Published in the Russian Federation
European Journal of Medicine
Has been issued since 2013.
ISSN: 2308-6513
E-ISSN: 2310-3434
Vol. 14, Is. 4, pp. 91-99, 2016

DOI: 10.13187/ejm.2016.14.91
www.ejournal5.com

UDC 616.6

Fibroblast Growth Factor 23: Review of its role in Clinical Medicine

Athena Myrou [a, *], Theodoros Aslanidis [b], Dimitrios Grekas [c]

[a] Internal medicine- Intensive Care Medicine, Thessaloniki, Greece
[b] Anesthesiology- Intensive Care Medicine,
National Center of Emergency Care, Thessaloniki Department, Greece
[c] School of Medicine, Aristotle University, Thessaloniki, Greece

Abstract

In the last decade, there is an ongoing interest about Fibroblast growth factor – 23. Its clinical significance seems to go far beyond hereditary disease. The current review presents the newest findings about this factor in several fields of medicine.

Along with its undoubted place in hereditary bone diseases and renal failure, in every stage, FGF23 role is far beyond clear. Further studies are needed to determine its place as prognostic, diagnostic or severity biomarker.

Keywords: Fibroblast Growth Factor 23.

1. Introduction

The FGF family

Fibroblast growth Factors (FGFs) are multifunctional proteins with a wide variety of effects; their role as biological signal facilitates a myriad of biological activities, ranging from issuing developmental cues (mesoderm induction, anterior-posterior patterning, limb development, and neural induction and development), maintaining tissue homeostasis, regulating metabolic processes, including keratinocyte organisation and wound healing. That's why; they often referred to as 'promiscuous growth factors (Finklestein, Plomaritoglou, 2001; Olsen et al., 2003).

The first discovery of FGF was made by Armelin in 1973. Today we know 22 structure-related signaling molecules in humans; thus, we are referring to them as FGF family. Today, FGFs are classified as intracrine, paracrine, and endocrine FGFs by their action mechanisms (Itoh et al., 2015). Paracrine and endocrine FGFs, which comprise 15 and 3 FGFs, respectively, are secreted signaling proteins. In contrast, intracrine FGFs, which comprise four FGFs, are intracellular proteins that are not functionally related to paracrine or endocrine FGFs. Endocrine FGFs comprise FGF19, FGF21, and FGF23. Members FGF1 through FGF10 all bind fibroblast growth factor receptors (FGFRs). Others (FGF11, FGF12, FGF13, FGF18) also known as FGF homologous factors 1-4 (FHF1-FHF4) or "iFGF", do not bind FGFRs and are involved in intracellular processes unrelated to the FGFs (Itoh, Ornitz, 2008); human FGF18 is involved in cell development and

* Corresponding author
E-mail addresses: taniamyrou@gmail.com (A. Myrou), thaslan@hotmail.com (T. Aslanidis), dgrekas@auth.gr (D. Grekas)

morphogenesis in various tissues including cartilage; human FGF20 was identified based on its homology to *Xenopus* FGF-20 (XFGF-20), etc.

1. This article focuses on FGF2-3: a molecule that is gaining more and more interest since its discovery, in 2000 (Pubmed search on "FGF23"/Fibroblast growth factor 23" retrieves 105 publications before 2000 and 980 from 2000-2015, search date 05/01/2016) (Itoh, Ornitz, 2004; Yamashita et al., 2000; Amin, 2014). The article reviews in brief, his structure and attempts to analyze its physiological and pathophysiological role.

2. Results

I. Structure and physiological role

Several tissues express FGF-23, such as bone tissue, bone marrow vessels, ventrolateral thalamic nucleus, thymus, and lymph nodes (Liu et al., 2003). Yet, the high levels of expression by osteocytes suggest that the bone tissue is the major source of FGF-23 (Liu, Quarles, 2007). The latter is a 32KD protein (251 amino acids), encoded in *FGF23 gene*, which in turn is located in chromosome 12p13 and composed by three exons (Amin, 2014). The protein contains a 24 starting signal amino acid peptid, an N-terminal region that contains the FGF homology domain (156 amino acids) and a novel 71–amino acid C-terminus (originally discovered by homology-based PCR screening of a mouse embryonic cDNA library), while the gene is phylogenetically grouped with FGF-19 and -21 gene products (Liu, Quarles, 2007).

