BMI does not predict mortality in older people. In their Longitudinal Study of Aging that examined 7527 participants 70 years old and older, they demonstrated reduced mortality in obese older people and showed that thin older people remained more likely to die than normal older people. A similar finding from Italy showed that a low BMI was a significant and independent predictor of shortened survival in hospitalized patients [12].

Blood pressure: Is hypertension protective?

The role of hypertension as a risk factor for increased cardiovascular or cerebrovascular events in the general population is indisputable [35–37]. Even high normal blood pressure confers a significantly greater risk of cumulative incidence of cardiovascular events [37]. Similar to the general population, several studies have also suggested that hypertension in dialysis patients is associated with increased mortality risk [38, 39], including the French Tassin data on long-duration hemodialysis [40, 41]. This has led several advisors to focus on predialysis blood pressure (e.g., systolic blood pressure >160 mm Hg) as an indicator of quality of care by hemodialysis units [39]. However, although hypertension in ESRD traditionally has been poorly controlled [42, 43], elevated blood pressure may not represent the primary risk for overall survival in dialysis patients [44–46]. Tassin data showing improved dialysis survival with blood pressure control [40, 41] may be confounded by other survival advantages since the patients treated with 6-hour, three times a week dialysis are reported not to be volume expanded; hence, it can be argued that low blood pressure in these individuals is less likely to indicate cardiac pump failure and more likely to reflect a desirable homodynamic state. Indeed, several recent studies, including those based on large sample sizes, failed to find that high blood pressure is an independent mortality risk factor [47, 48]. Findings presented by Lowrie et al [48], Duranti, Imperiali, and Sasdelli [44], Zager et al [47], and Iseki et al [49] from studies of large hemodialysis populations indicated surprisingly little or no risk associated with systolic hypertension. In a cross-sectional study of 936 hemodialysis patients in the HEMO Study, Cheung et al [50] reported no significant linear or nonlinear association between predialysis systolic blood pressure and any of the cardiovascular disease end points.

While contemporary thinking reiterates the link between hypertension and cardiovascular morbidity and mortality in the general population [35–37], recent studies of ESRD patients point to a link between low blood pressure and poor survival. Even though the adverse consequences of low blood pressure is not a new concept,

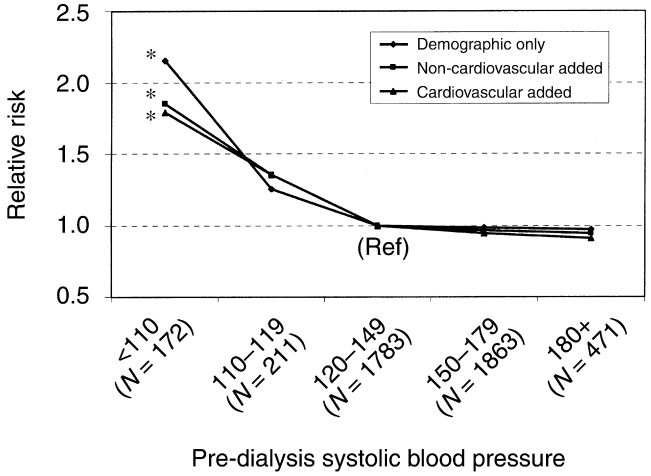

Fig. 3. Relative risk (RR) of death according to predialysis systolic blood pressure compared with the reference group of 120 to 149 mm Hg (RR = 1.00). Three separate models are shown according to the level of statistical adjustment. *$P < 0.0001$. Reprinted with permission from Port FK et al, *Am J Kidney Dis* 3:507–517, 1999 [51].

its impact on dialysis outcome and on cardiovascular mortality has been underappreciated. Iseki et al [49] showed a strong association between low diastolic blood pressure and risk of death in a cohort of 1243 hemodialysis patients who were followed up for 5 years. In this study, the death rate was inversely correlated with diastolic blood pressure, which per se showed a significant positive correlation with serum albumin and a negative correlation with age. Zager et al [47], in a study of more than 5000 hemodialysis patients followed up for a mean of 2.9 years, noted that the relative death rate for patients with predialysis or postdialysis hypotension (systolic blood pressure <110 mm Hg) increased to four times normal or greater than 2.5 times normal, respectively. Port et al [51] analyzed data from 4839 hemodialysis patients in the Case Mix Adequacy Study of the United States Renal Data System (USRDS) and found that when predialysis systolic blood pressure decreased below the reference group (120 to 149 mm Hg), the relative mortality risk increased and reached statistically significant values at pressure measurements less than 110 mm Hg (Fig. 3). Fleischmann, Bower, and Salahudeen [8] found that the cumulative hazard for dying was significantly influenced by the predialysis mean arterial pressure tertiles, with the lowest survival in the lowest third and the best survival in the upper third. A correlation of low predialysis systolic blood presssure with increased mortality has also been reported by Lowrie et al [48] and Duranti, Imperiali, and Sasdelli [44].

