IN DEPTH REVIEW

A brief update on FGF23 for the clinical nephrologist

Tobias Larsson[1,2], Hannes Olauson[2]

(1) Department of Nephrology, Karolinska University Hospital, Stockholm, Sweden
(2) Division of Renal Medicine, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm Sweden

Corrispondenza a: Tobias E. Larsson; Clinical Research Center (KFC), 6th floor, Novum, Karolinska University Hospital in Huddinge, SE-141 86 Stockholm, Sweden.; Tel:+46 8 51773660 Fax:+46 8 585 83 925 Mail: tobias.larsson@ki.se

A brief update on FGF23 for the clinical nephrologist

Fibroblast growth factor-23 (FGF23) is a hormone that controls homeostasis of calcium and phosphate metabolism in health and disease. Unlike most other hormones, FGF23 rises exponentially with declining kidney function, reaching extreme elevations in many end-stage renal disease patients. Clinical and experimental data further suggest that FGF23 is a very early biomarker of kidney injury, and its predictive value of adverse clinical outcomes has been confirmed across the entire spectrum of chronic kidney disease, including pre-dialysis and dialysis populations as well as renal transplant recipients. The questions if, how and when FGF23 will impact future clinical practice in nephrology remain open. Several putative trajectories have been outlined, including the use of FGF23 as a biomarker for selection of treatment, enrichment strategies in clinical trials, but also direct blockade of FGF23 signaling as a treatment target on its own. In this condensed review, we provide an update on FGF23 and briefly discuss its current and potential future role in chronic kidney disease.

Key words: calcium, chronic kidney disease, FGF-23, fibroblast growth factor-23, parathyroid hormone, phosphate, vitamin D

Introduction

It has been more than eight years since the term Chronic Kidney Disease – Mineral and Bone Disorder (CKD–MBD) was coined at the KDIGO Controversies Conference on Definition, Diagnosis, and Classification held in Madrid [1]. CKD–MBD is defined by the triad of bone- and laboratory abnormalities as well as vascular calcification, all components being linked to hard clinical endpoints such as fractures, cardiovascular morbidity and mortality. The initial triggers for CKD–MBD remain elusive, yet they emerge in the early course of CKD at estimated glomerular filtration rates of approximately 70 mL/min/1.73 m^2. Long-term biochemical consequences that unfold during CKD progression include a rise in fibroblast growth factor 23 (FGF23) and decrease in Klotho, hyperparathyroidism, hyperphosphatemia and vitamin D insufficiency. Despite the widespread use of dietary and pharmacological interventions targeting CKD–MBD such as dietary phosphate restriction, calcium supplementation, phosphate binders, vitamin D analogues and calcimimetics, robust evidence that such therapies translate into long-term clinical benefits are lacking. Consequently, nephrologists are largely confined to rely upon surrogate biomarkers to support clinical decision-

making. In this brief review, we provide a condensed update on clinical aspects of FGF23 and its potential relevance in future clinical practice.

Physiology of FGF23

FGF23 is a 32 kDa peptide hormone secreted from osteoblasts and osteocytes. It acts on the renal tubules to reduce phosphate reabsorption by decreasing the brush-border membrane abundance of the sodium-phosphate co-transporters Npt2a and c. FGF23 is also an "anti-vitamin D" hormone as it reduces the conversion from native 25-hydroxyvitamin D ($25(OH)_2D$) to active 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) by inhibiting renal 1-alpha-hydroxylase expression and further promotes vitamin D degradation by stimulating 24-hydroxylase expression [2]. In addition, FGF23 inhibits synthesis and secretion of parathyroid hormone (PTH) from the chief cells of the parathyroid glands [3] (full text) [4]. The main physiological effects and feedback loops of FGF23 are summarized in Figura 1.

On a cellular level, FGF23 exerts its endocrine actions by binding a receptor complex of a FGF receptor and Klotho on the cell surface, thus activating the MAPK/ERK pathway [5]. Whilst FGF receptors are ubiquitously expressed, Klotho expression is restricted to a limited number of tissues, most importantly renal tubules, parathyroid glands and choroid plexus, thus determining the tissue specificity for FGF23.

