spend money that could have been better spent elsewhere. In other words, proceeding with such not cost-effective care means denying better health care to other patients and to society.

How would the results of this study look like in a European setting? First, in contrast to our general belief, cost of dialysis in Europe may not be much lower. For instance, Van Biesen et al. [4] documented for Belgium a cost for in-hospital dialysis per year of €53 000 versus €32 000 for peritoneal dialysis, while in Lee et al., the cost in the first year was $64 000. Dialysis as such is borderline cost-effective in Europe as shown by Salonen et al. [5], with a cost per QALY of ±€40 000. Hence, one could argue that the incremental cost-effectiveness of intensified dialysis (the extra cost divided by the extra QALY’s versus the base case of three times per week) should remain below that value. Given the above, I doubt it.

Hence, if I were a payer (whether it would be an insur er or NHS responsible) I would not pay for this care, based on these results. I would invest much more in alternative non-in-centre based types of dialysis. I could of course request additional information and allow the use of intensified dialysis in a research setting, hence reimbursing it conditionally upon more evidence to be expected. This will likely reduce uncertainty, but this also costs money. A possible way out is to calculate the value of information beforehand. This method, based on modelling techniques, focuses on the value of obtaining further information that will reduce uncertainty [6]. If that value turns out to be lower than the cost of this further research, one may decide not to undertake this further research. Calculating this value of information may perhaps be a new challenge for Lee et al. [1].

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FGF-23 in dialysis patients: ready for prime time?*

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Summary

The discovery that fibroblast growth factor 23 (FGF-23) intimately connects skeletal biology and systemic mineral balance is one of the major breakthroughs of the last decade in renal medicine. In a recent observational study by Gutiérrez et al. [2] high FGF-23 levels emerged as a much strong predictor of death and the predictive power of this peptide was maintained even when this relationship was analysed within serum phosphate levels quartiles. Because FGF-23 levels can be lowered by reducing phosphate intake, provided that the FGF-23-death link is causal, the perspective arises that patients with normal phosphate...
levels but high FGF-23 may be targeted to a phosphate level lower than that currently recommended by guidelines.

Replicating these novel findings in different populations and in diverse clinical settings would give strength to the hypothesis that high FGF-23 is causally involved in the high mortality of dialysis patients. Yet these studies would still remain insufficient proof for definitively establishing a causal link. Definitive proof of causality may only derive from intervention studies, i.e. from studies where FGF-23 is modified by an appropriate intervention. At this stage it is unjustified to measure FGF-23 in clinical practice. However, this nice observational study is an alert that we should stay tuned to this ebullient research area.

Background

The discovery that fibroblast growth factor 23 (FGF-23) intimately connects skeletal biology and systemic mineral balance is one of the major breakthroughs of the last decade in renal medicine (reviewed by Danziger [1]). This growth factor is produced primarily in bones and requires a transmembrane protein, klotho, to facilitate cell surface interaction. FGF-23 in the kidney downregulates the activity of type IIa sodium phosphate co-transporter (NaPi-IIa) prompting phosphate excretion. FGF-23 also suppresses 1α hydroxylase. High FGF-23 levels are implicated in phosphate wasting, hypophosphataemia and low 1,25-dihydroxy vitamin D (1,25OH vit D) levels in X-linked hypophosphataemia and autosomal dominant hypophosphataemic rickets. Conversely, reduced FGF-23 signalling is the main trigger of tumoral calcinosis, a condition characterized by hyperphosphataemia, increased 1,25OH vit D levels and ectopic calcification.

FGF-23 levels show an early rise in CKD, perhaps before PTH, suggesting that this alteration may be responsible for the decline in the renal synthesis of 1,25OH vit D. However, the clinical relevance of high FGF23 in chronic kidney disease (CKD) is largely unknown. In a New England Journal of Medicine article, Gutiérrez et al. [2], report a nested case-cohort study in haemodialysis patients showing that, independently of other risk factors, high FGF-23 is a strong predictor of death. These findings indicate that the reach of this factor probably goes beyond rare, genetically determined disturbances of renal phosphate metabolism. Discussion on this study is an occasion for reflecting on how progress in medicine is realized and for examining the issue of causality in epidemiological studies.

The bench to bedside paradigm and FGF-23

Although engrafted into the lexicon of academia to define patient-oriented research, this paradigm in most cases does not adequately describe how progress in science is actually realized. Most often, starting from the phenomenology of human disease, it is the astute clinician that figures out a new hypothesis and inspires the clinical investigator and the basic scientist as well. On the other hand, ideas generated in the framework of basic science may provide testable etiological hypotheses for human disease. The research is a to and fro process from the clinical territory to the experimental laboratory and vice versa. Rarely, if ever, does biomedical experimentation have the linear and undirectional path predicated by the bench-to-bedside paradigm. FGF-23 is a case in point. FGF-23, i.e. the 23rd FGF family protein to be discovered, was isolated by chance by Tetsuo Yamashita while searching for mouse FGF-15 cDNA sequence in the ventrolateral thalamic nucleus of the brain [3]. Almost concurrent with these studies, FGF-23 was identified by the technique of positional cloning as the gene responsible for autosomal-dominant hypophosphataemic rickets and after just one year, FGF-23 was discovered to be the humoral factor responsible for hypophosphataemia and osteomalacia associated with neoplasia. The subsequent discovery that the osteoblast is a major source of FGF-23 [4] provided an additional, very relevant, element for the interpretation of the link between the bone and the kidney in patients with chronic kidney disease. Recent studies in genetically engineered mice indicate that FGF-23 controls bone mineralization also independently of the renal regulation of circulating phosphate levels [5]. FGF-23 knock-out mice exhibit increased NaPi-IIa activity leading to severe hyperphosphataemia and excessive bone mineralization. In comparison to mice lacking just the FGF-23 gene, double knock-out mice with deleted FGF-23 and NaPi-IIa genes display a reversal of hyperphosphataemia to hypophosphataemia. However, the skeletal mineralization excess observed in mice lacking FGF-23 remains unchanged, also in the absence of NaPi-IIa, indicating that FGF-23 has a role in controlling bone mineralization, independently of systemic phosphate levels.