The concept of a U-shaped curve linking increased mortality to low blood pressure was previously reported in a non-ESRD population by Cruickshank, Thorpe, and Zacharias [52] when they examined outcomes in the gen-

eral population undergoing antihypertensive treatment. Historically, hypertension is associated with concentric left ventricular hypertrophy (LVH), ventricular dilatation, ischemic heart disease, and congestive heart failure. However, after the development of cardiac failure, low blood pressure or hypotension predicts mortality and is a potential marker for severity of cardiac disease [38, 53]. In addition, patients presenting with baseline predialysis hypotension may possess such subclinically significant risk factors or comorbidities such as hypoalbuminemia, heart failure, and ischemic cardiomyopathy [49, 54]. Low blood pressure may be a reflection of autonomic neuropathy that, in turn, is a marker for more severe uremic complications. Because antihypertensive drug therapy may contribute to low predialysis systolic blood pressure, one may hypothesize that either overmedication (perhaps specific antihypertensive agents) or cardiac pump failure are the major contributors to the observed associations. To date, no study has examined the potential role of medication as a cause of low blood pressure and increased mortality in dialysis patients. Ongoing and future studies might address these issues.

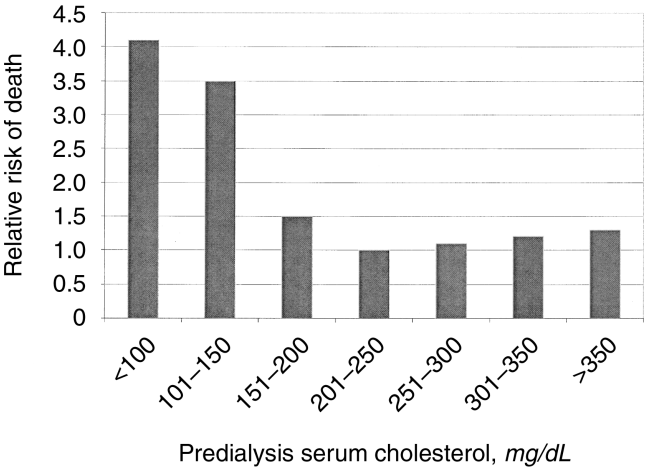

Fig. 4. Relative risk (RR) of death in hemodialysis patients according to serum cholesterol concentration compared to the reference group (cholesterol 200 to 250 mg/dL, RR=1.00). Reprinted with permission from Lowrie EG and Lew NL, *Am J Kidney Dis* 15:458-482, 1990 [5].

Serum cholesterol: Is hypercholesterolemia protective?

In the general population, hypercholesterolemia is a known risk factor for cardiovascular morbidity and mortality [55–57]. Among lipid components, increased serum levels of low-density liproprotein (LDL) and non-high-density lipoprotein (HDL) cholesterol appear to have the strongest predictive value for poor cardiovascular outcome, whereas HDL-cholesterol is generally considered protective in the general population [57].

In the Diaphane Collaborative Study Group, Degoulet et al [23] reported that a lower plasma total cholesterol level was associated with a significantly higher risk of death from cardiovascular disease in a cohort of 1453 French hemodialysis patients. Lowrie and Lew [5] analyzed a group of more than 12,000 prevalent hemodialysis patients and found that serum cholesterol level was inversely correlated with the risk for death in a multivariate logistic regression adjusting for several case-mix factors and biochemical parameters (Fig. 4). Avram et al [58] showed that serum cholesterol concentration was elevated in the long-term dialysis survivors. Fleischmann, Bower, and Salahudeen [8] studied 453 hemodialysis patients prospectively and showed that among lipids, the second and third tertiles of total cholesterol as well as LDL and HDL cholesterol were associated with better survival, although this was only a trend that was not statistically significant. More recently, Iseki et al [59] reported similar findings based on a sample of 1167 hemodialysis patients who were followed for up to 10 years. We showed similar findings in a small cohort of hemodialysis patients who were followed for up to 12 months [60]. Of note, some less recent studies in ESRD patients indicated an opposite direction of the serum cholesterol–mortality relationship, consistent with that seen in the general population. For example, a retrospective study of a cohort of 190 peritoneal patients with an average follow-up of 12 months and based on Cox model showed that an elevated serum cholesterol level was associated with increased mortality [61]. Nevertheless, this same study showed that a low serum creatinine concentration also predicted mortality (see below).

Similar findings regarding the association of low serum cholesterol and poor outcome have been reported for elderly persons who do not have ESRD [62–64]. For instance, Volpato et al [63] investigated the relationship between low cholesterol and mortality in older persons in a prospective cohort consisting of 4128 elderly patients with a mean age of 78.7 years and a median follow-up period of 4.9 years. They found that in those with a low serum cholesterol level, defined as $\leq$160 mg/dL, all-cause mortality was significantly higher than those with normal or high serum cholesterol concentrations. Krumholz et al [64] failed to show any significant association between hypercholesterolemia or low HDL-cholesterol and all-cause mortality, coronary heart disease mortality, or hospitalization for myocardial infarction or unstable angina in a cohort of persons older than 70 years.

