

UC Irvine

UC Irvine Previously Published Works

Title

The Latest Addition to the Inflammatory Homeboys in Chronic Kidney Disease: Interleukin-8

Permalink

<https://escholarship.org/uc/item/0g28d9tb>

Journal

Nephron, 102(2)

ISSN

1660-8151

Author

Kalantar-Zadeh, Kamyar

Publication Date

2006

DOI

10.1159/000088924

Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at <https://creativecommons.org/licenses/by/4.0/>

Peer reviewed

The Latest Addition to the Inflammatory Homeboys in Chronic Kidney Disease: Interleukin-8

See Panichi et al., pp. c51–c58

Kamyar Kalantar-Zadeh

Division of Nephrology and Hypertension, Los Angeles Biomedical Institute at Harbor-UCLA Medical Center, Torrance, Calif., and UCLA David Geffen School of Medicine, Los Angeles, Calif., USA

Despite many technical, clinical and scientific advances at the dawn of the 21st century, individuals with chronic kidney disease (CKD) undergoing maintenance dialysis continue to have a high mortality, currently approximately 15–20% per year in North America and Europe [1]. Conventional cardiovascular risk factors have been the target of practice guidelines based on the following three premises: (1) almost half of all excess deaths in dialysis patients are cardiovascular; (2) some cardiovascular risk factors such as hypertension, hyperhomocysteinemia and obesity are excessively common in dialysis patients, and (3) in the general population, classical cardiovascular risk factors have established links to clinical outcome. Based on this traditional way of thinking, the recent Kidney Disease Outcome Quality Initiative (K/DOQI) Guidelines on Cardiovascular Disease in Dialysis Patients [2] have continued the ongoing obsession of focusing on classical cardiovascular risk factors, despite the fact that decades of concentrating on Framingham guidelines that originate from the healthy general population data have not resulted in any major improvement in dialysis mortality. Moreover, both observational studies and clinical trials have consistently indicated the lack of conventional associations between mortality and such cardiovascular risk factors as hypercholesterolemia and hyperhomocysteinemia [3]. The most prominent negative clinical trial of recent origin is the 4D Study (*Die*

Deutsche Diabetes Dialyse Studie) [4], in which atorvastatin had no short-term or long-term effect on survival in diabetic dialysis patients. In fact, the known cardiovascular risk factors such as hypercholesterolemia paradoxically confer survival advantages in dialysis patients, a phenomenon known as ‘reverse epidemiology’ [5]. Hence, there must be other predominating conditions which are *specific* to dialysis patients and which have much stronger impact on survival of dialysis patients than Framingham risk factors.

Malnutrition-inflammation-cachexia (or complex syndrome (MICS) is a common condition in dialysis patients and has a strong association with poor outcome and death. To date, no single measurement has been found to have stronger association with mortality than serum albumin, a nutritional visceral protein and a negative acute phase reactant [6]. Similarly, serum C-reactive protein (CRP) and some circulating pro-inflammatory cytokines such as interleukin (IL)-6 are other indicators of MICS and are associated with death risk in dialysis patients [7]. However, the association between other circulating cytokines such as tumor necrosis factor- α and mortality has not been clearly or consistently shown in these patients [7, 8]. Moreover, although the utility of non-laboratory surrogates of MICS including erythropoietin hyporesponsiveness or ‘malnutrition-inflammation score’ in predicting poor outcome have also been studied, the reli-

ability of these apparently less objective surrogates in representing MICS is not yet completely clear [8]. Hence, the search for better biological markers of inflammation with stronger and more consistent mortality-predictability in dialysis patients continues.

In this issue of *Nephron Clinical Practice*, Panichi et al. [9] report the utility of circulating IL-8 measurement as a predictor of poor survival in 76 dialysis patients, who were followed for up to 18 months. In approximately half of the studied patients, plasma IL-8 concentration was above the 'normal range'. Plasma IL-8 showed moderate correlation with IL-6 and CRP. Like CRP and IL-6, IL-8 may also have a direct role in the atherosclerotic process and endothelial damage [10]. In comparative regression analyses, Panichi et al. [9] showed that IL-8 had an independent association with both all-cause and cardiovascular events and death. Although not unexpected, these are unprecedented findings in dialysis patients and strengthen the notion that inflammatory processes are important role players in poor clinical outcome observed in this patient population. This observational study had a small population and a smaller number of events. Hence, comprehensive multivariate adjustment was not possible. Furthermore, the cohort had a very small number of diabetic dialysis patients, which may limit the external validity of the study, since it does not represent a typical dialysis population in the 21st century. Moreover, hemodiafiltration is apparently performed in over 30% of patients in Italy, a practice pattern which is not the case in many other countries. Despite all these limitations, the

study by Panichi et al. [9] contributes to advancing our knowledge about the potential role of inflammation in poor outcome of dialysis patients.