2. FGF interacts with one of a family of four FGF receptors (FGFR, especially FGFR1c, 3c and 4c) that belong to type I transmembrane phosphotyrosine kinase receptors. Nevertheless, receptor activation needs a signaling complex formed by FGF, FGFR and Heparan sulfate proteoglycan (HSPG) which acts as a co-factor (Ornitz, 2000; Urakawa, 2006; Yu et al., 2005). Another signle-pass transmembrane protein, known as Klotho, is also required for FGF-23-induced receptor activation. Moreover, Klotho-FGFR coexpression seems to define tissue specificity (presence in kidney, parathyroid gland, pituitary gland and choroid plexus, absence in bone, lung, liver, skin, spleen) (Liu, Quarles, 2007).

As mentioned before, FGF-23 belongs *structurally* to FGF family. Yet, it is *functionally* included in a group of molecules called phosphatonins. Phophatonins are hormones that regulate phosphorus metabolism. sFRP-4 and MEPE (matrix extracellular Phosphoglycoprotein) are the other members of the group.

Regarding FGF-23, its principal target is kidney, where it regulates phosphate reabsorption and production of 1,25(OH)2D (Liu, Quarles, 2007). FGF23 inhibits both sodium-dependent phosphate reabsorption (by suppression of type 2a and 2c sodium-phosphate cotransporters expression) and 25-hydroxyvitamin D [25(OH)D]-1α-hydroxylase, while enhancing the expression of 25(OH)D-24-hydroxylase, in the proximal tubule. Thus, it causes phosphaturia leading to hypophosphatemia, and aberrant production and inappropriately low levels of 1,25(OH)2D (Shimada et al., 2004).

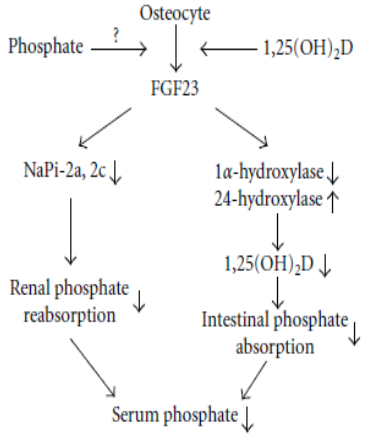

Fig. 1. Actions of FGF-23 (Saito, Fukumoto, 2009) (explanation see text)

The parathyroid gland is another target for FGF23, where it inhibits secretion of parathyroid hormone (PTH) (Shimada et al., 2004). On the other hand, direct action of FGF-23 on bones, its effect on pituitary gland and also in brain (where it is produced by ventrolateral thalamic nucleus) are not completely explored.

II. Clinical significance

1. Hereditary diseases

FGF23 disturbances are met in several hereditary diseases. In general, they are classified in two ways: a) syndromes of FGF23 excess and syndromes of FGF23 deficiency; and b) hypophosphatemic and hypephosphatemic disorders.

Autosomal Dominant Hypophospatemic Rickets (ADHR) (OMIM entry 193100...).

(ICD-10 E83.3, Phenotype MIM number 193100, gene FGF23, locus 12p13.32,). ADHR is a rare (less than 100 cases are described) familial disease, characterized by isolated renal phosphate wasting, hypophosphatemia, and inappropriately normal 1,25-dihydroxyvitamin D3 levels. Patients frequently present with bone pain, rickets, and tooth abscesses. Three heterozygous missense mutations around the processing site of FGF23 protein have been identified in ADHR families. These mutations replace 176Arg or 179Arg in FGF23 protein with other amino acids destroying R-X-X-R furin like cleavage domain motif. Therefore, it has been presumed that the cleavage of FGF23 protein between 179Arg and 180Ser is prevented by these mutations causing increased full-length FGF23 level. Cleaved FGF23 forms due to intracellular proteolysis lose their biological activities. *FGF23* mutations in ADHR result in impaired pro-teolysis of FGF23, resulting in increased serum levels of active FGF23. The disease shows incomplete penetrance, variable age at onset (childhood to adult), and resolution of the phosphate-wasting defect in rare cases. With treatment, prognosis is very good (Saito, Fukumoto, 2009; Orphanet-Autosomal Dominal...)