Serum creatinine: Is high better than low?

In the general population, a slight or moderate increase in serum creatinine has been shown to be an independent risk factor of cardiovascular disease [65–67]. A secondary analysis of the HOPE Study showed that in patients who had either preexisting vascular disease or diabetes mellitus and an additional cardiovascular risk factor, the presence of mild renal insufficiency signifi-

cantly increased the risk for subsequent cardiovascular events [65]. The HOT Study showed that a baseline elevation in serum creatinine is powerful predictors of cardiovascular events and death [66].

In dialysis patients, the serum creatinine, a reflection of muscle mass or meat ingestion and/or the degree of dialysis efficiency, has also been shown to be a predictor of mortality but in the opposite direction (i.e., those dialysis patients with a higher serum creatinine live longer). This is contrary to the notion that well-dialyzed dialysis patients with higher Kt/V should have lower serum creatinine concentrations compared to those in whom dialysis treatment is not adequate. Lowrie and Lew [5] found that the serum creatinine level was inversely correlated with the risk for death. Avram et al [58] found that the enrollment serum creatinine was significantly higher among long- and very long-term hemodialysis and peritoneal survivors. In the study by Tattersall, Greenwood, and Farrington [68], there was no significant change in the predialysis serum creatinine values for hemodialysis patients from the time they initiated dialysis as compared with their values 6 months later. These results suggest that the factors that link lower predialysis serum creatinine values to increased mortality in dialysis patients may be determined when the patients commence renal replacement therapy. In the 1992 USRDS Annual Report, the investigators analyzed hemodialysis patients initiating dialysis in 1986 and 1987 and found that increasing serum creatinine level was associated with decreasing mortality [69]. Fink et al [70] studied 5388 incident hemodialysis patients followed up for almost 2 years and found that serum creatinine level was inversely correlated with mortality risk. Among studies of peritoneal dialysis patients, a retrospective study of a cohort of 190 peritoneal patients with an average follow-up of 12 months and based on the Cox model found that a low serum creatinine was an independent variable significantly associated with increased risk of death [71].

Plasma homocysteine: Is high better than low?

Plasma total homocysteine (tHcys) has been established as a new risk factor for increased cardiovascular morbidity and mortality in the general population [72, 73]. Estimated survival among non-ESRD patients with coronary artery disease can be stratified according to plasma total homocysteine levels. Higher homocysteine levels are associated with a worse outcome [72]. A similar association as in the general population was found in some studies of dialysis patients (i.e., a higher plasma tHcys was found to be associated with increased risk of cardiovascular disease) [74–79].

However, conflicting findings have been reported regarding the association between the plasma tHcys level and the prevalence of cardiovascular disease in chronic renal failure patients. Bostom et al found no relationship between the fasting plasma tHcys level and the prevalence of cardiovascular disese in dialysis patients, using crude or multiple logistic regression analyses adjusted for other risk factors [80]. More recently Suliman et al [81, 82] found that among 117 hemodialyis patients, those with cardiovascular disease (60%) had significantly lower tHcys levels than those without cardiovascular disease, although both groups still had higher plasma tHcys levels than the general population. Wrone et al[83] performed a cross-sectional analysis of 459 dialysis patients, and showed that those with a history of cardiovascular disease had lower levels of predialysis plasma tHcys than those without a history of cardiovascular disease. This negative relationship persisted in multivariate analyses when controlling for predictors of cardiovascular disease, such as age, gender, and BMI. Mean plasma tHcys was higher in patients without a history of cardiovascular disease than in those with cardiovascular disease [83]. Of note, both of the above-mentioned studies found a statistically significant, positive correlation between predialysis plasma tHcys and albumin concentration, which is a known, strong predictor of mortality in dialysis patients. We have recently found a similar positive correlation in a sample of 368 hemodialysis patients, which may indicate that plasma tHcys is a nutritional and/or inflammatory marker in dialysis patients (abstract; Kalantar-Zadeh et al, *Am Soc Nephrol*, 13:222A, 2002). It is noteworthy that studies showing the inverse relationship in dialysis patients are all of recent origin. One reason why similar results had not been reported in the past may be related to publication bias that will be discussed later in this manuscript (see below).

However, these observations do not necessarily exclude the role of hyperhomocysteinemia as a risk factor for poor ESRD outcome, since other factors might be present that confound the relationship between tHcys levels and cardiovascular disease. Of particular importance is the fact that even studies that found a reverse epidemiology confirmed that tHcys was higher in dialysis patients as compared to the general population [82, 83]. Assuming that an increase in tHcys level carries an independent risk of cardiovascular, this may imply that almost all dialysis patients are already exposed to this risk. Thus, the apparently paradoxic association between tHcys and cardiovascular disease does not strictly conflict with the thesis that hyperhomocysteinemia is a risk factor for cardiovascular disease. However, within this population, those with the highest tHcys level may have some survival advantages due to better nutrition.

