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Reverse Epidemiology: A Spurious Hypothesis or a Hardcore Reality?

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Key Words
Hemodialysis patients · Cardiovascular death · Reverse epidemiology · Malnutrition-inflammation complex syndrome · Quality of life

Abstract
In maintenance hemodialysis (MHD) patients, associations between demographic, clinical and laboratory values and mortality, including cardiovascular death, are significantly different and, in some cases, in the opposite direction of those derived from the general population. This phenomenon, termed 'reverse epidemiology', is not limited to MHD patients but is also observed in populations that encompass an estimated 20 million Americans including those with an advanced age, heart failure, malignancies, and AIDS. A significant portion of this reversal may be due to the overwhelming effect of the malnutrition-inflammation complex syndrome (MICS). Since two thirds of MHD patients die within 5 years of initiation of dialysis treatment, traditional cardiovascular risk factors such as obesity, hypercholesterolemia and hypertension cannot exert a long-term deleterious impact, and instead, their short-term beneficial effects on MICS provides a survival advantage. In order to improve survival and quality of life in MHD patients, extrapolated ideal norms derived from the general population should be substituted with novel norms obtained from outcome-oriented epidemiologic analyses while accounting for the differential effect of MICS in different case-mix subgroups.

In the United States, there are approximately 300,000 individuals with end-stage renal disease (ESRD) who are dependent on maintenance hemodialysis (MHD) for their survival [1]. According to the USRDS estimates, the number of maintenance dialysis patients, over 90% of whom undergo MHD, will approach half a million or even higher by the year 2010 [2]. These individuals experience a low quality of life, high rates of hospitalization, and a high mortality rate, currently 20% annually. Despite many recent improvements in dialysis treatment and techniques [1, 3, 4], approximately two thirds of all MHD patients die within 5 years of initiation of dialysis treatment [1], a 5-year survival worse than that of the majority of patients with malignancies. The causes of death in MHD patients are diverse; however, at least half of all MHD patients presumably die of cardiovascular diseases [5].

Extrapolation of findings from the general population has led to decades of focusing on treating such *conventional* cardiovascular risk factors as obesity, hyperten-

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Table 1. Populations with reverse epidemiology

Population	Estimated census in the USA, millions
ESRD undergoing dialysis	0.3–0.4
Chronic heart failure	4–5
Advanced age (>75 years)	15–20
Nursing home residency	0.3–0.5
Advanced malignancies	0.4–0.8
AIDS	0.1–0.3
Total	21–27

ESRD = End-stage renal disease: MHD = maintenance hemodialysis.

sion, hypercholesterolemia and hyperhomocysteinemia in dialysis patients. Despite these interventions, survival has not improved substantially in the past two decades [1]. Additional efforts targeted other possible correlates of high dialysis mortality such as dialysis dose or dialysis membrane. However, several recent multicenter clinical trials, including the HEMO [6] and ADAMEX [7] studies failed to show any survival advantage of increasing dialysis dose or membrane in ESRD patients [7]. Hence, there appear to be other prevailing risk factors contributing to this substantial and persistent mortality rate in the dialysis population.

The Concept of Reverse Epidemiology

Many reports indicate that in MHD patients there is both a high prevalence of protein-energy malnutrition (PEM), up to 40% or more, and a strong association between this condition and greater morbidity and mortality [8–10]. In highly industrialized, affluent nations, malnutrition is an uncommon cause of poor outcome in the general population, where, instead, *over*-nutrition is highly prevalent and, being a risk factor for cardiovascular disease, has had immense epidemiologic impact on the burden of this disease and on shortened survival. In contrast, in MHD patients *under*-nutrition appears to be one of the most common risk factors for adverse cardiovascular events [11–14]. The term 'reverse epidemiology' has been used to describe this observation [11] in which certain markers, such as decreased body mass index (BMI), which predict a low likelihood of cardiovascular events and improved survival in the general population, become strong risk factors for increased cardiovascular morbidity and death in MHD patients. Moreover, some indicators of extreme over-nutrition such as obesity or even morbid obesity still predict improved outcome in MHD patients [5, 11, 14].

