of the a priori risk for SH. It would have been highly relevant to match initially the two cohorts of hypoglycaemic versus non-hypoglycaemic patients with regard to comparable diabetes durations and HbA1c values. Furthermore, the definition of SH followed numerous ICD-9 and -10 codes, thus probably covering a broad spectrum of hypoglycaemic episodes.

In summary, the heterogeneous definition of hypoglycaemia, the missing profound baseline characteristics, and not accounting for some of the potential risk modifiers could have confounded the results.

Conflict of interest statement. None declared.

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5. Greco D, Oisciotta M, Gambina F et al. Severe hypoglycaemia leading to hospital admission in type 2 diabetic patients aged 80 years or older. Exp Clin Endocrinol Diabetes 2010; 118: 215–219
doi:10.1093/ndt/gfr041

Advance Access publication 3 March 2011

Reply

Sir,

On behalf of all the authors, we thank Dr Holstein for his interest in our study. As noted in the paper’s discussion section, we share his surprise at the study’s findings and his interest in the role played by potentially confounding variables. In the analysis of our data, we adjusted for many known predictors of hypoglycaemia; however, the nature of our administrative data did not allow measurement of some potentially influential variables. We could not reliably determine the duration of diabetes in our population of elderly patients nor could we assess their level of glycaemic control. It is possible that the exclusion of these and other variables may have contributed to the lower risk of hypoglycaemia we observed in patients with impaired renal function. However, it should not be forgotten that the effect of impaired renal function on glyburide-induced hypoglycaemia is based largely on pharmacologic data [1,2]. Glyburide can certainly cause hypoglycaemia [3], as can impaired renal function [4], but outside of our study, the clinical interaction between these two variables has not been explored. Our findings support the multifactorial nature of hypoglycaemia in patients with diabetes and impaired renal function and suggest that the delayed clearance of partially active metabolites may not be as important at the population level as previously thought.

Conflict of interest statement. None declared.

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Targeting FGF23 and phosphorus in CKD: do not forget calcium

Sir,

Isakova et al. [1] examined the impact of dietary phosphorus restriction and phosphorus binder (lanthanum carbonate) on fibroblast growth factor 23 (FGF23) serum levels in patients with chronic kidney disease (CKD). While either intervention significantly reduced 24-h urinary phosphorus excretion and fractional urinary phosphorus excretion over the course of the 2-week study period, FGF23 levels were unaffected. These findings, contrasting with observations made in healthy individuals [2], are intriguing indeed.

First, reducing intestinal phosphorus load short term does not affect FGF23 levels in patients with CKD. The authors speculate that the duration of the intervention was probably too short for a CKD population, in which FGF23 levels are chronically elevated. The reasons for this lag time remain speculative. One aspect that was not touched upon was the role of calcium as determinant of FGF23 production. In vitamin D receptor-null mice, dietary calcium supplementation significantly increased FGF23 messenger RNA abundance [3]. In a recent intervention trial in CKD patients, a 6-week treatment with calcium acetate failed to decrease FGF23 levels, as opposed to sevelamer [4]. These findings indicate that calcium may be part of another feedback loop in bone and mineral homeostasis involving FGF23. Indeed, serum calcium is
independently associated with FGF23 in dialysis patients, transplant recipients and in patients with primary hyperparathyroidism [5].

It is well known that the dietary ratio of phosphorus to calcium is an important determinant of calcium bioavailability [6]. Both dietary phosphorus restriction and non-calcium-containing phosphate binders may substantially decrease this ratio and, in turn, enhance calcium bioavailability. We postulate that CKD patients not taking calcium supplements, being in tight or even negative calcium balance [7], are extremely sensitive to changes in intestinal calcium transport. In these patients, an increased calcium bioavailability as a result of a lower dietary phosphorus-to-calcium ratio may be translated in an increased intestinal calcium absorption, thus increased FGF23 production. This stimulation, at least temporarily (i.e. until a new steady state is reached), offsets the inhibition of FGF23 production, mediated by the simultaneously decreased phosphorus burden. An altered calcium bioavailability and intestinal transport thus represents a plausible explanation for the observation of a delayed response of FGF23 to dietary interventions targeting phosphorus in CKD. We acknowledge, however, that this hypothesis needs validation.

Second, the kidney appears to respond appropriately to reduced intestinal phosphorus load in the absence of changes in the phosphaturic hormones parathyroid hormone (PTH) and FGF23. Changes in renal phosphorus load, which are not captured by the blood sampling protocol, and yet to be defined phosphaturic factors such as intestinal phosphatonin [8], may explain this dissociation.

We agree that measures to restrict phosphorus loading (diet, phosphate binder therapy) should be considered at earlier stages of CKD than currently practiced. FGF23 might be an interesting biomarker to monitor and to guide interventions. Current evidence indicates that an altered calcium bioavailability and intestinal transport may affect the response of FGF23 to interventions targeting phosphorus in CKD.

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Reply

Sir,

Evenepoel et al. propose additional mechanistic explanations for the absence of significant changes in FGF23 in our pilot study. We agree with their hypothesis that enhanced bioavailability of dietary calcium resulting from dietary phosphorus restriction and use of a non-calcium-based phosphate binder may have stimulated FGF23 secretion and thereby offset the decrease in FGF23 that we expected to achieve following our interventions. While we did not evaluate stool calcium and phosphorus contents, the absence of significant changes in serum or urinary calcium or parathyroid hormone with dietary restriction or lanthanum carbonate suggests that the proposed improvement in intestinal calcium absorption may not have been sufficient enough to substantially increase calcium absorption to the extent that may have stimulated FGF23 secretion. Nonetheless, we concur with Evenepoel et al. that future physiologic studies should address the possibility of calcium-regulated FGF23 secretion, especially in the setting of dietary phosphorus manipulation. We further agree that additional intestinal phosphatoninss that we did not study may play an important role in phosphorus handling.

Conflict of interest statement. None declared.

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Epoetin bubble: a severe German case of Honi soit qui mal y pense

Sir,

I read with interest the challenging editorial from David Goldsmith on madness of crowds, puncturing the epoetin