REVIEW

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Lessons from effect of etelcalcetide on left ventricular hypertrophy in patients with end-stage kidney disease

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Purpose of review
Patients with end-stage kidney disease (ESKD) frequently develop left ventricular hypertrophy (LVH), which is associated with an exceptionally high risk of cardiovascular events and mortality. This review focuses on interventional studies that modify levels of fibroblast growth factor 23 (FGF23) and examine effects on myocardial hypertrophy, cardiovascular events and mortality.

Recent findings
Quantitative evaluations of trials of calcimimetics found no effects on cardiovascular events and cardiovascular and all-cause mortality when compared with placebo. However, a recent randomized, controlled trial of etelcalcetide versus alfacalcidol showed that etelcalcetide effectively inhibited the progression of LVH in comparison to vitamin D in patients on haemodialysis after 1 year of treatment. Prior to that, oral calcimimetic treatment has already been shown to reduce left ventricular mass in patients on haemodialysis, whereas treatment with active vitamin D or mineralocorticoids was ineffective in patients with ESKD.

Summary
Data from a recent trial of etelcalcetide on LVH suggest that FGF23 may be a possible therapeutic target for cardiac risk reduction in patients on haemodialysis. If these findings are confirmed by further research, it might be speculated that a treatment shift from active vitamin D towards FGF23-lowering therapy may occur in patients on haemodialysis.

Keywords
etelcalcetide, fibroblast growth factor 23, haemodialysis, myocardial hypertrophy

INTRODUCTION

In comparison to the general population, patients with chronic kidney disease (CKD) have a substantially higher risk for cardiovascular disease and mortality, making CKD a major public health problem [1]. In addition to the traditional atherosclerosis risk factors, which are manifested at a high prevalence in this population, CKD patients also commonly manifest left ventricular hypertrophy (LVH) [2]. LVH is associated with an increased risk of heart failure, diastolic dysfunction and cardiac arrhythmia in the form of sudden cardiac death, which likely results from sub-endocardial ischemia and increased pro-arrhythmic sensitivity [3].

It is estimated that up to 74% of patients have LVH at the beginning of dialysis treatment, thereby curtailing their 5-year survival prospects by approximately 55% [3]. Until recently, prevention of LVH progression in patients with CKD was not possible [4▪▪].

LVH forms early during the development of CKD and worsens with decreasing renal function [5]. Its development is a response to multifactorial processes and its main drivers in patients on haemodialysis are known to be chronic fluid overload, intradialytic weight gain, pressure overload and haemodynamic fluctuations during haemodialysis

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KEY POINTS

- LVH poses a major health issue in patients with ESKD, contributing to their cardiovascular morbidity and mortality.
- The calcimimetic ETL can effectively inhibit the progression of LVH in ESKD patients via the reduction of FGF23.
- Large body of evidence suggest that FGF23 may be directly linked with the development of LVH, and additional studies are needed to further test the approach of specifically targeting elevated FGF23 in patients with ESKD and sHPT.

treatment [6]. This review focuses on recent studies in this field. We discuss potential benefits of each intervention on three clinically important study outcomes: cardiovascular events (myocardial infarction, unstable angina, ischemic stroke and heart failure), mortality and LVH. We place a special emphasis on the contribution of elevated FGF23 to these adverse clinical outcomes.

FIBROBLAST GROWTH FACTOR 23 INDUCED LEFT VENTRICULAR HYPERTROPHY

FGF23 is a phosphaturic glycoprotein, which is produced and secreted by osteoblasts and osteocytes [7]. It is induced by PTH, vitamin D, dietary phosphate, aldosterone as well as proinflammatory cytokines. In the sense of a negative feedback loop, FGF23 in turn inhibits PTH and vitamin D synthesis [8,9]. It was shown to be an independent risk factor for cardiovascular and all-cause mortality [10]. The primary link between FGF23 and cardiovascular complications in both predialysis as well as dialysis patients is LVH. FGF23 levels rise progressively with declining renal function [11]. Together with rising FGF23, the left ventricular mass index (LVMI) increases and so does the occurrence of both eccentric and concentric cardiac hypertrophy [12]. In-vitro and animal studies provide possible explanations for the direct association between FGF23 and LVH. On the one hand, it has been postulated that FGF23 exhibits a direct effect on the myocardial cell hypertrophy via an activation of the FGF receptor 4 (FGFR4). The binding of FGF23 to FGFR4 leads to an activation of the PLCgamma/Calcineurin/NFAT-signalling axis, inducing hypertrophic growth of cardiac myocytes [13]. On the other hand, it has been proposed by other investigators that the pro-hypertrophic action of FGF23 on cardiac myocytes is a result of FGF23-induced sodium retention, fluid overload and arterial hypertension [14,15].