Autosomal Recessive Hyphosphatemic Rickets-1 (ARHR1)

(ICD-10 E83.3, Phenotype MIM number 241520, gene DMP1, locus 4q22.1) (OMIM entry 193100...).

ARHR is caused by inactivating mutations in dentin matrix acidic phosphoprotein (DMP1), a member of the SIBLING family of extracellular matrix protein that augments mineralization (18,33). Loss of DMP1 results in increased transcription of FGF23 by osteocytes), Dentin matrix protein 1 is noncollagenous extracellular protein, highly expressed in osteoblasts and osteocytes, in bone and teeth and belongs to a family of small integrinbinding ligand, N-linked glycoproteins (SIBLING) together with matrix proteins in calcified tissues such as dentin sialophosphoprotein (DSPP), integrin-binding sialoprotein (IBSP), matrix extracellular phosphoglycoprotein (MEPE), and osteopontin (Turan et al., 2010). Several homozygous mutations in *DMP1* gene were identified in patients with ARHR. However, it remains unclear how mutations in *DMP1* gene cause enhanced production of FGF23. Its phenotype profile includes Short stature; limited movement of spine and hip, calcification of the ligaments at the bony insertions sites, high bone density at the base of skull, clavicle and rib anomalies, enthesopathies and laboratory exams reveal how hypophosphatemia, low levels of serum 1,25-dihydroxyvitamin D, whereas serum calcium, parathyroid hormone, urinary calcium excretion are normal, and high circulating levels of FGF23 (OMIM entry 193100...; Turan et al., 2010, Masi et al., 2015).

Autosomal Recessive Hyphosphatemic Rickets-2 (ARHR2)

(ICD-10 E83.3, Phenotype MIM number 613312, gene ENPP1, locus 6q23.2)

Extremle rare disease that is caused by homozygous loss-of-function mutation in the ENPP1 gene; which encodes a protein called ectonucleotide pyrophosphatase/phosphodiesterase 1 (NPP1) (the latter is a major generator of extracellular pyrophosphate (PPi)). Because PPi inhibits calcification, inactivating mutations in ENPP1 gene are also responsible for generalized arterial calcification of infancy. In patients with ARHR2, high circulating levels of FGF23 have been described. FGF23 is a secreted protein, which reduces expression of sodium-phosphate co-transporters (NPT2a and NPT2c) resulting in renal phosphate wasting, diminishes the renal 1α-hydroxylase and increases the 24-hydroxylase activity. Moreover, FGF23 acts at the parathyroid gland to decrease parathyroid hormone synthesis and secretion. Currently, it is unclear how mutations in ENPP1 gene results in high FGF23 levels (Turan et al., 2010; Masi et al., 2015; OMIM entry...).

Hyperphosphatemic Familial Tumoral Calcinosis (HFTC)

(ICD-10 E83.3, Phenotype MIM number 613312, gene a) GALNT3-locus 2q24.2 b) FGF23-locus 12q13.32 c) KL-locus 13q13.1)

The disease causes hyperphosphatemia, hypercalcemia, elevated or inappropriately normal levels of 1,25 Vitamin D3 and ectopic calcifications which can be painful. GALNT3 mutations are the most often met. Yet, currently a Klotho gene mutation and 3 FGF23 gene mutations (Ser71Gly, Met96Thr, Ser129Phe) have been also described (Masi et al., 2015; ARHR2-International Osteoporosis Foundation...; OMIM entry 21190...; ADHR Consortium).

