Homocysteine and risk in end-stage renal disease: a matter of context

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Like blood pressure and cholesterol, hoocysteine shows a paradoxical inverse relationship with cardiovascular complications in end-stage renal disease (ESRD). A paper by Ducloux et al. in this issue adds perhaps decisive evidence on malnutrition-hypoalbuminemia as the main factor explaining the counterintuitive association between homocysteine and clinical outcome reported in previous studies.

## Reverse epidemiology in ESRD

The problem of the inverse, or reverse, epidemiology of ESRD is one of the most discussed topics related to the high risk of death in ESRD patients. Kalantar-Zadeh *et al.*, in particular, have devoted much attention to reverse epidemiology in ESRD and have discussed it in a wide perspective.[1] In general, the designation of 'inverse' or 'reverse' apparently alludes to counterintuitive, biologically unexpected effects. In reality, factual analysis almost always shows that there is no paradox in the relationship between risk factors and clinical outcomes in ESRD. The problem goes beyond renal failure and depends on the fact that a given outcome may have different proximate causes in different study populations. In the general population without cardiovascular complications, variables like BP maintain a monotonic association with clinical outcomes across a wide range of values. Starting from systolic BP values as low as 110 mm Hg, the higher the systolic BP, the higher the

risk of cardiovascular events.[2] This is a causal relationship, as reduction of BP by pharmacological or non-pharmacological (for example, salt intake reduction) interventions determines a proportional decrease in event rate. However, neither the strength of this relationship in the general population nor the undisputed efficacy of antihypertensive agents in preventing cardiovascular disasters should be taken as evidence that higher BP values always reflect a condition of proportionally higher risk. It is only in the population in which this relationship was observed that we should expect progressively higher BP values to be accompanied by a parallel risk increase. If we examine the same problem in patients with heart failure, the association is inverse rather than direct, because in this condition it is not hypertension but low BP (the result of ventricular pump failure and a surrogate of inadequate organ perfusion) that marks and determines a high risk of death (Figure 1). This concept is further highlighted by the fact that not only high systemic BP but also high pulmonary pressure predict better outcomes in high-risk patients.[3] Indeed, in pulmonary hypertension, the death rate is higher in patients with relatively lower pulmonary pressure than in those with relatively higher values, because in this particular setting, relatively lower pulmonary pressure reflects a more severe degree of right ventricular systolic dysfunction. The fact that the same

variable has opposite relationships with the same clinical outcome has long been considered a puzzling, paradoxical phenomenon. However, there is no paradox in an inverse relationship between systemic or pulmonary BP and death in patients with heart failure or pulmonary hypertension; this is just what we expect on the basis of pathophysiological knowledge. In clinical practice, no doctor questions the fact that two different interventions for arterial pressure are required in subjects with uncomplicated hypertension and in patients with heart failure. In subjects with uncomplicated hypertension, BP should be lowered to reduce left ventricular overload, and, conversely, in patients with compromised left ventricular systolic function, BP should be increased by interventions that directly or indirectly ameliorate ventricular performance. Similar problems exist with serum cholesterol. Cholesterol is directly related to cardiovascular outcomes in the general population. In contrast, in high-risk conditions characterized by high C-reactive protein (a measure of systemic inflammation), such as stroke, heart failure, and coronary heart disease, the relationship is J- or U-shaped. Again there is no paradox in this finding, because low cholesterol is just an element of the complex pathophysiological response to inflammation. In other words, in patients with severe cardiovascular complications, low cholesterol becomes a marker of the severity of inflammation, that is, of the ultimate event driver of these conditions. Thus it is no surprise that arterial pressure and cholesterol are inversely rather than directly related to clinical outcomes in a high-risk, relatively old population such as the ESRD population. In fact, Liu *et al.*[4] have nicely demonstrated that, in a well-selected incident cohort of dialysis patients without evidence of inflammation (C-reactive protein < 10 mg/dl), the risk of death was 3.2 times higher in patients with high cholesterol (>240 mg/dl) than in those with low cholesterol (<160 mg/dl), whereas, in the control cohort composed of patients with inflammation (C-reactive protein >

