Response to ‘Dietary alkalinization and darusentan for prevention of decline in glomerular filtration rate in rats fed a casein diet’


We thank Dr Bakker, Dr Gans, and Dr Navis for their interest in our recent KI publication linking diet-induced metabolic acidosis, endothelin receptors, and progressive nephropathy in the remnant kidney model of chronic kidney disease (CKD). We agree that our studies support the need for human studies to examine the effect of source of dietary protein, rather than the amount of dietary protein, on progression of CKD. Our earlier studies showed that dietary protein as casein that increases intrinsic acid production induces greater tubulointerstitial injury in Munich–Wistar rats with intact nephron mass than dietary protein as soy that does not increase intrinsic acid production. Despite greater tubulointerstitial injury induced by dietary casein, whole-kidney glomerular filtration rate (GFR) was not different from the animals eating dietary soy after 96 weeks. Our more recent publication on which the said investigators comment shows that dietary casein induced greater GFR decline than dietary soy after 12 weeks. Our earlier study links tubulointerstitial injury to the increased intrinsic acid production induced by dietary casein and our more recent study links GFR decline to metabolic acidosis induced by dietary casein. Use of selective endothelin receptor antagonists support that the tubulointerstitial injury in the intact kidney and GFR decline in the remnant kidney are mediated through endothelin receptors. Together, these data support that dietary casein-induced increased intrinsic acid production is injurious to the kidney but that this injury is more likely to lead to GFR reduction in the remnant than the intact kidney of Munich–Wistar rats. The investigators apparently agree with these points.

The investigators question if the data reported substantiate our conclusion that casein-induced kidney injury is mediated by metabolic acidosis and through endothelin receptors. They state correctly that neither daily excretion of net acid, NH_4^+, nor total acid was affected by darusentan, the endothelin A antagonist that ameliorated tubulointerstitial injury in animals with intact nephron mass and ameliorated GFR decline in remnant kidneys. The investigators also correctly state that darusentan did not affect the casein-induced systemic metabolic acidosis in these animals with remnant kidneys. They agree that the data reported support that darusentan ameliorates the deleterious effects of dietary casein on GFR of remnant kidneys but they argue that the data described above support that these beneficial effects of darusentan are independent of its effects on metabolic acidosis.

The last sentence of the abstract of our publication says ‘Our study suggests that the casein-induced decline in GFR of the remnant kidney is mediated by metabolic acidosis through endothelin A receptors’ (italics added). Our point is that metabolic acidosis induced by dietary casein induces the injury that leads to GFR decline through endothelin receptors. We do not state or mean to imply that darusentan exerts its beneficial effects to ameliorate GFR decline by reducing metabolic acidosis that then leads to an amelioration of GFR decline in remnant kidneys as apparently suggested by the investigators. Instead, we think that our data support the following scenario: dietary acid increases intrinsic acid production and metabolic acidosis, leading to stimulated kidney endothelin production as supported by increased urine endothelin excretion (Table 4), and the increased kidney endothelins then cause kidney injury that reduces GFR through endothelin A receptors. We agree with the investigators that darusentan renders its beneficial effects independent of metabolic acidosis. The point of our manuscript, however, is that the described beneficial effects of endothelin A receptor antagonism provided by darusentan is not by ameliorating metabolic acidosis but instead is by inhibiting the effects of increased kidney endothelin activity induced by metabolic acidosis that was in turn induced by dietary casein. In fact, our earlier studies show that increased kidney tubule acidification in remnant kidneys is mediated through endothelin B, and specifically not endothelin A, receptors. Consequently, we did not expect the endothelin A receptor antagonist to affect kidney acidification and this was indeed the case.

As stated, we support the call issued by these investigators to test the hypothesis that the source of dietary protein can influence the rate of GFR decline in CKD. Specifically, we hypothesize that diets high in acid-producing amino acids are associated with faster
GFR decline than diets low in acid-inducing amino acids. As Western diets are generally acid-inducing on balance\textsuperscript{6} and because of the difficulty faced by clinicians in effecting major diet changes in our patients, we suggest that a more practical hypothesis to test is whether adding non-food alkali such as NaHCO\textsubscript{3} or Na\textsuperscript{+}. Citrate to the usual western diet will slow the rate of GFR decline in CKD subjects eating a standard western diet. If this intervention slows, prevents, or stops GFR decline, this would be a comparatively inexpensive addition to the armamentarium of strategies to slow or stop CKD progression toward complete kidney failure.


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Does chemical structure of Gd-containing contrast agents contribute to mortality in nephrogenic systemic fibrosis?


To the Editor: I read with great interest the article by Swaminathan \textit{et al.}\textsuperscript{1} presenting the importance of high mortality in nephrogenic systemic fibrosis (NSF) and providing evidence that the short survival of these patients could be attributed to metal accumulation (gadolinium, aluminium, iron) in several inner organs, including heart and blood vessels. Although I completely agree with the authors, who wrote that they ‘...present several novel observations’ despite the fact that ‘there are several limitations’,\textsuperscript{1} some information is missing. For example, it would be interesting to know which Gd-containing contrast agents (GCCA) the patients received, and whether there was a difference in applied substances in patients who died and who are still alive.

As previously described, both transmetalation of GCCA and association with NSF are preferentially observed along with nonionic linear compounds.\textsuperscript{2–4} In contrast, macrocyclic compounds have up to now not been demonstrated as causing NSF.\textsuperscript{4}

Uncertainty about the chemical nature of GCCA used in patients who developed NSF and eventually died due to cardiac and vascular events limits our understanding of the disease and thus hampers efforts to prevent it.

Furthermore, of the 32 patients with NSF studied, Table 1 presented only data of the 10 patients who died.\textsuperscript{1} What are the demographics, and clinical conditions of the 22 remaining patients? In particular, it would be very interesting to know whether these two groups were different in some aspect.


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