X-linked hypophosphatemic rickets (XLH)

(ICD-10 E83.3, Phenotype MIM number 307800, gene PHEX, locus Xq22.11)

It is the most common form of hereditary hypophosphatemia (prevalence of approximately 1/20,000, affects both sexes). PHEX encodes an endopeptidase expressed predominantly in bone and teeth that regulates fibroblast growth factor 23 (FGF-23) synthesis through unknown mechanisms. PHEX mutations lead to increased circulating levels of FGF-23, a phosphate-regulating hormone (phosphatonin), that leads to reduced renal phosphate reabsorption and consequently abnormal bone mineralization (Masi et al., 2015; Orpha89936-X-linked hypophosphatemia...).

XLH is caused by inactivating mutations of Phex (9), a cell surface endopeptidase that also is located in osteocytes. Loss of Phex also results in increased expression of FGF23 in osteocytes. The mechanism whereby loss of DMP1 and Phex upregulates FGF23 gene transcription is not known.

Single nucleotide Polymorphisms (SNPs) in FGF23 gene

A SNP in the intron of *FGF23* (c.212-37insC) is significantly associated with higher serum FGF23 levels and cardiac abnormalities in children with Kawasaki disease, while three distinct SNPs in *FGF23 gene* (rs11063118, rs13312789 and rs7955866) are associated with an increased risk of prostate cancer, indicating that *FGF23* genetic variations increase prostate cancer susceptibility (Itoh et al., 2015).

2. Renal disease

Chronic renal disease

Chronic kidney disease (CKD) is a growing public health epidemic that is associated with a markedly increased risk of cardiovascular mortality. Disordered mineral metabolism and particularly, disordered phosphorus metabolism appears to be a contributing factor (Wahl, Wolf, 2012). No correlation between FGF-23 and serum phosphate levels has been found in individuals without overt renal disease (Marsell et al., 2008). Yet, as CKD progresses and renal function declines FGF-23 levels gradually increase (up to 1000-fold above normal range in End Stage Renal Disease(ESRD)). Similar results were observed in studies that evaluated FGF23 in pediatric CKD population Even though FGF23 increase at a very early stage of CKD, there is no increase in the accumulation of degraded FGF-23 (C-terminals FGF23 or cFGF23) in advanced CKD. Possible explanations include physiological compensation to stabilize serum phosphate levels as the number of intact nephrons declines, the release of unidentified FGF-23 stimulatory factors or loss of a negative feedback factor(s) that normally suppress FGF-23 by the failing kidney or, an increased secretion due to an end-organ resistance to the phosphaturic stimulus of FGF-23 because of a deficiency of the necessary Klotho cofactor (Russo, Battaglia, 2011; Wolf, 2012). The mechanisms of how FGF23 is removed from the circulation, where and how it is degraded remain unknown. That is why clearance by the (failing) kidney or dialysis does not appear to contribute meaningfully to the circulating level (Wolf, 2012). On the contrary, FGF23 levels decline rapidly following kidney transplantation in most patients with prompt allograft function, however, persistently elevated FGF23 levels in the very early-post-transplant period contribute to post-transplant hypophosphatemia (Economidou et al., 2009).

Data from Chronic Renal Insufficiency Cohort (CRIC) study suggested that FGF23 is superior to existing markers as a sensitive screening test to identify which patients are developing disordered mineral metabolism in early CKD (Feldman et al., 2003). Several other studies identified FGF23 as a risk factor for CKD progression. Whether FGF23 is acting as a biomarker of cases of CKD that are destined to progress most rapidly or it is a direct mediator of disease progression is currently unknown (Economidou et al., 2009). Nevertheless, numerous reports

relate high FGF23 levels with progression to ESRD, cardiovascular disease, transfusion needs, infection susceptibility and death in CKD (Kendrick et al., 2011; Tsai et al., 2016).