Even if inflammation is an important contributor to high death rate in patients with advanced CKD, single therapeutic strategies are not likely to be successful, because causes and consequences of inflammation may be numerous; other role-players such as malnutrition and oxidative stress are likely the additional contributors to inflammatory response. Hence, integrated interventions that target several aspects of the MICS in the form of combined nutritional treatment strategies with novel micronutrient components that have dominant anti-inflammatory and antioxidant properties should be tested. The ongoing focus on treating such risk factors as hypertension, hypercholesterolemia, obesity and hyperhomocysteinemia as recently advanced by K/DOQI [2] is likely to be fruitless. CKD patients, especially those undergoing maintenance dialysis, are very different than the general population. The characteristics of a surviving dialysis patient stand in a clear contradiction to those predicted by traditional cardiovascular risk factors. Hence, focusing on the management of these risk factors in dialysis patients would be similar to screening for cancer among patients who already have cancer with a poor prognosis. The MICS is such a 'disease' in dialysis patients. It may be time to abandon the Framingham obsession and seek to explore interventions that can correct the real risk factors of dialysis patients, namely inflammation, malnutrition, and oxidative stress.

References

- 1 United States Renal Data System: Excerpts from the USRDS 2004 Annual Data Report. *Am J Kidney Dis* 2005;45(suppl 1):S1-S28.
- 2 National Kidney Foundation I. Kidney-Dialysis Outcome Quality Initiative: K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. *Am J Kidney Dis* 2005;45.
- 3 Wrono EM, Hornberger JM, Zehnder JL, McCann LM, Coplon NS, Fortmann SP: Randomized trial of folic acid for prevention of cardiovascular events in end-stage renal disease. *J Am Soc Nephrol* 2004;15:420-426.
- 4 Wanner C, Krane V, Marz W, Olschewski M, Mann JF, Ruf G, Ritz E: Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *Engl J Med* 2005;353:238-248.
- 5 Kalantar-Zadeh K, Block G, Humphreys MH, Kopple JD: Reverse epidemiology of cardiovascular risk factors in maintenance dialysis patients. *Kidney Int* 2003;63:793-808.
- 6 Kalantar-Zadeh K, Kilpatrick RD, Kuwae N, McAllister CJ, Alcorn H, Kopple JD, Greenland S: Revisiting outcome predictability of serum albumin in hemodialysis patients: time dependency, changes over time and population attributable fraction. *Nephrol Dial Transplant* 2005;20:1880-1888; doi: 10.1093/ndt/gfh941.
- 7 Stenvinkel P, Ketteler M, Johnson RJ, Lindholm B, Pecoits-Filho R, Riella M, Heimbürger O, Cederholm T, Girndt M: IL-10, IL-6, and TNF- α : central factors in the altered cytokine network of uremia - the good, the bad, and the ugly. *Kidney Int* 2005;67:1216-1233.
- 8 Kalantar-Zadeh K, Kopple JD, Humphreys MH, Block G: Comparing outcome predictability of markers of malnutrition-inflammation complex syndrome in haemodialysis patients. *Nephrol Dial Transplant* 2004;19:1507-1519.
- 9 Panichi V, Taccola D, Manca Rizza J, Consani C, Ghiadoni L, Filippi C, Cristofani R, Paniccucci E, Migliori M, Sidoti A, Biagioli M, Boracelli M, Barsotti G, Tetta C: Interleukin-8 is a powerful prognostic predictor of all-cause and cardiovascular mortality in dialytic patients. *Nephron* 2006;102:c51-c58.
- 10 Moreau M, Brocheriou I, Petit L, Ninio E, Chapman MJ, Rouis M: Interleukin-8 mediates downregulation of tissue inhibitor of metalloproteinase-1 expression in cholesterol-loaded human macrophages: relevance to stability of atherosclerotic plaque. *Circulation* 1999;99:420-426.