Other Populations with Reverse Epidemiology

The reverse epidemiology observation is not unique to the dialysis population. Patients with congestive heart failure [15], geriatric populations [16] including elderly individuals in nursing homes [17], hospitalized patients [18], patients with malignancy [19], those living with AIDS [20], and possibly other vulnerable subpopulations also have been found to exhibit inverse associations for traditional risk factors. In general, there appear to be at least 20 million Americans who fall into a population demonstrating a reverse epidemiology of cardiovascular risk factors (table 1). Hence, a better understanding of the predictors of reverse epidemiology and its subsequent implications on survival in MHD patients may help improve the poor outcome in this and other similar but distinct populations.

Components of the Reverse Epidemiology

MHD patients not only have a reversed BMI–mortality association, but a worse survival has also been observed with a low, rather than a high, blood pressure (BP) [21], serum concentrations of cholesterol [12], homocysteine [22], creatinine [23], iron, and advanced glycation end products [24], among others. Adding to this reversal are findings indicating that high values of these risk factors are protective and actually appear to be associated with improved survival [25]. Of all these associations, however, the protective effect between high BP and mortality in MHD patients is among the most controversial ones, possibly due to a lack of theoretical biologic mechanism [21, 26]. Other examples of reverse epidemiology that are more accepted include the effect of potassium and calcium. In the general population, a higher intake of potassium is associated with better outcome including better BP control [27] and lower death due to stroke [28], whereas in dialysis patients higher serum potassium levels are associated with poor survival [23, 29]. Similarly, in the general population increased dietary calcium improves hypertension and risk of ischemic heart disease [27, 30], whereas in dialysis patients, increased calcium

intake is associated with higher coronary artery calcification [31, 32]. Serum bicarbonate also shows paradoxical associations with mortality in dialysis patients [33, 34].

Are There ESRD Patients without Reverse Epidemiology?

Transplanted ESRD patients with a well-functioning renal allograft do not appear to exhibit reverse epidemiology as studies have found that obesity, hypercholesterolemia and hypertension are strong predicators of increased mortality in renal transplant patients [35, 36], a phenomenon which can be referred to as the 'reversal of reverse epidemiology' or 'back to normal' [11]. On the other hand, chronic peritoneal dialysis (CPD) patients have inconsistent obesity-outcome associations and hence appear to have a transitional status. Some [37–42], but not all [43–45], studies in CPD patients have reported similar inverse weight–mortality relationship. McDonald et al. [43] examined 9,679 new adult patients who underwent an episode of peritoneal dialysis (PD) treatment in Australia or New Zealand over an 11-year 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 relationship between BMI and death during PD treatment. Abbott et al. [44] and Stack et al. [46] found similar associations between obesity and poor outcome in CPD patients and concluded that the clinical selection of HD vs. PD may be related to different predictors of survival among these 2 groups of the ESRD population.

Is the Malnutrition-Inflammation Complex the Cause of Reverse Epidemiology?

MHD patients not only have a high prevalence of PEM but also a higher occurrence rate of inflammation [47–52]. 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 MHD patients are not yet well defined, we have suggested the term 'malnutrition-inflammation complex syndrome' (MICS) to denote the important, and likely inter-related contribution of both of these conditions to ESRD outcome [53]. The MICS is a plausible cause of increased cardiovascular risk factors and other poor outcomes such as poor quality of life and increased hospitalization and mortality and refractory anemia. The etiology of PEM and inflammation in MHD patients is not very clear, but some probable causes have been discussed previously [54–59]. Some of these factors such as reduced food intake due to anorexia can lead to both PEM and inflammation and can also be a consequence of MICS. Hence, the known overlap between malnutrition and inflammation in MHD patients may have its root at the etiology level.

The reverse epidemiology may be caused or at least accentuated by the MICS in several ways (fig. 1). 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, the MICS may both cause these alterations and also be associated with increased mortality either caused by the illnesses that engender the MICS or the atherosclerotic cardiovascular diseases that seem to be promoted by the MICS [49, 60, 61]. Second, those with reduced cholesterol, creatinine, or BMI may be in a state of undernutrition, which may predispose to infection or other inflammatory processes [48]. Finally, when individuals are malnourished, they are more susceptible to the consequences of inflammatory diseases and inflammation-induced cachexia [62, 63], which we have called 'cachexia in slow motion' [64]. A recent study showed that a decreased appetite or anorexia in maintenance dialysis patients is associated with increased levels of proinflammatory cytokines and inflammatory markers [65]. Hence, any condition that potentially attenuates the magnitude of PEM or inflammation should be favorable to dialysis patients.