As a result, several approaches (apart from surgical-kidney transplantation and parathyroidectomy) have been developed to lower FGF23 levels: dietary manipulation by reducing dietary phosphate intake; phosphate binders, especially non-calcium such as sevelamer, lanthanum, or aluminum-magnesium, cinacalcet, velcacetide and vitamin D (natural or analogues). Other modalities like e.g. anti-FGF23-Ab or RAAS blockade to modulation of the FGF23/Klotho/phosphate axis are also under evaluation (Wolf, 2012; de Seigneux, Martin, 2016).

Acute renal failure

Various reports reveal FGF23 role in acute renal failure (ARF) and acute kidney injury (AKI). Thus, cFGF23 levels rise early in AKI following cardiac surgery and are independently associated with adverse postoperative outcomes (Leaf et al., 2016). Among patients with AKI, FGF23 levels are elevated and associated with greater risk of death or need for renal replacement therapy (Leaf et al., 2012). Even though there was however no association between FGF23 levels and the severity of AKI, in some AKI models, FGF23 rised more quickly than phosphate levels or NGAL (Zhang et al., 2011; Christov et al., 2013). Recent study report that activation of FGFR1 is essential for the high levels of FGF23 in acute and chronic experimental uremia (Hassan et al., 2016). More studies are needed to identify the clear role of FGF23 in AKI.

3. Burns

Severe burn results in acute bone resorption followed by a dynamic state, most likely due to changes brought about by the inflammatory and glucocorticoid responses to the injury (Klein et al., 2015). Recent studies found increased FGF23 in adult burn patient, suggesting that osteocytes may be apoptotic (Klein et al., 2015; Rousseau, 2015). Moreover, an interesting correlation between CRP and FGF23 was found (Rousseau et al., 2014).

4. Stroke and Subarachnoid Hemorrhage (SAH)

In 2014 Northern Manhattan Study (NOMAS) found that elevated FGF23 was a risk factor for overall stroke and ICH events, in particular in a racially and ethnically diverse urban community, independent of chronic kidney disease (Wright, 2014). Later, the same investigators reported that carotid atherosclerosis may be a mechanism through which FGF23 increases cardiovascular events and stroke (Shah, 2015). Moreover, there is an association between elevated FGF23 and small vessel disease and magnetic resonance imaging-defined brain infarction in men, independent of chronic kidney disease (Wright et al., 2016). In Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, higher FGF23 concentrations were associated with higher risk of cardioembolic but not with other stroke subtypes in community-dwelling adults (Panwar, 2015). Finally, Söderholm and Engström report a relation of FGF23 with increased risk of incident SAH in subjects from the general population (Söderholm, Engström, 2015).

5. Neoplams

Phosphaturic mesenchymal tumor mixed connective tissue variants (PMTMCT)

PMTMCT is an extremely rare tumor of soft tissue which is typically associated with oncogenic osteomalacia (OO) or tumor induced osteomalacia (TIO). Classic histologic features of PMTMCT include osteoclast-like giant cells, spindle to stellate primitive mesenchymal cells, microcysts, and prominent vascularity, both blood vessels and lymphatics. FGF23 was identified as a causative humoral factor for TIO, which is quite rare in childhood FGF23 was shown to be abundantly expressed in tumors causing TIO Circulatory FGF23 levels are elevated in virtually all patients with TIO The surgical removal of responsible tumors results in normalization of FGF23 levels; while therapeutic approaches against FGF23 have also been used (Liao, 2013; Kinoshita, Fukumoto, 2014).

Prostate and ovarian cancer

As mentioned in Hereditary Diseases section, several studies relate SNPs of FGF23 or FGF23 levels with increased risk of prostate and ovarian cancer (Kim et al., 2014; Feng et al., 2013; Tebben et al., 2005).

6. Other

Results from a new study suggest that Increased serum FGF23 and placental growth factor (PLGF) levels and the presence of positive correlation between PLGF and Psoriasis area and severity index (PASI) score probably reflects the inflammatory state and insulin resistance seen in psoriasis (Okan et al., 2016).