Other possible examples of reverse epidemiology

Excess parathyroid hormone (PTH) has long been considered detrimental to the health of patients, including those with ESRD [84]. PTH has been implicated as a multisystem uremic toxin, and hyperparathyroidism can

be a debilitating complication in dialysis patients [84]. Hyperphosphatemia that is closely related to hyperparathyroidism is associated with increased mortality in dialysis patients [85]. Avram et al [86] studied prospectively the relationship between the enrollment serum intact PTH and all-cause mortality in 345 hemodialysis and 277 peritoneal dialysis patients for 14 years and found that lower than expected levels of PTH in uremic patients are associated with increased mortality. Moreover, Guh et al [87] recently reported similar findings that low levels of serum PTH at entry and lower time-dependent PTH levels predict mortality in hemodialysis patients. Avram et al [86] hypothesized that inadequate protein intake, phosphorus intake or both result in impaired development of the expected secondary hyperparathyroidism and in the excess mortality risk inherent with malnutrition. However, to date epidemiologic studies have shown a positive association between a high serum phosphorus and poor outcome among ESRD patients [85, 86]. Hence, the association between serum PTH and outcome in dialysis patients may be unrelated to serum phosphorus and may reflect other aspects of nutritional status.

Another example is serum ferritin and its association with anemia. In the general population, a low serum ferritin is a marker of iron deficiency and anemia that may not respond to erythropoietin unless iron is repleted [88]. However, in ESRD patients, a high and not a low serum ferritin is associated with a more severe and refractory anemia [89, 90]. This may be due to hyporesponsiveness to erythropoietin, which can occur in the setting of the malnutrition-inflammation complex syndrome (MICS) in dialysis patients [60], especially since ferritin is an acute phase reactant [89, 90].

Finally, another possible example of risk factor reversal is the association between the amount of energy (calorie) or food intake and mortality. In the general population, an increased energy intake may be associated with increased BMI and hypercholesterolemia and, hence, with a higher mortality rate and risk of cardiovascular disease [91, 92]. In contrast, in dialysis patients increased protein intake, estimated from the urea generation and urea kinetics, may lead to an improved nutritional status, reflected by an increased albumin level, and a better survival [93–95]. However, data in dialysis patients are mostly based on indirect measurements of protein intake and studies concerning the possible association between energy (calorie) intake and dialysis outcomes are yet to be developed.

POSSIBLE EXPLANATIONS FOR REVERSE EPIDEMIOLOGY

The concept of reverse epidemiology appears at first to be confusing, especially because hypertension, obesity, and high levels of serum cholesterol, creatinine, and homocysteine are established risk factors for ischemic heart disease in the general population. The paradox becomes even more paramount when it is recognized that it is not a question of the existence or lack of an association between these risk factors and the clinical outcomes, but often the complete reversal and indeed the opposite direction of this relationship. Hence, there must be prevailing conditions that are characteristically present in dialysis patients that render them more susceptible to a poor outcome when low body mass, low blood pressure, or decreased serum values of cholesterol, creatinine, and homocysteine are present. Several suggested explanations are offered for this inverse association. Survival bias, time discrepancies among competing risk factors, the MICS, and several other hypotheses are presented as possible causes.

Survival bias

Since dialysis patients have undergone specific processes of selection and survival, their characteristics may not be similar to the general population. Therefore, the relationship between the risk factors and outcomes may have been modified. According to an analysis based on the National Health and Nutrition Examination Survey [96], in the United States there are over 10 to 20 million patients with chronic kidney disease (CKD) and an elevated serum creatinine due to a chronic, irreversible and probably progressive damage to the kidney. However, according to the USRDS data [1], the number of people with ESRD is approximately 400,000 at this time and is projected to increase to almost 650,000 by the year 2010. This constitutes only a small fraction (less than 5%) of the large pool of CKD patients in the United States. Current thinking suggests that a large population of CKD patients will not live long enough to develop ESRD and commence maintenance dialysis. One explanation for this phenomenon is that CKD patients have a high mortality rate since many of them have severe and complex comorbid conditions, such as diabetes mellitus, hypertension, and atherosclerotic vascular disease. Moreover, renal disease with proteinuria or an increased serum creatinine by itself is an independent risk factor for greater morbidity and mortality, particularly from atherosclerotic heart and cerebrovascular diseases [65, 66]. Thus, many CKD patients do not reach ESRD due to their high mortality. This can explain 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, however, is 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" individuals may be considered as "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 comprise the ESRD population might be "exceptional individuals" who successfully survived the conventional (traditional) risk factors, which are often present strongly in CKD patients. Hence, the assumption that the epidemiology of cardiovascular risk factors is the same in ESRD individuals 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 (i.e., the dialysis patients). A similar trend is observed in elderly individuals, who have reached advanced age possibly due to survival advantages, and they also are reported to have a different epidemiology with different cardiovascular disease risk factors than the general population [11, 13, 34].

