F spokesperson FG23 levels in CKD may independently play a pathogenic role in CV morbidity, it is not easy to understand how much of this putative pathogenic role should be ascribed to the FG23 per se or to the above quoted primary conditions causative for the FG23 increase [8]. In particular, the reduced tissue α-Klotho availability has recently gained much credit as a primary CV pathogenic factor [9, 10].

However, even if this is the case, uncertainties would still remain on what the FG23 level threshold is above which the pathogenic role starts to be evident. In fact, looking at the results of the study by Faul et al. [6], the FG23 levels associated with a pathogenic effect on cardiac mass in the experimental models were manifoldly higher than those found in the clinical observational section of the same study. Overall, when the effects of FG23 have been blocked with monoclonal anti-FG23 antibodies in an experimental animal model of CKD, even if hyperparathyroidism was better controlled, the net result was a net increase in animal mortality [13], these data cast some doubt on the putative direct pathogenic effect of FG23.

However, a basic limitation in making clear any message on the role of the circulating levels of FG23 is represented by the lack of a widely accepted gold-standard method for dosing this hormone. In fact, circulating FG23 is present as both intact-
FGF23 and C-terminal fragment(s). There are available assays for measuring all these forms, however most of the published studies have limited themselves to use only one of these methods. Just citing the most relevant limitations related to this point, it is worth stressing that it is well accepted that the full activity of FGF23 is held by the intact molecule, while conflicting results have been reported on the possible activity of the C-terminal fragment(s), since some authors reported on a possible maintained activity [14] while others suggested a potential antagonist effect of C-terminal fragment(s) on the main activity of the full moiety [15]. Second, since there are multiple available assays for the measurement of the intact molecule, it has been clearly shown that there is limited comparability among the different available assays measuring either the intact or the C-terminal molecule [16, 17]. Furthermore, critical preanalytical problems have been reported, with a trend to an increase and a reduction of the C-terminal and intact molecule, respectively, when the sample is maintained at room temperature for >30 min in the absence of protease inhibitors [18].

To complicate the interpretation of FGF23/Klotho system, recent studies suggest that quite similar analytical problems might be encountered for the assessment of circulating levels of Klotho too [19, 20].

It is well recognized that vascular calcification in CKD patients is an active and cell-regulated process driven by a great number of putative causal factors inducing local phenotypic transdifferentiation of vascular smooth muscle cells towards an osteochondrogenic phenotype [21].

Recent studies suggested that FGF23 could also play some role in the CV disease of CKD patients, showing that FGF23 can be expressed both in cardiomyocytes and in the calcified aorta wall, suggesting that in addition, and probably independently of the circulating levels of FGF23, the tissue expression of this protein might play a potential direct pathogenic role [22, 23]. In this issue of the Nephrology, Dialysis and Transplantation journal, van Venrooij et al. [24] report on the expression of FGF23 in the coronary arteries of the explanted hearts in more than half of the 50 patients who received a heart transplantation. The renal function was lower in patients whose coronary arteries expressed FGF23 than in patients with no FGF23 coronary expression, though part of the positive patients had completely normal renal function. Another important finding of this study was that FGF23 protein was coexpressed with its main receptors (FGFR-1 and FGFR3) and its co-receptor Klotho. Furthermore, the degree of FGF23 expression was positively correlated with coronary calcium score and with the expression of a specific osteocyte protein (DMP1). Interestingly, the expression of FGF23 was mainly evident in infiltrating macrophage cells. Other authors had recently reported on an association between circulating FGF23 levels and markers of inflammation in CKD patients [25], the potential links between FGF23 and inflammation being manifold (Figure 1). These hypothetical links are mainly pertinent to systemic inflammatory conditions. However, at variance with these previous studies, the results from van Venrooij et al. seem to suggest that FGF23 expression in the coronary wall is mainly associated with local more than systemic inflammation, given that the authors did not find any difference in systemic inflammatory markers between patients with and without FGF23 expression in the coronary arteries. These results fit well with those from a recent study which demonstrated that the accumulation of macrophage foam cells in established atherosclerotic lesions is mainly derived from ‘in loco’ macrophage proliferation within the lesion and not from monocyte recruitment from circulation [26].

However, these results raise new questions which are far from being answered. The first point to be clarified regards whether the increased, either circulating or local, levels of FGF32 are a primary or secondary event in relationship to the vascular inflammation and/or to the calcification process. The second point to be demonstrated is whether increased FGF23 plays a promoting or a protective role in the vascular disease. The third point to be clarified is whether the FGF23, secreted by the infiltrating macrophages, actively contributes to these

![Figure 1: Potential relationships between FGF23 and inflammation: OB, osteoblast; OC, osteocyte.](https://academic.oup.com/ndt/article-abstract/29/8/1447/1940091)
roles or if it simply represents a marker of a trans-differentiation process of macrophage itself toward an osteochondrogenic cell. Furthermore, a point to be addressed concerns whether this extra-skeletal production of FGF23 can contribute to its increased circulating levels in the same way of other pathological conditions (e.g. tumor-induced osteomalacic syndromes). Finally, it is not completely clear whether the potential positive or negative effects of FGF23 on the vascular wall are mediated or not by Klotho.

Overall, in addition to all the uncertainties listed in the previous paragraphs, it still remains to be ascertained which of the cardiovascular pathological conditions are mainly associated with higher FGF23 levels. In fact, while some studies reported an independent association between circulating FGF23 concentration and the severity and extent of coronary artery stenosis or with the progression of coronary calcifications [27, 28], other recent data seem to suggest a prevalent association of FGF23 levels with left ventricular mass and heart failure but not with ischaemic heart disease [29, 30].

In conclusion, the study from van Venrooij et al. sheds further light on this ever more complicated issue, though at the same time it also raises new unanswered questions.

As for any experimental study, we look forward to seeing replication of these unexpected and exciting results in further studies, and, if confirmed, future research could further clarify this increasingly complex issue.

Any new piece to be added in this tangled puzzle will be welcome.

CONFLICT OF INTEREST STATEMENT

The results presented in this paper have not been published previously in whole or part.

(See related article by van Venrooij et al. FGF23 protein expression in coronary arteries is associated with impaired kidney function. Nephrol Dial Transplant 2014; 29: 1525–1532.)

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