Other investigators report that in mice model acute exercise, exhaustive exercise, and chronic exercise, increased serum FGF23 levels. Exercise-stimulated FGF23 promotes exercise performance via controlling the excess Reactive Oxygen Species production and enhancing mitochondrial function in skeletal muscle, which reveals an entirely novel role of FGF23 in skeletal muscle (Li et al., 2016).

Finally, in African Americans with type 2 diabetes lacking advanced nephropathy, FGF23 concentrations were independently associated with subclinical coronary artery disease (Freedman et al., 2015).

3. Conclusion

Along with its undoubted place in hereditary bone diseases and renal failure, in every stage, FGF23 role is far beyond clear. Further studies are needed to determine its place as prognostic, diagnostic or severity biomarker.

References

ADHR Consortium – ADHR Consortium. Autosomal dominant hypophosphataemic rickets is associated with mutations in FGF23. Nature Genet. 2000; 26: 345-348

Amin, 2014 – *Amin R.* (2014). Renal Klotho and mineral metabolism, Department of Clinical Science, Intervention and Technology, Division of Renal Medicine, Karolinska Institutet, Stockholm, Sweden 2014. Available from: https://openarchive.ki.se/xmlui/bitstream/handle/ 10616/41939/ Thesis_Risul_Amin.pdf?sequence=1

ARHR2-International Osteoporosis Foundation... – ARHR2-International Osteoporosis Foundation. Available from: http://www.iofbonehealth.org/osteoporosis-musculoskeletal-disorders/skeletal-rare-disorders/autosomal-recessive-hypophosphatemi-0 (accessed 17/04/2016)

Christov et al., 2013 – *Christov M, Waikar SS, Pereira RC, Havasi A, Leaf DE, Goltzman D, Pajevic PD, Wolf M, Jüppner H. Plasma* (2013). FGF23 levels increase rapidly after acute kidney injury. *Kidney Int*. 84(4): 776-785.

de Seigneux, Martin, 2016 – *de Seigneux S, Martin PY.* (2016). Phosphate and FGF23 in the renoprotective benefit of RAAS inhibition. *Pharmacol Res*. 106: 87-91.

Economidou et al., 2009 – *Economidou D, Dovas S, Papagianni A*, Pateinakis P, Memmos D. (2009). FGF-23 levels before and after renal transplantation. *J Transplant*. 379082.

Feldman et al., 2003 – Feldman HI, Appel LJ, Chertow GM, Cifelli D, Cizman B, Daugirdas J, Fink JC, Franklin-Becker ED, Go AS, Hamm LL, He J, Hostetter T, Hsu CY, Jamerson K, Joffe M, Kusek JW, Landis JR, Lash JP, Miller ER, Mohler ER, III, Muntner P, Ojo AO, Rahman M, Townsend RR, Wright JT. (2003). The Chronic Renal Insufficiency Cohort (CRIC) Study: design and methods. *J Am Soc Nephrol*. 14: P. 148–153.

Feng et al., 2013 – *Feng S, Dakhova O, Creighton CJ, Ittmann M.* (2013). Endocrine fibroblast growth factor FGF19 promotes prostate cancer progression. Cancer Res. 73(8): 2551-2562.

Finklestein, Plomaritoglou, 2001 – *Finklestein S.P., Plomaritoglou A.* (2001). Growth factors. In Miller L.P., Hayes R.L., eds. Co-edited by Newcomb J.K. Head Trauma: Basic, Preclinical, and Clinical Directions. New York: Wiley, pp. 165–187.

Freedman et al., 2015 – *Freedman BI, Divers J, Russell GB, Palmer ND, Bowden DW, Carr JJ, Wagenknecht LE, Hightower RC, Xu J, Smith SC, Langefeld CD, Hruska KA, Register TC.* (2015). Plasma FGF23 and Calcified Atherosclerotic Plaque in African Americans with Type 2 Diabetes Mellitus. *Am J Nephrol*. 42(6): 391-401.