It should be noted that many epidemiologic studies in ESRD patients are based on a mixed pool of incident and prevalent dialysis patients (i.e., those who have started dialysis recently and those who have been on dialysis for a number of years are treated equally in such studies). This may lead to what epidemiologists call "incidence-prevalence" or "survival" bias, which per se is a form of selection bias [97]. In other words, those incident patients who had more risk factors or were more vulnerable to such risks did not survive long enough to be included in a cross-sectional study that encompasses many prevalent patients who have been on dialysis for a number of years and who hence over-represent ESRD patients who have exceptional survival advantages. Indeed, the majority of incident dialysis patients die, especially due to the exceptionally high ESRD mortality rate, currently approximately 20% in the United States [1]. Hence, even longitudinal studies that are based on a mixture of incident and prevalent dialysis patients may be heavily influenced by a survival bias [98]. Survival bias can potentially exert a strong influence on both epidemiologic studies and clinical trials, especially when patients who have varying degrees of duration of dialysis are enrolled together [97, 98]. In this regard, it is possible that the concept of reverse epidemiology is a consequence of systematic errors in epidemiologic data analysis [83]. However, some epidemiologic data based exclusively on incident dialysis patients still show the same risk factor reversal [25], indicating that this phenomenon cannot be solely explained by survival bias.

Time discrepancies among competitive risk factors

Survival advantages that exist in obese, hypertensive, hypercholesterolemic, hypercreatininemic, or hyperhomocysteinemic dialysis patients may, in the short-term, outweigh the harmful effects of these risk factors on cardiovascular disease in the long-term. Since dialysis patients have a mortality risk that is greater than the general population [2], the long-term effects of these risk factors on future mortality may be overwhelmed by the short-term effects of other factors on dialysis mortality. Indeed, it may be difficult, if not impossible, to observe a significantly greater life expectancy with reduction of the traditional risk factors in 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.

An example of this time discrepancy in non-ESRD populations may concern obesity and underweight. In the general population in the United States, as well as in most industrialized countries, manifestations of over-nutrition such as overweight/obesity and hypercholesterolemia are major risk factors for cardiovascular mortality [15–19, 56, 57]. These are also countries where people have a greater life expectancy compared to individuals in other parts of the world. Studies of risk factors of cardiovascular mortality are essentially based on these populations. In contrast, in developing countries, which represent the majority of the world's population, under-nutrition is still a powerful determinant of poor clinical outcome and morbidity and mortality, leading to a shorter life expectancy [99–101]. A hypothetical demonstration of the combined effect of competitive risk factors (over- versus under-nutrition) is presented in Figure 5.

Thus, in dialysis patients who have a short life expectancy, any factor that may improve short-term survival, such as high blood pressure, obesity, and hypercholesterolemia may exert a desirable effect on longevity, whereas conditions that are traditionally associated with long-term survival such as rigorous blood pressure control, low body weight-for-height, and low serum cholesterol and homocysteine, may be less relevant. Such factors may even be harmful if they cause, represent, or aggravate states of under-nutrition, hypotension or cardiac failure.

Malnutrition inflammation complex syndrome (MICS)

Measures of protein-energy malnutrition (PEM) and inflammation are major predictors of clinical outcome in dialysis patients [3–5, 7, 9]. Dialysis patients with cardiovascular disease have a higher prevalence of malnutrition and hypoalbuminemia and a lower protein intake than those without cardiovascular disease [7, 102]. Several studies report strong relationships between hypoalbuminemia and cardiovascular disease in dialysis patients and suggest that hypoalbuminemia is an important risk factor for cardiovascular disease in these individuals [54, 103–105]. Cardiac diseases such as heart failure may engender anorexia and, if sufficiently severe, may independently induce muscle wasting, which is also known as cardiac cachexia [102, 106]. However, it is not completely clear how cardiac disease, inflammation, hypoalbumi-

