Response to 'Adynamic Bone Disease and MICS'

Kidney International (2007) **71,** 1327; doi:10.1038/sj.ki.5002264

We appreciate the important thoughtful points raised by Dr Heaf[1] regarding adynamic bone disease (ABD). ABD may indeed be a secondary phenomenon and a consequence of the malnutrition–inflammation complex syndrome (MICS), which is also associated with hypoalbuminemia, increased serum levels of proinflammatory cytokines, protein–energy wasting, and poor outcome in maintenance dialysis patients.[2] A recent study in 44 chronic peritoneal dialysis patients showed that low serum albumin was associated with ABD.[3] Although we are not aware of any study that indicates a direct causal effect of inflammation on ABD in chronic kidney disease, *in vitro* parathyroid hormone (PTH) secretion is suppressed by interleukin-6,[4] a strong proinflammatory cytokine that is associated with poor outcome in maintenance-dialysis patients. Interleukin-1 beta (IL-1β), another proinflammatory cytokine, may also suppress PTH secretion. In another *in vitro* study, PTH secretion from cultured parathyroid tissue slices was significantly inhibited in media containing IL-1β.[5] This effect may be mediated through the specific IL-1 receptors that upregulate the calcium-sensing receptor mRNA leading to apparent low bone turnover.[5] Indeed in the foregoing study, the inhibitory effect of IL-1β could be counteracted by the IL-1 receptor antagonist (IL-1ra),[5] indicating that the inflammation-induced suppression of PTH can potentially be overcome by treatment of MICS in individuals with chronic kidney disease. Hence, interventions that can improve hypoalbuminemia and kidney disease wasting by correcting malnutrition and/or by mitigating inflammation, for example, via IL-1ra *anakinra*, may be more promising approaches for the management of ABD rather than decreasing the dose of or withholding activated vitamin D analogs.

In our study, the MICS could indeed explain a large portion of the association between low PTH and increased death rate. However, in our epidemiologic study, inflammatory markers and cytokines were not measured. Hence, controlling for MICS was suboptimal, which may explain the existence of the residual association between low PTH and death after multivariate adjustment. Moreover, many patients with low PTH did not receive paricalcitol,[6] which may be another explanation for high mortality in this group. Nevertheless, any dose of paricalcitol is associated with better survival compared to no paricalcitol administration, including in those with low PTH levels.[6] As Dr Heaf suggested, we plan to perform additional subgroup analyses to examine more carefully the association of ABD and MICS in maintenance-dialysis patients.

K Kalantar-Zadeh has received honoraria from Abbott (manufacturer of calcitriol (calcijex) and paricalcitol (zemplar)).

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Don't be so BOLD: Potential limitations in the use of BOLD MRI for studies of renal oxygenation

Kidney International (2007) **71,** 1327–1328; doi:10.1038/sj.ki.5002321

To the Editor: Blood oxygen level-dependent contrast magnetic resonance imaging is used for studies of intrarenal oxygenation[1] and has been touted as a useful non-invasive diagnostic tool in renal medicine. The validity of this technique as an indicator of parenchymal oxygenation, however, relies on the assumption that tissue oxygenation varies with blood oxygenation. We recently found that in both rabbits and rats renal cortical and medullary tissue pO_2 can remain remarkably stable in the face of changes in renal blood flow,[2] even if renal oxygen consumption does not change.[3] We also observed increased renal venous blood oxygen content with increasing renal blood flow, despite stable tissue pO_2.[3] These observations support the concept that diffusional shunting of oxygen from arteries to veins increases with increased renal blood flow and so contributes to dynamic regulation of renal oxygenation.[3] The possibility that similar mechanisms operate in the human kidney raises concerns over the reliability of clinical assessment of renal tissue oxygenation using blood oxygen level-dependent magnetic resonance imaging. Our data indicate that changes in the oxygen level of blood in the renal circulation, as evidence by altered renal venous pO_2, do not necessarily reflect changes in tissue pO_2. The possibility that kidney vascular oxygenation and tissue oxygenation may vary

independently was suggested by Mason,[1] and our recent data[3] show that it actually occurs. We suggest that blood oxygen level-dependent magnetic resonance imaging requires further validation for use in estimating renal oxygenation. One possible approach would be to use newer functional magnetic resonance imaging techniques that employ extracellular pO_2 reporter molecules.[4]

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Response to 'Don't be so BOLD: Potential limitations in the use of BOLD MRI for studies of renal oxygenation'

Kidney International (2007) **71,** 1328;. doi:10.1038/sj.ki.5002324

It is indeed gratifying that our caveats and concerns have been validated. We believe that the BOLD investigations can be very useful, since they are noninvasive, using blood as the reporter molecule. However, as the correspondents[1] recognize there is interplay of oxygen delivery, consumption, and clearance, and thus, assumptions are needed when inferring changes in tissue pO_2. Moreover, arteriovenous (AV) shunting may separate tissue and capillary phenomena from bulk AV measurements.

The correspondents cite their recent observations in rat and rabbit kidney cortex and medulla on the basis of polarographic electrodes, fluorescent fiber optic probes, and arterial and venous blood samples.[2] An MRI approach could be even more powerful by interrogating multiple locations simultaneously and providing quantitative pO_2 based on reporter molecules, such as hexafluorobenzene[3] or hexamethyldisiloxane.[4] However, routine use in deep organs, such as kidney, has been hindered by difficulty in placing the exogenous reporter molecule, albeit using a very fine needle. We certainly encourage such investigations. In the meantime, it would be interesting to apply BOLD MRI to the models of Evans *et al.* The BOLD measurements would be expected to be sensitive to capillary oxygenation, which may or may not be associated with bulk venous blood following major shunting. It could also be valuable to apply both T1 and T2* measurements, since these are attributable, respectively, to tissue[5] and vascular oxygenation.[6]

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Does Sevelamer reduce mortality by slowing of progression of coronary calcification?

Kidney International (2007) **71,** 1328–1329; doi:10.1038/sj.ki.5002316

To the Editor: We found the *post hoc* survival analysis of Sevelamer in the incident hemodialysis patients thought provoking.[1] It is known from Dr Block's original study that, as compared to Calcium-containing binders, Sevelamer slowed the progression of coronary artery calcification (CAC) scores at 18 months.[2] The current analysis shows that mortality was predicted by phosphate binder use in the first 18 months (lower mortality with Sevalamer) and by 'baseline' CAC score, but not by CAC score at 18 months. This begs the question as to whether the slowing of progression of CAC score using Sevelamer has any direct effect on survival or is it possible that the survival benefit of Sevelamer is independent of effects on calcification? Since the patients underwent EBCT at regular intervals up to 18 months, the authors are in unique position to examine if change (delta) in CAC score at 18 months had any direct effect on survival.