as proteinuria at this stage would, to a large extent, reflect severe glomerular sclerotic changes rather than the early haemodynamic changes of glomerular hypertension that would be amenable to improvement by inhibition of the renin angiotensin aldosterone system (RAAS). Also a tubular component to the proteinuria reflecting extensive tubulointerstitial damage at this stage of CKD would not be affected by ACEi or ARB [1].

We appreciate the effect of loss of lean muscle mass on estimated glomerular filtration rate (eGFR). Patients included in this study had access to dietician advice and none of them had significant weight loss over the period of the study as documented by stable weights at every clinic visit. Moreover, instant muscle mass loss upon discontinuation of RAAS inhibitors has not been previously reported.

Blood pressure (BP) control increased slightly but significantly 12 months after stopping ACEi/ARB. However, 53% of patients had BP levels within the recommended target (<130/80 mmHg). The explanation we proposed for improving of eGFR inspite of the observations on BP is that this may reflect the improved reflection of the least affected remaining functioning glomeruli through restoration of remnant glomerular hyperfiltration. At this advanced stage of CKD, loss of autoregulation may mean that excessively low BP targets in older patients may cause more harm than good.

We agree with the authors that the change in eGFR is potentially multifactorial including systemic as well as intrarenal haemodynamic changes, intra- and extrarenal arterial and arteriolar sclerosis, which are all common in this age group. We have excluded, to the best of the clinical indications, renal artery stenosis and that was clearly mentioned in our manuscript. Age-related vascular sclerosis is most likely in older patients with CKD, another reason to use RAAS inhibitors with caution in this population.

Conflict of interest statement. None declared.


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CD40/CD40L and cardiovascular risk in patients on haemodialysis: a role for soluble CD40?

Sir,

We read with attention the paper by Desideri et al. (1) recently published in Nephrology Dialysis and Transplantation.

The authors of the RISchio Cardiovascolare nei pazienti afferenti all’ Area Vasta Dia In Dialisi (RISCAVID) study evaluated the involvement of the CD40/CD40L pathway in the increased cardiovascular risk of patients on haemodialysis (HD).

In particular, they demonstrated a strong correlation between combined cardiovascular morbidity and mortality and plasma levels of the soluble form of CD40L (sCD40L). This molecule, mainly produced by platelets, interacts with CD40/CD40L leading to a chronic activation of this pathway and predisposing HD patients to develop a proatherothrombotic state.

These results are very interesting but, aiming to better define the role of the co-stimulatory CD40 system in atherosclerosis and different clinical settings, the presence of another important factor should be considered: the soluble form of CD40 (sCD40).

sCD40 is produced by B cells by alternative splicing of CD40 gene and/or by proteolytic cleavage of the membrane form of CD40 and acts as a natural antagonist of the CD40/CD40L interaction (2). As a result of this inhibition, the ability of sCD40 to reduce immunoglobulin production by B lymphocytes and T-cell activation has been demonstrated (3).

HD patients, when compared to healthy subjects, present high sCD40 serum levels which, associated to a reduction of CD40 membrane expression on B cells, set up the presence of a whole imbalance in the CD40 pathway in this clinical setting (4).

In addition, high sCD40 levels in HD have been related to a deficient response to Hepatitis B Virus vaccination, whereas the reduction of sCD40 levels obtained by treatment with a high permeability dialytic membrane has been associated to a significant increase of anti-HBs antibody titre (5).

Therefore, it seems now clear that sCD40 plays a pivotal role in regulating an immune response in HD patients.

However, while several studies have explored the effects of sCD40 on immunity, the involvement of this molecule in the cardiovascular risk in HD has never been investigated so far.

The results of the RISCAVID study show that the CD40/CD40L activation, mediated by sCD40L, could be an important event in the atherosclerotic process in HD. It is probable that sCD40, which may be considered the counterpart of sCD40L, since it inhibits the CD40/CD40L interaction, has protective effects on the HD-related atherothrombotic risk. This finding could highlight a new aspect of the complex relationship between immune and cardiovascular systems.
At present, no data on this issue are available, but we think that the role of sCD40 on the cardiovascular risk profile in HD is worthy to be investigated in specifically designed longitudinal studies, considering its high potential clinical impact.

Conflict of interest statement. None declared.


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Reply

Sir,

We greatly appreciated the interesting letter by Esposito [1], commenting on our recent demonstration of a strong correlation between cardiovascular morbidity and mortality and plasma levels of the soluble form of CD40L in patients on haemodialysis (HD) [2]. The hypothesis that the soluble form of CD40, i.e. the cognate receptor of CD40L, might play a role in modulating CD40/CD40L activity in patients on HD is intriguing and deserves consideration. In this regard, during the last years, several studies have proposed the involvement of CD40/CD40L in atherothrombotic disease [3]. CD40L is cryptic in unstimulated platelets while it is expressed on the surface of platelets within seconds after platelet activation and then cleaved to generate a soluble trimeric fragment [3]. Multiple platelet agonists, including collagen, thrombin and adenosine diphosphate, are able to induce the exposure of soluble CD40L from platelets [3]. Thus, circulating levels of soluble CD40L represents a biomarker of platelet activation. In addition, the soluble CD40L is considered to possess full biological activity being able to bind CD40 and activate CD40/CD40L signaling [3]. On the other hand, soluble CD40 is generated by alternative splicing of the CD40 gene and/or by proteolytic cleavage of the membrane form of CD40 on B cell and acts as a decoy receptor, thus representing a natural antagonist of the CD40/CD40L pathway [4]. HD patients, when compared to healthy subjects, present high soluble CD40 levels which may be the result of an increased expression of membrane-bound CD40, an increased generation of soluble CD40 or a decreased elimination of this soluble receptor [5,6]. According to this latter hypothesis, increased serum soluble CD40 concentrations were mostly found in anuric HD patients compared to those with residual renal function [6]. In addition, in these patients there is a reduction of CD40 membrane expression on B cells, suggesting a reduced soluble CD40 generation, was also found [6]. On the other hand, it is conceivable that increased circulating levels of soluble CD40 in patients on HD might also reflect an increased expression of CD40 on different cell lines, including monocyte/macrophages, endothelial cells, smooth muscle cells and platelets, potentially involved in the atherosclerotic process [4]. Thus, it is not unlikely that the increased CD40 level in patients on HD could be interpreted in the light of a global up-regulation of CD40/CD40L activity at vascular levels rather than as a counterbalancing of soluble CD40L. Obviously, we completely agree with Esposito on the opportunity to investigate the potential role of sCD40 on the cardiovascular risk profile in patients on HD in a specifically designed longitudinal study.

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