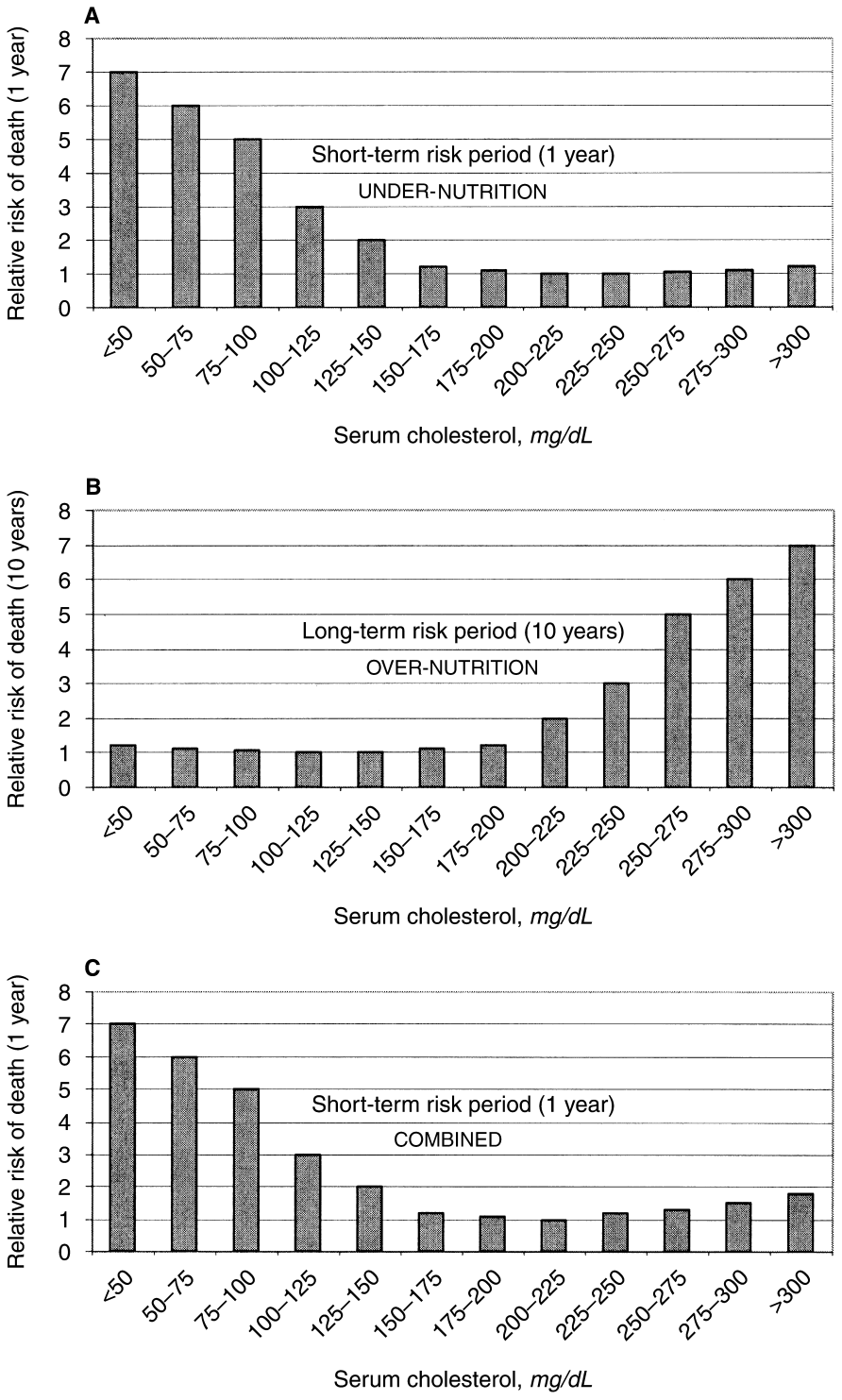

Fig. 5. A hypothetical representation of combining two competing risk factors with time discrepancy. (*A*) A low serum cholesterol in the setting of under-nutrition is a short-term marker of mortality (1-year scale). (*B*) A high serum cholesterol in the setting of over-nutrition leads to an increased mortality rate over a long-term interval (10-year scale). (*C*) After combing both impacts, the short-term risk factor pattern (under-nutrition associated hypocholesterolemia) predominates.

nemia, and other measures of PEM in dialysis patients are interrelated [106, 107]. It has been postulated that the common link among these conditions is inflammation [7, 54, 103, 104, 106, 108]. A common mechanism for the development of cardiovascular disease and PEM in dialysis patients may be cytokine activation associated with reduced renal function or other proinflammatory conditions in dialysis patients. Frequent contact with dialysis membranes, vascular access grafts or catheters or dialysate, or peritoneal dialysis fluid may each constitute a proinflammatory condition [7, 109]. Increased release or activation of inflammatory cytokines, such as interleu-

kin-6 (IL-6) or tumor necrosis factor-α (TNF-α), may suppress appetite, cause muscle proteolysis and hypoalbuminemia, and may be involved in the processes that lead to atherosclerosis [66, 104, 110]. Nevertheless, the degree to which PEM in dialysis patients is caused by inflammation is not clear [7, 110]. Some studies suggest that PEM and inflammation each independently contribute to hypoalbuminemia and subsequently increase morbidity and mortality [105]. Since 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 two conditions to each other and to outcomes in dialysis patients are not yet well defined, MICS has been suggested to denote the important contribution of both of these conditions to ESRD outcome [7, 60]. Some investigators have used other terminologies such as "malnutrition inflammation atherosclerosis" (MIA) to emphasize the importance of atherosclerosis as the consequence of MICS [54, 110]. Furthermore, oxidative stress may play an important integral part in the associations between inflammation, malnutrition and atherosclerosis, since variations of serum albumin may be correlated not only with outcome but also with inflammation, cardiovascular disease, and serum cholesterol and tHcys concentrations [111, 112]. No matter what it is called or caused by, the theory of reverse epidemiology in ESRD is compatible with the existence of MICS or MIA and its interplay with the traditional risk factors.