FGF23 levels are known to be modified by medication used for the therapy of sHPT. It was previously reported that its levels rise under the use of vitamin D analogues by at least 40% while they decrease under the calcimimetic therapy with cinacalcet by over 30% [16,17]. This was confirmed by the PARADIGM trial, which studied cinacalcet versus vitamin D treatment over 1 year. In addition, both treatments showed similar reductions in iPTH [18].

THE EFFECT OF CALCIMIMETIC TREATMENT ON ALL-CAUSE MORTALITY, CARDIOVASCULAR MORTALITY AND CARDIOVASCULAR EVENTS

Unlike in the primary analysis of the EVOLVE trial, a secondary analysis of patients dichotomized according to the achieved FGF23 reduction showed that patients with a more than 30% FGF23 reduction exhibited a lower cardiovascular event rate of cardiovascular death and major cardiovascular events [19]. However, so far, a cardiovascular risk reduction through calcimimetic therapy *per se* has not been shown.

Palmer *et al.* [20▪▪] recently published a review and meta-analysis on calcimimetic agents on sHPT. This work primarily focused on the achievement of a target reduction in iPTH and incidence of hypocalcaemia by cinacalcet, etelcalcetide (ETL) and evocalcet. As additional outcomes, all-cause mortality, cardiovascular mortality and heart failure were analysed. The analysis of 30 trials for all-cause mortality showed no detectable differences between interventions. In addition, cinacalcet versus placebo showed no difference in the rate of cardiovascular mortality. Ten trials were used for the analysis for heart failure, also showing no difference between treatments. The authors concluded that many treatment estimates were imprecise, which may have led to the reported uncertainty and low confidence of findings.

TREATMENT-INDUCED MODIFICATION OF LEFT VENTRICULAR HYPERTROPHY IN HAEMODIALYSIS

The hypothesis that FGF23 reduction by calcium sensitizers could lead to a reduced progression of LVH in patients on dialysis was evaluated in a recent trial. [4▪▪]. One year of ETL treatment led to a decrease in FGF23 and an inhibition of LVMI progression, while further increase of FGF23 and subsequently LVH was observed under active vitamin D treatment with alfacalcidol. This result is in line with the findings of a previously published much smaller trial by Choi *et al.* [21]. The investigators

showed a reduction of LVMI determined by echocardiography through 20 weeks of oral calcimimetic treatment in 12 haemodialysis patients (LVMI 162.8 ± 76.9 versus 138.9 ± 44.6 g/m^2 posttreatment) [22]. LVH has also been a target for other therapeutical options in haemodialysis patients. A randomized clinical trial published a decade ago compared 125 versus 120 haemodialysis patients receiving frequent versus conventional dialysis (six versus three sessions per week). A risk reduction regarding the composite outcomes of death or change in LVM resulted from frequent haemodialysis treatments [23]. In light of a very challenging practical implication of such a frequent and intense therapy, other options were studied. A more recent trial compared the effects of spironolactone versus placebo on the evolution of LVH in 97 haemodialysis patients [24]. After 40 weeks of treatment, LVMI remained constant with no significant differences between treatment groups. No influence on LVMI progression was also shown in a recent trial, which included 99 haemodialysis patients from New Zealand comparing low-sodium dialysate with conventional dialysate for 12 months [25▪].

Therefore, a therapeutic modification of LVMI has proven to be rather difficult in this specific patient collective, but calcimimetic treatment could possibly present a promising new option in this field.

