Homocysteine and reverse epidemiology

Sir,

The paper by Suliman et al. ‘The reverse epidemiology of plasma total homocysteine as mortality risk factor is related to the impact of wasting and inflammation’ [1] tries to address the very important issue of the strange opposite clinical behaviour of some well-recognized mortality risk factors [in the paper, total homocysteine (tHcy) levels] in the haemodialysis population as compared to the general population. The authors suspect that this ‘reverse relationship’ between tHcy and outcome could be due to the effect of certain confounding factors such as age, gender, GFR, plasma folate, serum cholesterol, mean arterial BP, cardiovascular disease and diabetes. The inclusion of all these parameters in the Cox proportional hazards model, either for all cause and CVD adjusted mortality, did not change the ‘reverse’ nature of the relationship, in fact not significant, between tHcy and mortality. Inclusion in the model of nutritional and inflammatory markers, was associated with a ‘normalization’ of the relationship between tHcy and mortality, and this is taken by the authors as strong support of the effect of wasting and inflammation on tHcy, when evaluating this parameter as a risk factor for morbidity and mortality in haemodialysis (HD) patients. However, this statement lacks any support, since the supposed relationship between tHcy levels and mortality after adjustment for all variables plus nutritional and inflammation markers is not statistically significant (HR of low tHcy for all cause mortality was 0.73; CI: 0.33–1.60. HR for cardiovascular mortality was 0.78; CI: 0.34–1.76). Moreover, the very wide range of CI limits indicates the extreme weakness of the suggested association. For this reason, the message of the paper, the message in the title: ‘The reverse epidemiology of plasma total homocysteine as mortality risk factor is related to the impact of wasting and inflammation’, although theoretically plausible, is not supported by the data.

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Chair and Division of Nephrology
Spedali Civili and University of Brescia
Brescia, Italy

Ezio Movilli


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Reply

Sir,

We thank Dr Movilli for his comments and for the interest shown in our study [1]. We agree that there was no statistically significant difference in hazard ratio after adjustment for inflammation and wasting. In our paper, this was clearly acknowledged, and several study limitations were discussed. We should note that the small size of our study population limits the statistical power leading to widening confidence intervals. Not withstanding this and other limitations of our study, the reversal of the direction of the associations after multivariate adjustment for surrogates of inflammation and wasting indicates a trend with possible biological plausibility. Indeed, patients with higher total serum homocysteine (tHcy) levels tended to have lower mortality before adjustment for inflammation-wasting, whereas after adjustment they had a 27% higher all-cause and 22% higher cardiovascular mortality. Consistent with our foregoing findings, a recent study by Ducloix et al. [2] found that tHcy in haemodialysis (HD) patients with inflammation-wasting syndrome was inversely related to all-cause mortality, but this association was in the opposite direction in HD patients without the inflammation-wasting. Although these studies may not provide sufficient explanation for the reverse epidemiology phenomenon, they show that the inflammation-wasting confounds the background association between tHcy and mortality in CKD and that this effect may be so overwhelming that it may even reverse the direction of the associations. Prospective studies including larger numbers of patients are required to better examine the true aetiology of the enigmatic phenomenon of reverse epidemiology of tHcy in CKD.

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Mohamed E. Suliman
Peter Stenvinkel
Abdul Rashid Qureshi
Kamyar Kalantar-Zadeh
Bengt Lindholm


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Removal of BNP and inflammatory cytokines by haemodiafiltration in refractory heart failure