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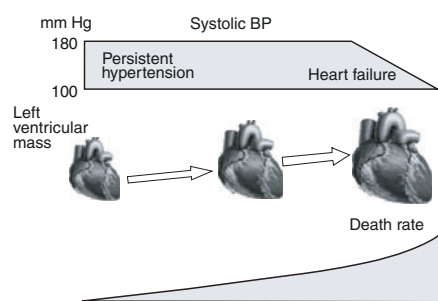
Figure 1 | Long-term relationship among systolic pressure, left ventricular mass, and death rate in the dialysis population. Persistent hypertension (along with other factors) generates and progressively aggravates left ventricular hypertrophy up to a point where heart failure supervenes. Heart failure lowers blood pressure (BP) and eventually causes death, thus generating an inverse association between BP and mortality.

10 mg/dl), the death risk was 38% lower in patients with high cholesterol.

Hyperhomocysteinemia and clinical outcomes in ESRD

Hyperhomocysteinemia is another risk factor considered as a puzzling problem in ESRD.[5] To date, six prospective cohort studies have examined the relationship between the plasma concentration of homocysteine on the one hand, and death and atherosclerotic complications on the other hand, in patients with ESRD, and the results are disparate. It is worth noting that the study by Mallamaci et al.,[6] which reported a positive association, did not include patients with heart failure, a condition notoriously characterized by severe inflammation. Furthermore, it appears to be of foremost importance that more than 70% of circulating homocysteine is disulfide-bonded to protein, mostly to albumin.[7] Adjustment for serum albumin was performed in the (positive) study by Mallamaci et al., whereas no such adjustment was performed in the (negative) study by Suliman et al.[8] In a more recent study by Kalantar-Zadeh et al., adjustment for albumin rendered largely insignificant the apparent (unadjusted) inverse association between this sulfur amino acid and hospitalization and death.[9] Regardless of the analytical strategy adopted in these studies, there was no interpretative disagreement among authors report-

ing positive and negative associations. Suliman et al. commented that "the paradoxical reverse association between homocysteine and clinical outcome in ESRD patients does not, as such, refute a possible role for homocysteine in the vascular pathogenesis"; and Kalantar-Zadeh et al. added, "The positive correlation between homocysteine and markers of protein-energy nutritional status… may partially, but not fully, explain the paradoxical association between homocysteine and mortality." Thus, negative associations — rather than negating homocysteine vasculotoxicity — most likely reflect the highly deleterious effects of inflammation and malnutrition. The study by Ducloux et al. in this issue of KI[10] adds perhaps decisive evidence on malnutrition-associated hypoalbuminemia as an important confounder in the interpretation of the effect of circulating homocysteine on death and cardiovascular events in ESRD. Indeed, as in the above-mentioned study by Liu et al. dealing with serum cholesterol,[4] Ducloux et al. found that homocysteine tended to be inversely related to all-cause death rate in inflamed, malnourished patients (third versus first homocysteine tertile, relative risk = 0.78 (95% confidence interval: 0.47–01.02)) but that it showed an opposite association with the same outcome in well-nourished, uninflamed dialysis patients (relative risk = 1.55 (95% confidence interval: 1.12–4.72)). Genetic epidemiology provides additional evidence that hyperhomocysteinemia is a potential driver of cardiovascular events in ESRD patients. At variance with studies based on the measurement of plasma homocysteine — an indicator influenced by both environmental and genetic factors — studies based on genetic markers of hyperhomocysteinemia are not confounded by environmental factors influencing plasma homocysteine.[11] In this regard it is interesting to note that in a survey of dialysis patients, homocysteine was negatively associated with past cardiovascular complications, whereas these events maintained a positive association with the TT genotype of the C677T polymorphism of the MTHF gene (a gene variant that determines an increase in plasma homocysteine).[12] By the same

token, in another survey aimed at exploring potential predictors of arterio-fistula thrombosis, a positive association was reported between this polymorphism and arteriovenous fistula outcome.[13]