Regulation of FGF23

Despite intense efforts the current understanding of FGF23 regulation, especially with regard to its circulating levels, are incomplete. In physiology, serum phosphate level and intestinal phosphate absorption stimulate FGF23 as part of a negative feedback loop. The same is true for vitamin D and PTH [6]. Importantly, calcium also regulates FGF23, and hypocalcemia may offset the stimulatory effect of phosphate and PTH on FGF23 [7] (full text). Recent data suggest that certain preparations of intravenous iron can induce a transient elevation in FGF23 and result in a subsequent hypophosphatemia [8]. Additional studies suggest a regulation of FGF23 by leptin and estrogen but this regulation appear less relevant and is likely secondary to altered bone metabolism [9] [10] (full text).

Pathophysiology in renal failure

In CKD, there is a progressive rise in FGF23 with declining kidney function [11]. Several known factors contribute such as hyperphosphatemia, hypercalcemia, secondary hyperparathyroidism (sHPT) and Klotho deficiency. There are most likely additional unknown uremic factors that could also stimulate FGF23 expression, for example through modulation of FGF receptors in the bone [12]. The increase in FGF23 in early stages of CKD has traditionally been viewed as a compensatory mechanism to prevent the development of hyperphosphatemia and sHPT. However, as renal function declines the tissue level of Klotho decreases which causes FGF23 resistance [13]. The exponential increase in FGF23 ultimately results in concentrations within the pharmacological range in many dialysis patients. It is unknown whether such levels are a consequence of merely an increased synthesis or also reflects reduced clearance. Nevertheless, extreme elevations in FGF23 and a parallel tissue-depletion of its co-receptor Klotho may have deleterious clinical consequences in CKD. A guidance to the expected concentration range of FGF23 as a function of GFR is illustrated in Tabella 1 and the dynamics of FGF23 in CKD, and its determinants and effects in different strata of renal function is depicted in Figura 2. In acute kidney injury, FGF23 rises as early as within a few hours after the damage episode [14]. It may be related to reduced Klotho level

and renal FGF23 resistance or other unknown factors released from the kidney; or perhaps due to altered glomerular handling of mineral metabolites that is not immediately captured by reciprocal changes in serum or urine.

Epidemiology

In a hallmark study from 2008 Gutiérrez and colleagues provided the first evidence that FGF23 is independently associated to mortality in incident hemodialysis patients [15] (full text). This was followed by a large number of studies linking FGF23 to mortality, faster CKD progression rate and other adverse outcomes, especially cardiovascular disease (CVD), throughout all strata of CKD [16] (full text) [17] [18] (full text) [19] (full text) These studies consistently demonstrate that FGF23 has a higher predictive value than other traditional mineral metabolites. Recent studies have extended these observations to the general popu-