Sir,

We read with great interest the paper by Libetta et al., recently published in your journal [1]. It evaluates the role of intermittent haemodiafiltration (iHDF) in refractory congestive heart failure (CHF), and tries to explore the pathophysiological mechanisms for restoration of diuretic responsiveness. However, in our opinion, a close look at the methodology of the study gives rise to a few concerns that could adversely affect the results and conclusions.
First, brain natriuretic peptide (BNP) is degraded and eliminated from plasma primarily by neutral endopeptidase; glomerular filtration has only a minor role in its removal [2]. In this study, both diuretic therapy and iHDF significantly lowered circulating levels of BNP. The authors hypothesize that rapid and significant decrease of BNP in iHDF patients is due to rapid plasma volume reduction. While this can be true in the diuretic group, it should be interpreted cautiously in the iHDF group, due to the role of filtration in removal of BNP. In fact, a number of studies exploring the use of BNP in assessing the extracellular fluid volume in dialysis patients have failed to find any correlation between BNP levels and pre- and post-dialysis hydration status [3,4]. Therefore, it is more likely that BNP reduction in the iHDF group is mainly related to its removal by filtration rather than a reflection of a change in plasma volume. Besides, after termination of iHDF therapy, levels of BNP immediately started to rise, while the levels continued to decrease in the diuretic group during the 30-day follow-up period (Figure 1 of that paper). This implies that volume status might actually have been better preserved over time in the diuretic group, and that decrease in BNP levels were mainly due to removal by iHDF.

Second, the authors observed a significant reduction of pro-inflammatory cytokines in the iHDF group and concluded that lowering of these cytokines is associated with a strong reduction of BNP in these patients (used as an indicator of improvement of cardiac function). However, since the inflammatory state per se is not modified by using iHDF, it is not clear why authors have hypothesized that removal of these cytokines (simultaneously with elimination of anti-inflammatory cytokines) would have a positive impact on cardiac function. Indeed, the authors failed to show any simultaneous increase in the levels of anti-inflammatory cytokines, which remained below detectable limits during the whole period of the study. Besides, the fact that the authors did not find any correlation between serum levels of BNP and pro-inflammatory cytokines in iHDF patients can reflect the differences in kinetics and removal rate of these substances with iHDF rather than a change in the inflammatory state and/or volume status.

In summary, we agree with the authors that iHDF demonstrates short-term efficiency in rapid removal of fluid and solutes (including BNP and inflammatory cytokines) in patients with diuretic-resistant CHF. However, the pathophysiological mechanisms for restoration of diuretic responsiveness and potential impact of iHDF on CHF-associated chronic inflammatory state need further studies specifically designed to address these issues.

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Division of Nephrology, Hypertension, and Transplantation Amir Kazory A. Ahsan Ejaz University of Florida, Gainesville Florida, USA
Email: amir.kazory@medicine.ufl.edu

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Reply

Sir,

We thank Dr Kazory and Dr Ejaz for their interest in our study [1]. There is conflicting evidence for the role of dialytic clearance of BNP; it is clear that larger studies are required to assess thoroughly the impact of the dialysis process on serum BNP levels [2]. In our study, iHDF induces rapid and significant decreases of BNP, and levels of BNP rise slowly, not immediately, but only after 30 days.

Second question: accumulating evidence indicates that pro-inflammatory cytokines play a pathogenic role in CHF by influencing heart contractility, inducing hypertrophy, and promoting apoptosis or fibrosis, contributing to the continuous myocardial remodelling process [3,4]. Our study demonstrated a significant reduction of pro-inflammatory cytokines IL-8 and MCP-1 in iHDF patients, while TGF-β and IL-10 levels remained unchanged and below detection limits. Therefore, the balance between pro-inflammatory (reduced) and anti-inflammatory (unchanged) cytokines is favourable in CHF patients on iHDF; in other words, iHDF removing pro-inflammatory cytokines can partially improve the inflammatory state.

We agree that the potential impact of iHDF on CHF-associated chronic inflammatory state should be further evaluated in future prospective studies.

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1. Units of Nephrology, Dialysis, Transplantation Carmelo Libetta1
2. Department of Respiratory Diseases Vincenzo Sepe1
3. IRCCS Policlinico San Matteo Manuela Zucchi1
4. University of Pavia Patrizia Pisacco1
5. University of Pavia Laura Cosma1
6. Department of Cardiology and Federica Meloni2
7. Department of Health Sciences Carlo Campana3
8. Medical section of epidemiology and Teresa Rampino3
cardiovascular medicine, University of Pavia Cristina Monti3
9. Pavia Luigi Tavazzi3
10. Italy Antonio Dal Canton1

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