The existence of paradoxic risk factors could be accentuated by the MICS, possibly in several ways. First, patients who are underweight or who have a low serum cholesterol, creatinine, or homocysteine, may be suffering from the MICS and its poor outcome. Thus, MICS may both cause these alterations and also be associated with increased mortality either caused by the illnesses that engender the MICS or the cardiovascular disease that seems to be promoted by the MICS [106, 113, 114]. Second, the above paradoxic factors may indicate a state of under-nutrition, which may predispose to infection or other inflammatory processes [7]. Finally, it has been argued that when individuals are malnourished, they are more susceptible to the ravages of inflammatory diseases [113]. Hence, any condition that potentially attenuates the magnitude of PEM or inflammation should be favorable to dialysis patients. This notion can explain why there is a reverse epidemiology of cardiovascular risk factors in dialysis patients, especially since almost all the so-called nontraditional protective factors, such as obesity, hypercholesterolemia, hypercreatininemia, and hyperhomocysteinemia, are related to nutritional status. Suliman et al [81, 82] have reported a more specific example of the contribution of the MICS to risk factor reversal concerning with hyperhomocysteinemia in dialysis patients. In their study, plasma tHcys levels were shown to be dependent on nutritional status, protein intake, and serum albumin in hemodialysis patients. Hemodialysis patients with cardiovascular disease had lower tHcys levels as well as a higher prevalence of malnutrition and hypoalbuminemia than those without cardiovascular disease. Furthermore, in another study plasma tHcys was shown to rise during treatment of malnourished peritoneal dialysis patients with an amino acid–containing peritoneal dialysate (1.7 g methionine/day) [115]. The presence of MICS may further reinforce this relationship by suppressing serum albumin, which is an important carrier protein for plasma tHcys [81, 82, 106].

The puzzling inverse relationship between a low blood pressure and poor outcome in the dialysis population might also be accounted for by nutritional status and/or inflammation. Iseki et al [49] showed a significant association between a low diastolic blood presssure, hypoalbuminemia, and risk of death in a cohort of hemodialysis patients. They analyzed the causes of death with regard to the relationship between serum albumin and blood pressure in 1243 hemodialysis patients who were followed for up to 5 years. The death rate was inversely correlated with diastolic blood pressure, which per se was positively correlated with serum albumin and negatively correlated with age. Hence, hypotension may in some cases be a manifestation of MICS in hemodialysis patients.

Other hypotheses

Goldberg, Tindira, and Harter [116] suggest that the paradigm of coronary artery disease in ESRD shifts from solely traditional risk factors, such as age, diabetes, hyperlipidemia, and hypertension, to a number of additional factors that may regulate coronary event rates in a different way in uremia. Theoretically, hypotension and under-nutrition can contribute to the increased relative risk of death by several mechanisms, such as acute coronary syndrome, autoregulation dysfunction, ischemia, and arrhythmiagenecity [117, 118]. These factors, if indeed altered or exaggerated in uremic milieu, may provide an environment in dialysis patients, in whom hypotension and undernutrition may become more influential than the traditional risk factors in the development of cardiovascular disese.

Chronic inflammatory processes may independently predispose to both malnutrition and atherosclerosis. IL-6 predicts hypocholesterolemia [119], malnutrition [120, 121], and atherosclerosis [122, 123] in dialysis patients. Inflammation can indeed lead to hypocholesterolemia in ESRD patients [59, 119]. Moreover, chronic infusion of IL-1 or TNF-α (cachectin) has been shown to cause anorexia, rapid weight loss, and a decline in body protein stores [124]. Hence, given the fact that inflammation is more common in ESRD patients as compared to the general population [104, 120], inflammation by itself may

precede under-nutrition and lead to the risk factor reversals in individuals with ESRD.

There may be other confounding factors that may explain some of the risk factor reversals in dialysis patients. Both low body mass and low blood pressure may be consequences of cigarette smoking [125, 126] and/or congestive heart failure [102, 106], conditions that are associated with increased ESRD mortality. These conditions may also be associated with an increased prevalence of inflammation and malnutrition [127, 128]. Heart failure may engender anorexia and may independently induce cachexia [106]. A low blood pressure, a potential indicator of severe heart disease, is thus associated with poor outcome [53]. Moreover, a low blood pressure may be caused by autonomic neuropathy that, in turn, can be the result of uremic toxicity or the ravages of diabetes [129]. Hence, it may not be normo- or hypotension per se that is detrimental but rather the underlying cause of low blood pressure (i.e., cardiac pump failure and/or autonomic neuropathy).