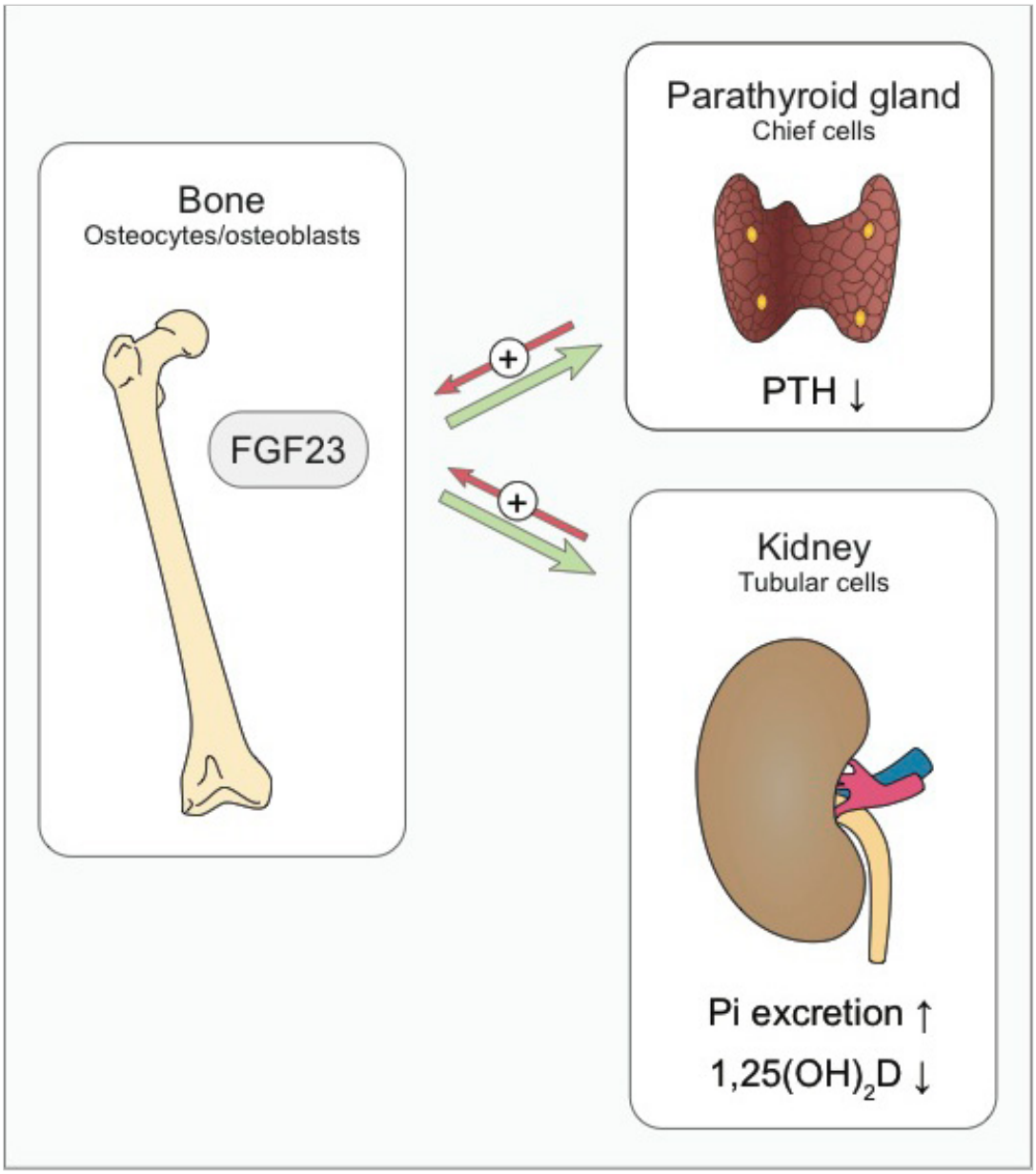

Figura 1.
Physiological effects of FGF23

lation and individuals free of CKD, showing a graded relationship between FGF23 and CVD and mortality also in individuals with preserved renal function [20] [21] [22]. Collectively, these results suggest that FGF23 may serve as a novel biomarker to predict adverse clinical outcomes, especially in CKD patients.

Tabella 1. Expected concentration range of FGF23 as a function of GFR

Population	Intact FGF23 (pg/mL)	C-terminal FGF23 (RU/mL)
Normal renal function	20-60	25-70
CKD 2	25-80	30-150
CKD 3	40-120	50-300
CKD 4	80-500	100-1000
CKD 5	250-1250	400-2000
ESRD	500-50 000	1000-100 000

Expected concentration range of FGF23 in healthy individuals and across the spectrum of CKD based on large-scale FGF23 measurements in epidemiological cohorts.