MICS and Atherosclerotic Cardiovascular Disease

In the general population it has been shown that such indicators of inflammation as an increased serum C-reactive protein level are stronger predictors of cardiovascular events than low-density lipoprotein-hypercholesterolemia [66]. Hence, by virtue of its inflammatory component, MICS may potentiate atherosclerotic cardiovascular disease in dialysis patients [67–69]. MHD patients with coronary heart disease often have hypoalbuminemia and elevated levels of acute-phase reactants [68]. Moreover, progression of carotid atherosclerosis during dialysis may be related to interleukin-6 levels [70]. Data indicate that inflammatory processes may promote proliferation and infiltration of inflammatory cells into the tunica

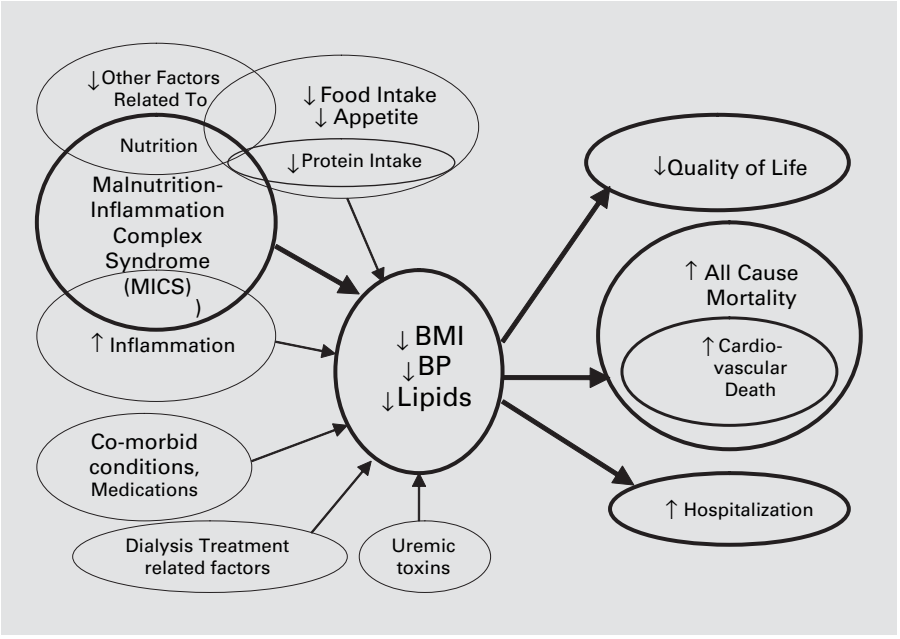

Fig. 1. Schematic representation of the causes and consequences of the reverse epidemiology.

intima of small arteries including the coronary arteries, which leads to consequent coronary and other vascular diseases [70, 71]. Inflammation might also cause direct endothelial dysfunction via a stimulation of intercellular adhesion molecules in ESRD patients [72]. The association between elements of MICS and atherosclerosis has been underscored by some investigators who have chosen the term 'malnutrition-inflammation-atherosclerosis' (MIA) for this entity [73, 74].

The Reality of Reverse Epidemiology

Efforts to obtain a better understanding of the distribution, etiology and components of the reverse epidemiology in MHD patients is of paramount importance, as the annual mortality and hospitalization rate among MHD patients remains very high [11]. The HEMO Study failed to demonstrate improved survival in MHD patients by changing dialysis dose or membrane. Elucidating a potentially modifiable predictor of both 'traditionally' protective health factors and increased mortality in MHD patients, such as MICS, could lead to urgently needed, effective, targeted interventions in this population [6].