What we need now: multifactorial intervention studies

At this stage, we are faced with the problem of performing well-powered intervention studies aimed at establishing whether lowering plasma homocysteine produces beneficial effects in dialysis patients. Trials based solely on folic acid are probably inadequate to test the hypothesis, because folic acid lowers but largely fails to normalize plasma homocysteine in ESRD[14] and leaves the problem of malnutrition lurking in the background. Perhaps the best approach is a multifactorial intervention targeting malnutrition, inflammation, hyperhomocysteinemia, and oxidative stress. In this regard, acetylcysteine appears to be a promising drug.[15] Indeed, when given intravenously during dialysis, this antioxidant safely brings plasma homocysteine levels into the normal range and produces an improvement in endothelial dysfunction. Long-term administration of this drug reduced cardiovascular-event rate in ESRD patients[16] in the sole study available so far. The study by Ducloux et al.[10] makes a strong call for intervention studies in ESRD. The exceedingly high cardiovascular mortality of patients with ESRD makes such studies not only scientifically important but also ethically mandatory if we are to curb this problem on which very little therapeutic progress has been made so far.

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Inflammation and dyslipidemia in nephropathy: an epidemiologic perspective

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The association of dyslipidermia and inflammatory markers with decreased renal function has been reported in several large epidemiologic studies. In this issue, Lin *et al* examine these associations among middle-aged and older type 2 diabics, a population at high risk for chronic kidney disease. Their findings support a role for these factors in the pathogenesis of progressive renal disease.

The crucial role of dyslipidemia in the progression of proteinuric kidney disease was first described systematically more than 20 years ago by Moorhead *et al.*[1,2] They proposed a model in which quantitative and qualitative changes in circulating lipoproteins, representing metabolic responses to proteinuria, result in mesangial-cell injury, activation, and proliferation, as well as injury to glomerular epithelial cells and basement membrane. The resulting cellular injury and activation in turn lead to excess production of extracellular matrix and progressive glomerulosclerosis. Concurrently, accelerated atherosclerosis induced by the hyperlipidemia, and progressive tubulo-interstitial fibrosis as a reaction to reabsorption of filtered lipoproteins, contribute to the global nephrosclerosis process, resulting ultimately in chronic renal failure.

Since the publication of this hypothesis, a considerable body of evidence from *in vitro* and *in vivo* animal model experiments has supported this model of progressive renal injury. These studies have also revealed the importance of an intermediate inflammatory process in contributing to the progressive nephrosclerosis. This inflammation is characterized histologically by a monocyte/macrophage infiltrate and at the molecular level by increased production of chemokines including tumor necrosis factor-α, RANTES, vascular cell adhesion molecule, and intercellular adhesion molecule. Central to this model of lipid nephrotoxicity mediated by monocytic inflammation is the concept of a positive-feedback loop, in which the progressive mesangial, epithelial, and tubulo-interstitial injury results in worsening proteinuria and renal filtration function, which in turn lead to more severe dyslipidemia and inflammation. Moorhead termed this feedback loop the "lipoprotein injury cycle."[2]

The implication of these findings from experimental models is that one could prevent or at least attenuate the process of progressive nephrosclerosis through interventions aimed at certain mediators of this cycle. However, it has not been clear whether these lipid and inflammatory factors are important in the development and progression of diverse forms of human kidney disease. Except for very rare inherited deficiencies of lipoprotein metabolism, humans with isolated dyslipidemia but without other risk factors do not generally develop progressive glomerulosclerosis, in contrast to the experimental models described by Moorhead *et al.* and others. On the other hand, it is entirely plausible that in the setting of primary renal disease or systemic conditions known to injure the kidney (for example, sustained hyperglycemia or systemic hypertension), these factors play a major role in the initiation and progression of kidney disease.

However, there are considerable methodological challenges to demonstrating these effects in large, heterogeneous human populations. As with all observational epidemiologic research, the accurate ascertainment of exposures and

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