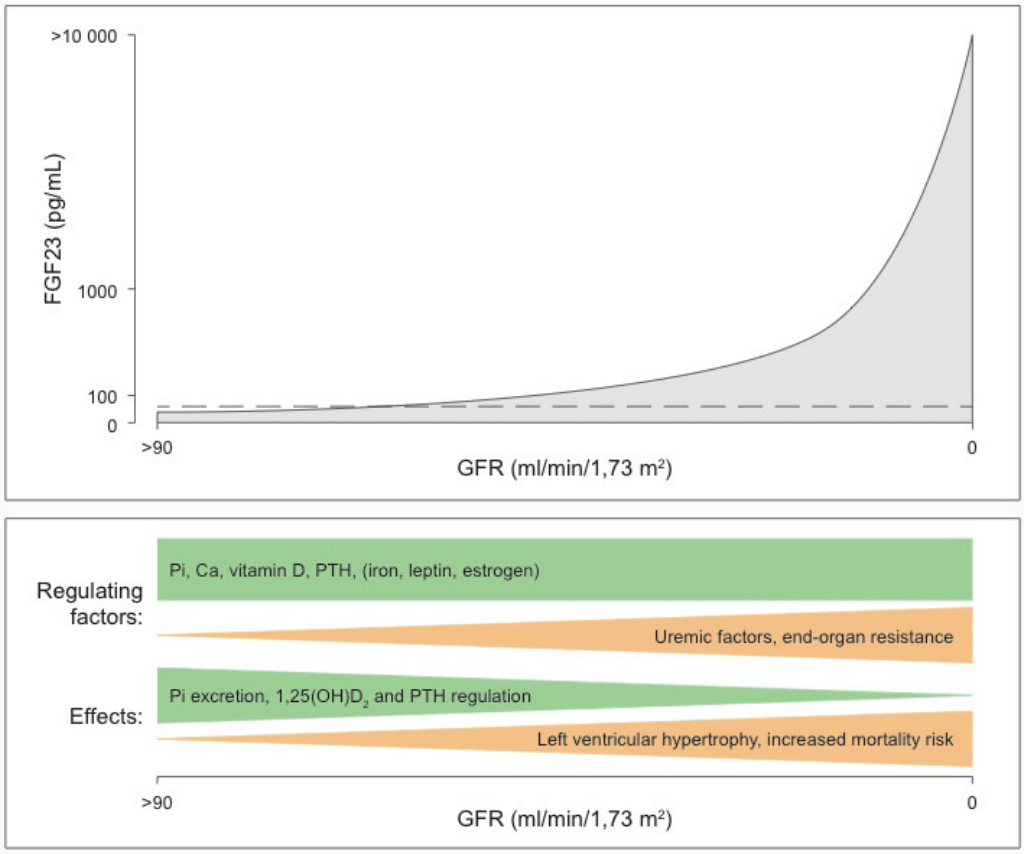

Figura 2.
Effects and regulation of FGF23 in CKD

Is FGF23 a biomarker or contributor to mechanism of disease?

The compelling observational data that links FGF23 to adverse outcomes has ignited mechanistic research aimed at elucidating whether FGF23 is purely a biomarker portraying a complex array of metabolic disturbances, or if high circulating FGF23 may be harmful on its own. The identification of FGF23 as a direct stimulator of myocardial growth provided the first mechanistic evidence that FGF23 indeed should be regarded as a uremic toxin, at least in dialysis patients, most of who suffer from tremendous elevations of serum FGF23 [23]. Another previously ignored aspect was that FGF23 signaling in the heart was independent of Klotho. These findings should prompt additional research to explore non Klotho-dependent effects of FGF23, particularly in the context of renal fibrosis, endothelial function and vascular calcification. Nevertheless, targeting FGF23 in CKD has proved to be a delicate matter. Treatment of CKD rats with neutralizing FGF23 antibodies improved the bone phenotype and biochemical profile but also resulted in increased vascular calcification and mortality [24]. However, a moderate reduction in FGF23 in dialysis patients, in whom renal handling of mineral metabolites is less relevant, may potentially be cardio-protective given the link between FGF23 and left ventricular hypertrophy.

FGF23 assays and normal reference range

Circulating levels of FGF23 can be quantified from serum or plasma by commercially available antibody-based assays (ELISA). Biologically active intact FGF23 has a half-life of approximately one hour and is enzymatically cleaved into inactive C-terminal and N-terminal fragments. There are two principally different types of available assays; one that recognizes intact FGF23 exclusively, and one that detects both intact FGF23 and inactive C-terminal fragments. Intact FGF23 appears to be the predominant form in both physiology and in CKD [25]. In certain rare hereditary disorders the processing of FGF23 is disturbed which results in an altered ratio between intact and cleaved FGF23, requiring measurement with both assays to accurately determine the circulating levels. However, in physiology and in CKD there is a strong correlation between the two assays and they appear essentially interchangeable [26]. Some studies comparing the two assays have found a slightly stronger relationship with C-terminal FGF23 to adverse outcomes [15] (full text) [18] (full text). Approximated reference values for the two most commonly used FGF23 kits (from Kainos and Immutopics) are presented in Tabella 1.

Should FGF23 be a standard clinical measurement?

For the time being routine FGF23 measurement in clinical practice cannot be recommended for several reasons. There are fundamental gaps in our knowledge about its regulation and organ-specific consequences at different stages of CKD. Objective FGF23 thresholds that predict clinical meaningful outcomes are lacking and information on circulating FGF23 currently does not provide therapeutic guidance. Additional longitudinal and interventional studies that specifically explore the clinical utility of FGF23 measurement are warranted.

Current therapeutic strategies that modifies FGF23 in CKD

As expected, clinical data have shown that phosphate-binding therapy, especially non-calcium based binders, reduce FGF23 levels [27] (full text). Cinacalcet also lowers FGF23, probably through multiple mechanisms including reduced serum PTH, calcium and phos-

phate [28] (full text). In contrast, vitamin D therapy consistently increases serum FGF23 both in dialysis and non-dialysis patients [29] [30]. Iron therapy stimulates FGF23 expression but the exact mechanisms remain to be elucidated and appear to be depending on the properties of iron preparations used [8]. Other drugs targeting bone metabolism, such as bisphosphonates, are also likely to modify FGF23 expression although less relevant in advanced CKD stages.