Finally, a less well-substantiated hypothesis represents the notion that what we consider as reverse epidemiology (the stronger impact of under nutrition) may indeed be the natural epidemiology in human and that the so-called conventional epidemiology (over-nutrition) is a new and unusual phenomenon in human history [130]. 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, these populations indeed live longer than ever. Moreover, with aging, the detrimental effects of obesity, over-nutrition, and hypertension may diminish if not disappear, a similar trend that can be observed in ESRD population as well.

CONCLUSION

The reversal of certain key risk factors in dialysis patients poses serious questions. Is the increasing prevalence of obesity and its detrimental impact to health in the general population of any relevance in dialysis patients? Do overnutrition, obesity, hypertension, or hypercholesterolemia that promote atherosclerosis and mortality in the general population prevent poor outcome in dialysis patients, and if so how? Should dialysis patients be advised to increase their nutrient intake in order to gain weight and to increase their serum cholesterol, creatinine, and homocysteine levels? Should their target blood pressure be higher? Can these reversed relationships be used to establish therapeutic goals?

Publication bias may have handicapped or delayed reporting such paradoxical findings in dialysis patients as the association between plasma homocysteine and cardiovascular disease in dialysis patients, since the investigators' first impression upon encountering results with inversed association may be to consider them erroneous or flawed and hence be reluctant to report them [131]. However, as more reports indicative of reverse epidemiology in ESRD have been published recently, more investigators may be encouraged to report their similar findings. This may explain why more frequent reports and publications consistent with the reverse epidemiology have emerged only recently.

It is important to appreciate that some of the discussed risk factors may represent different biologic or medical phenomena in ESRD patients as compared to the general population. Serum creatinine, for instance, is a reflection of renal function in the general population, whereas it is essentially representative of skeletal muscle mass and/or meat ingestion as well as the dose of dialysis in ESRD patients. Similarly, a pre-dialysis blood pressure measurement may represent a different underlying disease processes in hemodialysis patients who are often volume overloaded. Thus, a low predialysis blood pressure in patients who are likely to be volume expanded is more probably due to a sick heart, whereas in the general population it may more likely indicate excellent circulatory homodynamics. Hence, the etiology of "reverse epidemiology" in dialysis patients may be quite different for various risk factors, and the term "reverse epidemiology" may be a misnomer. Nevertheless, it is important to first exhaust the possibility of a single unifying entity to be accounted for all or most of the abovementioned risk factor reversals. We believe that PEM and inflammation (MICS) are the best candidates.

Despite all these concerns, the evidence is strong that a risk factor paradox indeed exits in those who reach ESRD and who continue to have an unacceptably high rate of mortality, currently approximately 20% in the United States. This high mortality rate has not substantially been changed in the recent years despite aggressive efforts toward an optimal management of traditional risk factors in these individuals. Hence, it is important to explore the causes of reverse epidemiology and to ascertain how best to reverse these associations in dialysis patients. We believe that in dialysis patients more attention should be focused on optimal management of undernutrition and inflammation based on the mechanisms responsible for the reverse epidemiology. However, premature or radical conclusions to discontinue antihypertensive or antihyperlipidemic treatment should be avoided until such information is forthcoming. For instance, the antihypercholesterolemic agent, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor or such antihypertensive agents as angiotensin-converting enzyme inhibitors may have an anti-inflammatory effect, which can be beneficial in the management of the elements of MICS and improved outcome in dialysis patients irrespective of the existence of reverse epidemiology [132–135]. It is also important to appreciate that

most of the examples of reverse epidemiology do not apply to renal transplant recipients, in whom obesity and hyperlipidemia are still reported to be quite common and strong risk factors for cardiovascular disease and poor outcome [136].

Although data presented in this review suggest that a higher body mass, hypertension, and hypercholesterolemia are associated with reduced morbidity and mortality in the vulnerable population of ESRD, it is possible that, in the long run, overweight patients may suffer from more cardiovascular consequences if they could survive sufficiently long [137]. Therefore, extended observations with sequential measurement of BMI, blood pressure, and serum levels of cholesterol, creatrinine, homocysteine and other relevant markers should be helpful to identify different subgroups of dialysis patients who may have traditional epidemiology as well as those who have reverse epidemiology. As more effective treatments for ESRD patents become available, it is possible that there may be a reversal of the reverse epidemiology and a return of the traditional epidemiology to many subgroups of dialysis patients, as is currently found in kidney-transplant patients. The question may remain unanswered as to what is indeed the normal epidemiology and what is reverse. Randomized, prospective, controlled clinical trials to examine the reversal of the traditional associations or the paradoxic risk factors will be most beneficial to the maintenance dialysis patients.

NOTE ADDED IN PROOF

A recent analysis by Lowrie et al [138], based on 43,334 MHD patients, also showed an improved survival in those with higher BMI values.

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