As nature did not predict dialysis—what we can learn from FGF23 in end-stage renal disease?

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The fibroblast growth factor 23 (FGF23)/klotho system has raised a lot of attention in the past 10 years. Genetic knock-out models demonstrated that failure of this system produces a phenotype of premature ageing and especially a failure to excrete phosphate resulting in significant hyperphosphataemia and vascular calcification [1,2]. FGF23 is synthesized in the bone, and osteocytes increase FGF23 production in response to elevated phosphate and calcitriol [3]. Therefore, FGF23 may be a key adaptive factor preventing early hyperphosphataemia in progressive chronic kidney disease (CKD). In the preterminal phases of CKD, FGF23 may become a valuable biomarker of phosphate load and phosphate exposure, perhaps analogous to the predictive value of HbA1C in the evaluation of diabetes control.

The central target organ of FGF23 appears to be the kidney, where tubular phosphate reabsorption and 1-alpha-hydroxylase expression are suppressed. These features raised the question which role FGF23 might play in dialysis patients (CKD stage 5D), the CKD stage where end-stage kidney failure is firmly established and neither substantial phosphaturic effects can be caused nor an already almost lost calcitriol synthesis can be substantially further suppressed.

The European study by Jean and colleagues in this issue – in this cohort, patients were undergoing an extended dialysis exposure of 3 × 5 to 3 × 8 h per week. Especially the latter mode generally leads to enhanced phosphate removal often enabling reductions in phosphate binder treatment [7]. Interestingly, there were no significant differences in absolute FGF23 and phosphate serum levels regarding time on dialysis within this study, but potential differences in concomitant phosphate binder dosages were not reported. In the presence of similar mean phosphate levels, the absolute median C-terminal FGF23 levels were higher in the European than in the US study population despite the probability of enhanced dialytic phosphate removal in the former group. Of course, comparisons of different cohorts are almost invalid due to differences in general dialysis exposures (incident versus prevalent), residual diuresis, nutritional status, assay characteristics,

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FGF23 levels and mortality/morbidity in CKD stage 5D may be 3-fold: end-stage kidney disease is illustrated. The association between P and FGF23 levels and fractional P excretion (FeP) from normal renal function towards their regulatory interaction, FGF23 is a biomarker of the cardiovascular damage potential of phosphate loads (partly independent of the magnitude of phosphate levels).

Fig. 1. The time course of serum FGF23 levels, serum phosphate (P) levels and fractional P excretion (FeP) from normal renal function towards end-stage kidney disease is illustrated. The association between P and FGF23 levels and mortality/morbidity in CKD stage 5D may be 3-fold: (a) P is a direct mortality factor causing cardiovascular damage; (b) FGF23 is a direct mortality factor causing cardiovascular damage; or (c) through their regulatory interaction, FGF23 is a biomarker of the cardiovascular damage potential of phosphate loads (partly independent of the magnitude of phosphate levels).

Another issue that should be systematically addressed in the future is the impact of treatment with calcitriol or other active vitamin D analogues on FGF23 serum levels, since these compounds may have direct and indirect (by increasing phosphate absorption) stimulatory effects on FGF23 secretion. Jean et al. found a somewhat higher proportion of individuals with active vitamin treatment in their highest quartile of FGF23 levels, while the US study had intentionally excluded this confounder. If FGF23 levels can be directly influenced by this concomitant treatment, the question will however remain whether and in which stage of CKD, FGF23 suppression or stimulation is beneficial or potentially harmful.

These interpretations on the clinical interactions between FGF23 and the mode of phosphate lowering, vitamin K-dependent proteins and active vitamin D use may seem a little far-fetched and are highly speculative. However, if they prove to possess substance they might translate into clinical implications in the years to come. Presently, we are learning progressively more that supports the probability that FGF23 may become a key biomarker in both CKD patients not on dialysis and those in stage 5D. We still need to learn far more about the effects of interventions including different phosphate binder regimens, active vitamin D treatment and diet on FGF23 regulation. We will then need to define absolute cut-off levels of FGF23 concentrations predisposing for mortality risk or representing insufficient phosphate control in the different CKD stages. The dialysis stage is very intriguing with regard to the understanding of FGF23 regulation, since extracorporeal replacement of target organ failure was certainly not primarily included in the master plan of evolution.

Conflict of interest statement. None declared.

(See related article by G. Jean et al. High levels of serum fibroblast growth factor (FGF)-23 are associated with increased mortality in long haemodialysis patients. Nephrol Dial Transplant 2009; 24: 2792–2796.)

References

Preserving residual renal function in peritoneal dialysis: volume or biocompatibility?

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Leaving life-style issues aside, preservation of residual renal function (RRF) is seen as one of the main clinical benefits of peritoneal dialysis (PD) as a treatment modality choice. The majority of studies have indicated that RRF is relatively well preserved in comparison to haemodialysis (HD) [1,2] and two major hypotheses have emerged to explain this difference: (i) relative stability of volume status—perhaps even a tendency to develop hypervolaemia in PD compared to HD, where fluctuations in volume are common, especially when attempts are made to control blood pressure principally by manipulation of volume and (ii) the biocompatibility of the dialysis fluids. In the case of HD, there is evidence that ultrapure dialysate preserves RRF [3], whereas in PD it has been suggested that the newer biocompatible fluids, which contain reduced levels of glucose degradation products (GDPs), lead to reduced circulating levels of these potentially nephrotoxic substances [4].

This volume of Nephrol Dial Transplant contains two articles that address the issue of preservation of RRF in PD patients that shed further light on this debate. Liao and colleagues presented data on RRF from a large cohort study of Taiwanese PD patients, identifying factors associated with preservation, whereas the randomized controlled trial from Kim et al. reported the effect of a biocompatible low GDP solution on a number of endpoints, including RRF.

CANUSA was the seminal study that drew attention to the importance for residual renal function in PD patients. This only became clear, however, on re-analysis of the study in 2001 [5] following the reports from single-centre studies such as the Stoke PD Study [6] that it was the RRF component and not the peritoneal small solute clearance that was associated with survival. Because RRF changes with time on treatment, CANUSA treated it as a time-related component and not the peritoneal small solute clearance that is associated with better survival in Taiwanese patients is hardly surprising. In addition, they also observed an increase in technique failure, both death censored as well as when combined with death, in patients with a faster decline in RRF, an issue that was not addressed in the CANUSA re-analysis.

The difficulties of design and analysis of studies that explore RRF are not trivial. In the case of observational cohort studies, because RRF is in itself associated with patient survival, interpretation of data can be influenced by informative censoring. For example, in the past this may have led to an over-estimate of the true difference between modality-associated preservation of RRF, as the transfer rate between modalities is likely to have been asymmetric, leading to a selection pressure in favour of patients...