FGF23 in future clinical practice

FGF23 holds potential as a useful biomarker in future clinical practice in several regards such as diagnostic improvements and discrimination of CKD-MBD subtypes, selection of most appropriate individual CKD-MBD treatment, monitoring of treatment effect over time as well as determination of optimal timing for such interventions. As already mentioned, such benefits remain unproven and must be carefully addressed in clinical trials before routine FGF23 measurement can be recommended.

Anti-FGF23 therapy may be a potential trajectory in dialysis patients to alleviate cardiac toxicity, however the hurdles of systemic toxicity, specificity and efficacy of such therapy in the context of a uremic environment and other dominating risk factors appear substantial.

Another possible application of FGF23 screening may be in the design of randomized clinical trials in which FGF23 could be used as a risk stratification factor and/or marker of treatment response. Importantly, preliminary post-hoc data from the EVOLVE trial suggested a clear treatment benefit in terms of survival and cardiovascular endpoints in those individuals who received cinacalcet and who responded with a relatively greater reduction in serum FGF23 level.

Conclusion

FGF23 is an early biomarker of CKD-MBD and recent data suggest a direct mechanistic link between elevated FGF23 and cardiovascular pathology. Currently we discourage FGF23 measurement in clinical practice until more information, especially pre-defined FGF23-related endpoints based on clinical trial data, becomes available. Future randomized clinical trials should test whether FGF23 is a modifiable risk factor and if FGF23 can be used for enrichment strategies and identification of patient subgroups more likely to benefit from a specific treatment. If any of these scenarios can be proven, FGF23 measurements will undoubtedly provide a substantial added value to patients and clinicians for optimal care of CKD-MBD.

References

[1] Moe S, Drüeke T, Cunningham J et al. Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney international 2006 Jun;69(11):1945-53

[2] Shimada T, Hasegawa H, Yamazaki Y et al. FGF-23 is a potent regulator of vitamin D metabolism and phosphate homeostasis. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2004 Mar;19(3):429-35

[3] Krajisnik T, Björklund P, Marsell R et al. Fibroblast growth factor-23 regulates parathyroid hormone and 1alpha-hydroxylase expression in cultured bovine parathyroid cells. The Journal of endocrinology 2007 Oct;195(1):125-31 (full text)

[4] Ben-Dov IZ, Galitzer H, Lavi-Moshayoff V et al. The parathyroid is a target organ for FGF23 in rats. The Journal of clinical investigation 2007 Dec;117(12):4003-8

[5] Urakawa I, Yamazaki Y, Shimada T et al. Klotho converts canonical FGF receptor into a specific receptor for FGF23. Nature 2006 Dec 7;444(7120):770-4

[6] Olauson H, Larsson TE FGF23 and Klotho in chronic kidney disease. Current opinion in nephrology and hypertension 2013 Jul;22(4):397-404

[7] Rodriguez-Ortiz ME, Lopez I, Muñoz-Castañeda JR et al. Calcium deficiency reduces circulating levels of FGF23. Journal of the American Society of Nephrology : JASN 2012 Jul;23(7):1190-7 (full text)

[8] Wolf M, Koch TA, Bregman DB et al. Effects of iron deficiency anemia and its treatment on fibroblast growth factor 23 and phosphate homeostasis in women. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2013 Aug;28(8):1793-803

[9] Tsuji K, Maeda T, Kawane T et al. Leptin stimulates fibroblast growth factor 23 expression in bone and suppresses renal 1alpha,25-dihydroxyvitamin D3 synthesis in leptin-deficient mice. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2010 Aug;25(8):1711-23

[10] Carrillo-López N, Román-García P, Rodríguez-Rebollar A et al. Indirect regulation of PTH by estrogens may require FGF23. Journal of the American Society of Nephrology : JASN 2009 Sep;20(9):2009-17 (full text)

[11] Larsson T, Nisbeth U, Ljunggren O et al. Circulating concentration of FGF-23 increases as renal function declines in patients with chronic kidney disease, but does not change in response to variation in phosphate intake in healthy volunteers. Kidney international 2003 Dec;64(6):2272-9