Hassan et al., 2016 – *Hassan A, Durlacher K, Silver J, Naveh-Many T, Levi R.* (2016). The fibroblast growth factor receptor mediates the increased FGF23 expression in acute and chronic uremia. *Am J Physiol Renal Physiol*. 310(3): F. 217-21.

Itoh et al., 2015 – *Itoh N, Ohta H, Konishi M.* (2015). Endocrine FGFs: physiology, evolution, pathophysiology and pharmacotherapy. *Front Endocrinol (Lausanne)*. 29(6): 154.

Itoh, Ornitz, 2004 – *Itoh N, Ornitz DM* (2004). Evolution of the Fgf and Fgfr gene families. *Trends Genet*. 20: 563–569.

Itoh, Ornitz, 2008 - *Itoh N, Ornitz DM*. (2008). Functional evolutionary history of the mouse Fgf gene family. *Developmental Dynamics*. 237 (1): 18–27.

Kendrick et al., 2011 – *Kendrick J, Cheung AK, Kaufman JS, Greene T, Roberts WL, Smits G, Chonchol M* (2011). HOST Investigators. FGF-23 associates with death, cardiovascular events, and initiation of chronic dialysis. *J Am Soc Nephrol*. 22(10): 1913-1922

Kim et al., 2014 – *Kim HJ, Kim KH, Lee J, Oh JJ, Cheong HS, Wong EL, Yang BS, Byun SS, Myung SC*. (2014). Single nucleotide polymorphisms in fibroblast growth factor 23 gene, FGF23, are associated with prostate cancer risk. *BJU Int*. 114(2): 303-310.

Kinoshita, Fukumoto, 2014 – *Kinoshita Y, Fukumoto S*. (2014). Anti-FGF23 antibody therapy for patients with tumor-induced osteomalacia. *Clin Calcium*. 24(8): 1217-1222.

Klein et al., 2015 – *Klein GL, Herndon DN, Le PT, Andersen CR, Benjamin D, Rosen CJ*. (2015). The effect of burn on serum concentrations of sclerostin and FGF23. *Burns*. 41(7): 1532-1335.

Leaf et al., 2012 – *Leaf DE, Wolf M, Waikar SS, Chase H, Christov M, Cremers S, Stern L*. (2012). FGF-23 levels in patients with AKI and risk of adverse outcomes. Clin J Am Soc Nephrol. 7(8):1217-1223.

Leaf et al., 2016 – *Leaf DE, Christov M, Jüppner H, Siew E, Ikizler TA, Bian A, Chen G, Sabbisetti VS, Bonventre JV, Cai X, Wolf M, Waikar SS*. (2016). Fibroblast growth factor 23 levels are elevated and associated with severe acute kidney injury and death following cardiac surgery. *Kidney Int*. 89(4): 939-48.

Li et al., 2016 – *Li DJ, Fu H, Zhao T, Ni M, Shen FM*. (2016). Exercise-stimulated FGF23 promotes exercise performance via controlling the excess reactive oxygen species production and enhancing mitochondrial function in skeletal muscle. *Metabolism*. 65(5): 747-756.

Liao, 2013 – *Liao E*. (2013). FGF23 associated bone diseases. Front Med. 7(1): 65-80.

Liu et al., 2003 – *Liu S, Guo R, Simpson LG, Xiao ZS, Burnham CE, Quarles LD*. (2003). Regulation of fibroblast growth factor 23 expression but not degradation by PHEX. *J Biol Chem*. 278: 37419-26.

Liu, Quarles, 2007 – *Liu S, Quarles LD*. (2007). How fibroblast growth factor 23 works. J Am Soc Nephrol 2007; 18:1637-47.

Marsell et al., 2008 – *Marsell R, Grundberg E, Krajisnik T, Mallmin H, Karlsson M, Mellström D et al*. (2008). Fibroblast growth factor-23 is associated with parathyroid hormone and renal function in a population-based cohort of elderly men. *European Journal of Endocrinology*. 158(1):125-129

Masi et al., 2015 – *Masi L, Agnusdei D, Bilezikian J, Chappard D, Chapurlat R, Cianferotti L, Devolgelaer JP, El Maghraoui A, Ferrari S, Javaid MK, Kaufman JM, Liberman UA, Lyritis G, Miller P, Napoli N, Roldan E, Papapoulos S, Watts NB, Brandi ML*. (2015). Taxonomy of rare genetic metabolic bone disorders. Osteoporos Int. 2015; 26(10): 2529-2558.