A recent epidemiological study by Liu et al. [75] showed that MICS may be a reasonable cause of the inverse association between serum cholesterol and mortality in MHD patients. Surprisingly, however, the authors concluded that their study indicated that hypercholesterolemia was a main death correlate in ESRD patients and questioned the wisdom of the reverse epidemiology hypothesis and its clinical application. We argued that this study had a relatively small sample (823 patients), which was not representative of US patients who receive dialysis [76]. For instance, the median age of US incident dialysis patients is 64.5 years [77], whereas in the study by Liu et al. [75] it was 57.2 years for all patients and 53.7 years for those without MICS. The renal transplant rate in the US dialysis population is approximately 5.5/100 patient-years [77]. One would thus expect 103 in the cohort of Liu et al. [75], but this is significantly less than the 153 the authors reported. Hence, the younger age and the higher transplant rate in this study indicate a significantly healthier than average dialysis population. Moreover, the authors stated that their findings supported aggressive treatment of hypercholesterolemia in dialysis patients, despite the authors' own analyses in the subgroup of patients with MICS who comprised 75% of all patients of their study, which indicated either inverse or no association between total serum cholesterol and outcome even after adjustments for MICS. These findings indicated a strong association between elements of malnutrition and inflammation and prospective mortality in dialysis pa-

tients. Furthermore, the so-called 4D Trial failed to show improved cardiovascular outcome among dialysis patients who received atorvastatin vs. placebo, as presented at the 2004 meeting of the American Society of Nephrology. Hence, the treatment of MICS may have a higher priority than treatment of hypercholesterolemia or other conventional cardiovascular risk factors in dialysis patients [3].

Moreover, there is some justification for hypothesizing that decreasing serum cholesterol in MHD patients would be harmful, since the lipoprotein pool may serve as an effective scavenger to bind with and neutralize the circulating lipopolysaccharides (i.e. bacterial endotoxin) in patients with heart failure and fluid overload [78], a common condition in patients receiving dialysis. Low serum lipoproteins, including cholesterol, may be associated with an increased level of unbound circulating lipopolysaccharides and a higher prevalence of inflammation and cachexia [78, 79]. To our knowledge, there are hardly any published studies suggesting that high cholesterol levels and obesity are related to impaired survival among patients with chronic illness. Therefore we caution against Liu et al.'s [75] use of the term 'spurious' for the paradoxically inverse associations that have been consistently observed between such conventional risk factors as hypercholesterolemia and obesity and improved survival in maintenance dialysis patients.

Future Steps

Since over two thirds of MHD patients die within 5 years of initiation of dialysis treatment, we hypothesize that traditional cardiovascular risk factors such as obesity, hypercholesterolemia and hypertension do not have enough time to exert their long-term deleterious impact. In other words, dialysis patients die sooner of undernutrition before they can die of the more protracted results of overnutrition. Hence, the existent clinical indicators of overnutrition paradoxically protect MHD patients against the short-term fatal effects of MICS. Since nutritional or inflammatory states may be modifiable, altering nutritional and inflammatory markers, rather than treating obesity and hypercholesterolemia, may improve outcome under this hypothesis. Indeed, losing weight may be associated with higher death rates [5]. Therefore, treatment of MICS may have much higher priority than treating obesity of hypercholesterolemia, if the goal is saving lives.

A recent epidemiologic analysis of a large MHD patient database indicated that improving hypoalbuminemia in these patients can prevent 15,000–20,000 deaths/year in the USA [80]. Another recent study has shown that those MHD patients who gain weight over time have significantly less all-cause and cardiovascular deaths than those who lose weight [5, 80]. However, Asian-American MHD patients, like most CPD patients, may be an exception, in whom obesity may not be protective but deleterious [5]. Hence, before testing these hypotheses by launching expensive clinical trials, it is important to know how MICS and reverse epidemiology are engendered and through which mechanisms it is associated with poor outcome in different racial and case-mix subgroups of MHD patients. This may be achieved by conducting less expensive types of studies, i.e. well-designed epidemiological studies with time-dependent covariates as we have initiated [5]. Therefore, in order to improve survival and quality of life in MHD patients, extrapolated ideal norms derived from the general population should be replaced with novel norms obtained from outcome-oriented epidemiologic analyses of national databases while accounting for differential effect of MICS in different case-mix subgroups.

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