[12] Wöhrle S, Henninger C, Bonny O et al. Pharmacological inhibition of fibroblast growth factor (FGF) receptor signaling ameliorates FGF23-mediated hypophosphatemic rickets. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2013 Apr;28(4):899-911

[13] Koh N, Fujimori T, Nishiguchi S et al. Severely reduced production of klotho in human chronic renal failure kidney. Biochemical and biophysical research communications 2001 Feb 2;280(4):1015-20

[14] Christov M, Waikar SS, Pereira RC et al. Plasma FGF23 levels increase rapidly after acute kidney injury. Kidney international 2013 Oct;84(4):776-85

[15] Gutiérrez OM, Mannstadt M, Isakova T et al. Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. The New England journal of medicine 2008 Aug 7;359(6):584-92 (full text)

[16] Jean G, Terrat JC, Vanel T et al. High levels of serum fibroblast growth factor (FGF)-23 are associated with increased mortality in long haemodialysis patients. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 2009 Sep;24(9):2792-6 (full text)

[17] Isakova T, Xie H, Yang W et al. Fibroblast growth factor 23 and risks of mortality and end-stage renal disease in patients with chronic kidney disease. JAMA : the journal of the American Medical Association 2011 Jun 15;305(23):2432-9

[18] Fliser D, Kollerits B, Neyer U et al. Fibroblast growth factor 23 (FGF23) predicts progression of chronic kidney disease: the Mild to Moderate Kidney Disease (MMKD) Study. Journal of the American Society of Nephrology : JASN 2007 Sep;18(9):2600-8 (full text)

[19] Wolf M, Molnar MZ, Amaral AP et al. Elevated fibroblast growth factor 23 is a risk factor for kidney transplant loss and mortality. Journal of the American Society of Nephrology : JASN 2011 May;22(5):956-66 (full text)

[20] Ix JH, Katz R, Kestenbaum BR et al. Fibroblast growth factor-23 and death, heart failure, and cardiovascular events in community-living individuals: CHS (Cardiovascular Health Study). Journal of the American College of Cardiology 2012 Jul 17;60(3):200-7

[21] Ärnlöv J, Carlsson AC, Sundström J et al. Serum FGF23 and risk of cardiovascular events in relation to mineral metabolism and cardiovascular pathology. Clinical journal of the American Society of Nephrology : CJASN 2013 May;8(5):781-6

[22] Ärnlöv J, Carlsson AC, Sundström J et al. Higher fibroblast growth factor-23 increases the risk of all-cause and cardiovascular mortality in the community. Kidney international 2013 Jan;83(1):160-6

[23] Faul C, Amaral AP, Oskouei B et al. FGF23 induces left ventricular hypertrophy. The Journal of clinical investigation 2011 Nov;121(11):4393-408

[24] Shalhoub V, Shatzen EM, Ward SC et al. FGF23 neutralization improves chronic kidney disease-associated hyperparathyroidism yet increases mortality. The Journal of clinical investigation 2012 Jul 2;122(7):2543-53

[25] Shimada T, Urakawa I, Isakova T et al. Circulating fibroblast growth factor 23 in patients with end-stage renal disease treated by peritoneal dialysis is intact and biologically active. The Journal of clinical endocrinology and metabolism 2010 Feb;95(2):578-85

[26] Smith ER, McMahon LP, Holt SG et al. Method-specific differences in plasma fibroblast growth factor 23 measurement using four commercial ELISAs. Clinical chemistry and laboratory medicine : CCLM / FESCC 2013 Oct;51(10):1971-81

[27] Oliveira RB, Cancela AL, Graciolli FG et al. Early control of PTH and FGF23 in normophosphatemic CKD patients: a new target in CKD-MBD therapy? Clinical journal of the American Society of Nephrology : CJASN 2010 Feb;5(2):286-91 (full text)

[28] Wetmore JB, Liu S, Krebill R et al. Effects of cinacalcet and concurrent low-dose vitamin D on FGF23 levels in ESRD. Clinical journal of the American Society of Nephrology : CJASN 2010 Jan;5(1):110-6 (full text)

[29] Wesseling-Perry K, Pereira RC, Sahney S et al. Calcitriol and doxercalciferol are equivalent in controlling bone turnover, suppressing parathyroid hormone, and increasing fibroblast growth factor-23 in secondary hyperparathyroidism. Kidney international 2011 Jan;79(1):112-9

[30] Hansen D A randomised clinical study of alfacalcidol and paricalcitol. Danish medical journal 2012 Feb;59(2):B4400