Are the high mortality rates in dialysis patients mainly due to cardiovascular causes?

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It is a well-known fact that chronic dialysis patients have a markedly increased mortality compared to the general population. In a recently published analysis of the European Renal Association–European Dialysis and Transplant Association Registry, the mortality rate in incident dialysis patients was 192 per 1000 person-years, while it was only 12.05 in the general population \cite{1}. Despite the emphasis on the importance of accelerated atherosclerosis and cardiovascular death in dialysis patients \cite{2}, the excess mortality in them was due to both cardiovascular (39\%) and non-cardiovascular (51\%) causes. The distribution of the causes of death was not different from that in the general population. The standardized mortality ratio for cardiovascular death was 42.9 in dialysis patients compared to 4.9 in the general population. For non-cardiovascular death, these figures were 57.1 and 7.0. This ‘normal’ distribution of mortality causes may lead to a different view on risk factors for mortality in dialysis patients. Also, factors that have been linked to cardiovascular death are often associated with non-cardiovascular mortality. This has been found for C-reactive protein \cite{3}, fetuin A \cite{4} and possibly troponin T \cite{5}, making it likely that death from various causes is often associated with the presence of an acute-phase reaction.

Causes of non-cardiovascular causes of death

Infections and malignancies are the most common causes of non-cardiovascular death \cite{1}. Septicaemia and pneumonia are the most common infections in dialysis patients associated with death \cite{6–8}. The presence of a non-native vascular access device, including a central venous catheter, is the most important cause for sepsicaemia or bacteremia leading to death in haemodialysis (HD) patients \cite{6}. The hazard ratio for peritoneal dialysis (PD) patients was not different from that in HD patients with an arteriovenous fistula.

Pneumonia is the other serious infection in dialysis patients. The adjusted hazard ratio for death was 5 in an analysis of the Medicare database in the USA \cite{8}. In multivariate analysis, not only the presence of chronic obstructive pulmonary disease but also HD as initial treatment was associated with a higher chance of getting pneumonia compared to PD. The lower incidence of sepsicaemia in PD patients compared to HD is not unexpected, the lower...
incidence of pneumonia is more difficult to explain. It may be that unmeasured co-morbidity is one of the causes, but also the fact that HD is predominantly practiced in institutional sessions. This may lead to greater exposure levels to microorganisms, but this theory is pure speculation.

**Immune dysfunction in chronic kidney disease**

The high incidence of infections and inflammation in dialysis patients points to the importance of dysfunction of the immune system in patients with end-stage renal disease (ESRD) and on dialysis. The various disturbances have been summarized in a recently published review [9]. These include signs of immunosuppression and immune activation of both the innate immunity and the adaptive immunity systems. ESRD is associated with down-regulation of toll-like receptors leading to reduced stimulation of the innate immunity system but also with increased serum levels of various cytokines. Impaired renal function is probably the cause of the latter. With regard to the adaptive immunity, the synthesis of immunoglobulins is impaired [10, 11], due to a reduced number of memory B cells [11]. This may be the cause of the well-known hyporesponsiveness to vaccinations [12].

**Is immune dysfunction dependent on dialysis modality?**

The reported difference in the incidence of infections in HD patients compared to PD raises the possibility of a difference in the immune status between the groups, as illustrated in Table 1. From the current literature, it is not possible to point to one or two differences because most of them have been done either in HD or in PD patients, and only a few compared the two treatment modalities. These include an *in vitro* study from Spain, where serum from PD patients had no inhibitory effect on lymphoblastogenesis, while pre- and post-HD serum showed up to 51% inhibition [14]. A cross-sectional study in children showed that the number of B lymphocytes was lower in those treated with HD compared to those on PD [15]. A study comparing monocyte HLA-DR expression and apoptosis showed some attenuation of uremic immune dysfunction in PD patients compared to HD [16].

Mannose-binding lectin is an important component of immune defence mechanisms. Low serum levels have been found, both in HD and PD patients, but without a difference between the two groups [17]. All the above data suggest that some differences in host defence may exist between the two dialysis modalities but that the effect of chronic kidney failure is probably more important.

The similarity of immune dysfunction in non-dialysed patients with Stage 5 chronic kidney disease, HD and PD patients, as found in most studies, suggests inhibition by uremic waste products. An analysis in an incident cohort of 1010 dialysis patients showed that a high baseline serum phosphate level was associated with a 25% increased incidence rate of all infections [18]. This was not influenced by parathyroid hormone levels. When analysed for the kind of infections, hyperphosphataemia was a risk factor for sepsicaemia and osteomyelitis, but not for respiratory infections.

**Table 1. Incidence rates (per 100 patient-years) of sepsicaemia and pneumonia in HD and PD patients in the USA**

<table>
<thead>
<tr>
<th></th>
<th>HD (per 100 patient-years)</th>
<th>PD (per 100 patient-years)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septicaemia</td>
<td>17.5</td>
<td>8.0</td>
<td>[7]</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>29.0</td>
<td>18.2</td>
<td>[13]</td>
</tr>
</tbody>
</table>

*Data from the United States Renal Data System.*

It is unclear whether phosphate itself is the culprit or whether it represents other, poorly dialysable uraemic toxins.

**Conclusions**

Inflammation is related to infections, but also to atherosclerosis, resulting in cardiovascular mortality [19, 20]. Consequently, the reported excess mortality due to infections may result in an underestimation of the long-term effects of immune dysfunction in the dialysis population. Strategies to quantify the impact of predefined parameters of immune dysfunction in individual patients and their effects on mortality and morbidity, should be investigated in order to develop therapeutic approaches.

It can be concluded that research on the effects of biomarkers on outcome should always address cardiovascular as well as non-cardiovascular causes of death and should take the possible addition of effects into account.

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**References**

Cells face constant microenvironmental changes that require them to adapt. If these fluctuations are beyond a certain threshold, cells become stressed and their viability is not complete, which excludes the migratory properties of epithelial cells [8] and it contributes to pathological changes, including tubular atrophy and interstitial fibrosis [9, 10].

Master regulators of EMT include extrinsic signals such as transforming growth factor-β or WNT signalling [11] and intrinsic signals such as HIF-1α-mediated responses to hypoxia [12]. The distinction between extrinsic and intrinsic signals is not purely conceptual because they each rely on fundamentally different biological processes. Extrinsic mediators of EMT are molecules that activate EMT programs after binding to membrane receptors and promote signal transduction, suggesting that the signal originates from outside the cell and is part of a communication network. In the case of intrinsic mediators, the stress signals originate within the cell (such as hypoxic signals that activate HIF-1α signalling) and activate EMT programs. The ability of a cell to sense stress signals suggests that adaptive programs may be activated in response to injury and promote EMT. Therefore, whether EMT is a phenotypic expression of adaptive responses to stress requires further investigation.

Keywords: endoplasmic reticulum stress; epithelial injury response; epithelial-to-mesenchymal transition; kidney

New insights on stress-induced epithelial phenotypic changes

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