This brief history of the FGF-23 discovery is exemplary in showing that palindromic searches activated by unrelated scientific questions formulated by disparate investigators rather than a linear ‘bench-to-bedside approach’ shaped the discovery of a factor of major relevance in human physiology. This new knowledge is perhaps an advancement for the understanding of the bone–kidney link of the same order of that brought about by cardiac natriuretic peptides in the clarification of the cardio–renal link in the late 1970s. A new important research area has been inaugurated and the clinical study by Gutierrez may give fresh scientific impetus to translational research related with FGF-23.

Causality in epidemiologic studies and FGF-23

Determining the relationship between a given risk factor and the occurrence of disease is one of the most tantalizing tasks of medical research. When faced with this problem, the investigator may set up a laboratory experiment where two otherwise identical groups of animals are confronted, one group harbouring the risk factor in question and the other without such a factor. Confounding in an experiment of this kind is unlikely because, with the exception of the factor being tested, by protocol all factors that may affect the outcome are equalized. This is exactly the approach followed by Sitara et al. [5], in the above-mentioned study aimed at establishing whether or not FGF-23 may disturb bone mineralization independently of serum phosphate.

The hypothesis that high FGF-23 impinges upon mortality may be tested in animal models reproducing the biochemical profile of dialysis patients (see below, last paragraph) and can be usefully explored in observational
studies in the dialysis population. To this end, we can measure FGF-23 at baseline and then follow up dialysis patients and see whether mortality rate is predicted by plasma levels of this hormone. Such an exercise is a very delicate matter because confounding of the link between FGF-23 and death by known and unknown risk factors is most likely in observational studies. Dialysis patients with relatively high FGF-23 levels may also have a higher risk factor burden than patients with relatively low levels and this difference rather than FGF-23 per se may be responsible for higher mortality. However, modern statistical modelling techniques applied to data derived from sound observational studies provide a potent instrument for minimizing the effect of confounding factors [6]. In other words, we may consider the observational study as a sort of experiment where we control confounding factors that may disturb the appreciation of the effect of FGF-23 on mortality by multivariate analysis. This is accomplished by a statistical model including FGF-23 and all risk factors whose causal role in determining the outcome is reasonably well demonstrated. This is exactly the approach used by Gutierrez et al. [2], who adjusted the analysis by a comprehensive list of laboratory values, age, sex, race and ethnicity, cause of renal failure, blood pressure, body mass index, coexisting conditions and vascular access at initiation of dialysis. In this study high FGF-23 levels emerged as a much strong predictor of death and its predictive power was maintained even when this relationship was analysed within serum phosphate level quartiles (Figure 1). These authors hypothesize that high FGF-23 may cause vascular damage by non-selective activation of receptors implicated in cardiac hypertrophy and atherosclerosis or that increased FGF-23 levels may reflect damage attributable to prolonged exposure to high phosphate. Because FGF-23 levels can be lowered by reducing phosphate intake, the suggestion arises that this biomarker may be responsible for higher mortality.

Replicating these novel findings in different populations and in diverse clinical settings would give strength to the hypothesis that high FGF-23 is causally involved in the high mortality of dialysis patients. Yet these studies will remain insufficient proof for definitively establishing a causal link. In observational studies we can control just for risk factors that could be measured in the same studies. The possibility of residual confounding, i.e. confounding by risk factors that are measured imprecisely and by unmeasured and unknown risk factors, cannot be excluded in such studies. Definitive proof of causality may only derive from intervention studies, i.e. from studies where FGF-23 is modified by an appropriate, well-targeted intervention. To this end, we may go back to the bench and design a study in rats with renal failure (remnant kidney model) and high FGF-23. These rats can be randomized to an intervention that selectively reduces FGF-23 signalling (e.g. microRNA that negatively regulate the gene expression of the receptor of this growth factor, an experimental manoeuvre successfully applied to reduce angiotensin type 1 receptor expression [7]), to a non-selective intervention that lowers FGF-23 levels, i.e. low phosphate intake, and to a control group. In the clinical research arena the Mendelian randomization theory offers another interesting research option [8]. Because assortment of genes at mating occurs randomly, this theory holds that, unlike classic observational studies, association studies based on single nucleotide polymorphism that regulate FGF-23 levels are unconfounded by behavioural and environmental factors (e.g. phosphate balance) that can modify FGF-23 because these factors usually do not alter genotype. Polymorphisms in the FGF-23 gene that control circulating

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**Fig. 1.** Left panel: odds ratio for death associated with FGF-23 quartiles. The risk of death increases progressively from the first to the fourth quartile. Right panel: Odds ratio for death associated with a 1 unit increase in the log-transformed FGF-23 level within phosphate quartiles. The risk of death attributable to FGF-23 is the same across phosphate quartiles indicating that high FGF-23 predicts death independently of serum phosphate and thereby it provides prognostic information beyond phosphataemia in ESRD.
FGF-23 plasma levels can be identified and then tested in DNA banks of existing cohort studies in dialysis patients. If these and other studies are positive, we can eventually move on to design an appropriate clinical trial in humans.

At this stage what should the clinical nephrologist do after reading the Gutierrez paper? Should he or she rush to measure FGF-23 in dialysis patients? The answer is a frank no. This study is simply hypothesis generating in that it has no element that may induce a change in clinical practice. However, this nice observational study is an alert that we should stay tuned to this ebullient research area.

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