SHOULD CALCIMIMETIC TREATMENT BE MORE FREQUENTLY USED AND TARGETED AT FGF23 LEVELS?

In an editorial published by Murray *et al.* [26▪▪] in the same issue of *Circulation Research*, it was discussed that perhaps FGF23 could pose a more suitable target regarding the modification of cardiovascular risk in end-stage kidney disease (ESKD) than iPTH, the measurement of which is performed on a regular basis in haemodialysis wards, aiming at its reduction. Despite a number of clinical practice guidelines, advising on PTH control, no exact treatment strategy or even ideal PTH target are described. Wolf postulates that the current approach might omit those patients, who show elevated levels of FGF23, while their PTH levels are within or below the target range. On the basis of that knowledge, he suggests a randomized trial using ETL versus placebo, titrated to FGF23. The outcomes of this trial would be the hard endpoints: cardiovascular mortality, hospitalization for heart failure and atrial fibrillation.

Outside of the described potential trial, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines already provide room for an increased use of calcimimetics for the treatment of sHPT, as vitamin D analogues are not recommended as first-line therapy, but can merely be considered as a therapeutic option among others. On the basis of the recent findings on FGF23-induced LVH, it may be interesting to regularly quantify FGF23 levels in patients on dialysis and eventually also patients with CKD not on dialysis. However, a clear recommendation would necessitate further studies. Known problems with treatment and drug adherence in patients on dialysis led to the suggestion that oral therapy may not always be preferred over systemically administered drugs post dialysis such as ETL [27,28].

NEW INSIGHTS ON THE ASSOCIATION OF VITAMIN D ANALOGUES WITH CARDIAC HEALTH

Our recent study observed an increase of LVMI in patients on maintenance haemodialysis that have been treated with alfacalcidol for 1 year [4▪▪], although it remains unclear whether this merely resulted from the natural course of LVH progression under haemodialysis or if the active vitamin D treatment was an effect modifier.

Vitamin D deficiency is known to be linked with cardiovascular disease as well as total mortality in the general population and its prevalence is even higher in CKD patients [29]. Therefore, its negative impact on cardiovascular health is generally thought to be even greater than the general population [30]. Vitamin D deficiency was shown to be independently related to LVH progression in ESKD patients [31,32]. The PRIMO trial investigated the impact of a 48-week active vitamin D paricalcitol versus placebo treatment in CKD patients with mild to moderate LVH with CMR. Despite the previously described association between vitamin D and LVH in CKD, no significant difference in the change of LVMI between the two groups was found [33]. It is important to point out though that the PRIMO study investigated a patient collective with a GFR of 15–60 ml/min/1.73 m^2 not on dialysis.

In 2019, Manson *et al.* [34] published the results of a US-wide, randomized, placebo-controlled trial analysing the effects of cholecalciferol for the prevention of cardiovascular disease among the general population above the age of 50 without CKD. They showed that a supplementation with vitamin D did not result in a lower incidence of major cardiovascular events or death from cardiovascular causes.

In order to verify that vitamin D treatment does not additionally contribute to LVH progression in ESKD, a randomized controlled trial would be required, which interestingly enough has not been conducted yet. Some investigators say because some institutional review boards would consider such an

application unethical because of the lack of equipoise. However, by looking carefully at the available data from observational studies, it becomes evident that such a trial is not at all unethical and in fact should be performed rather soon to prevent potential futility of widely used treatment recommendations with vitamin D for the reduction of LVH and cardiovascular events in dialysis patients.

CONCLUSION

LVH poses a major risk factor leading to increased cardiovascular morbidity and mortality in ESKD. Until recently, no prophylactic and therapeutic interventions were available. Even though, so far, there is little evidence for a decreased risk of major cardiovascular endpoints through calcimimetic treatment, intravenous ETL was shown to inhibit a further progression of LVH in haemodialysis through FGF23 reduction. This finding supports the evidence that FGF23 has a direct effect on the pathogenesis of myocardial hypertrophy and could be a promising target for therapeutic intervention.

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Conflicts of interest

Dr Dörr and Dr Oberbauer have a patent 'Methods of treating left ventricle hypertrophy'.

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