Okan et al., 2016 – *Okan G, Baki AM, Yorulmaz E, Doğru-Abbasoğlu S, Vural P*. (2016). Fibroblast Growth Factor 23 and Placental Growth Factor in Patients with Psoriasis and their Relation to Disease Severity. *Ann Clin Lab Sci*. 46(2): 174-179.

Olsen et al., 2003 – *Olsen SK, Garbi M, Zampieri N, Eliseenkova AV, Ornitz DM, Goldfarb M, Mohammadi M*. (2003). Fibroblast growth factor (FGF) homologous factors share structural but not functional homology with FGFs. *The Journal of Biological Chemistry*. 278 (36): 34226–36.

OMIM entry 193100... – OMIM entry 193100-Hyphosphatemic rickets, autosomal dominant. Available from: http://www.omim.org/entry/193100 (accessed 14/04/2016)

OMIM entry 193100... – OMIM entry 193100-Hyphosphatemic rickets, autosomal recessive 1. Available from: http://www.omim.org/entry/241520 (accessed 15/04/2016)

OMIM entry 21190... – OMIM entry 21190-Tumoral calcinosis, familial. Available from: http://www.omim.org/entry/211900 (accessed 18/04/2016)

OMIM entry... – OMIM entry 613312 Hyphosphatemic rickets, autosomal recessive 2. Available from: http://www.omim.org/entry/613312 (accessed 15/04/2016)

Ornitz, 2000 – *Ornitz DM* (2000). FGFs, heparan sulfate and FGFRs: Complex interactions essential for development. Bioessays 2000; 22: 108–112.

Orpha89936-X-linked hypophosphatemia... – Orpha89936-X-linked hypophosphatemia – Orhpanet. Available from: http://www.orpha.net/consor/cgibin/Disease_Search.php?lng=

EN&data_id=11911&Disease_Disease_Search_diseaseGroup=307800&Disease_Disease_Search_diseaseType=OMIM&Disease%28s%29/group%20of%20diseases=X-linked- hypophosphatemia &title=X-linked (accessed 20/04/2016)

Orphanet-Autosomal Dominal... – Orphanet-Autosomal Dominal Hypophosphatemic Rickets. Available from: http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Expert=89937 (accessed 15/4/2016)

Panwar, 2015 – *Panwar B, Jenny NS, Howard VJ, Wadley VG, Muntner P, Kissela BM, Judd SE, Gutiérrez OM.* (2015). Fibroblast growth factor 23 and risk of incident stroke in community-living adults. Stroke. 46(2): 322-328.

Rossaint et al., 2016 – *Rossaint J, Oehmichen J, Van Aken H, Reuter S, Pavenstädt HJ, Meersch M, Unruh M, Zarbock A.* (2016). FGF23 signaling impairs neutrophil recruitment and host defense during CKD. J Clin Invest. 2016;126(3):962-974

Rousseau et al., 2014 – *Rousseau AF, Damas P, Ledoux D, Cavalier E.* (2014). Effect of cholecalciferol recommended daily allowances on vitamin D status and fibroblast growth factor-23: an observational study in acute burn patients. *Burns*. 40(5): 865-870.

Rousseau, 2015 – *Rousseau AF, Damas P, Ledoux D, Lukas P, Carlisi A, Le Goff C, Gadisseur R, Cavalier E.* (2015). Vitamin D status after a high dose of cholecalciferol in healthy and burn subjects. Burns. 41(5): 1028-1034.

Russo, Battaglia, 2011 – *Russo D., Battaglia Y.* (2011). Clinical signigicance of FGF23 in patients with CKD. *Int J Nephr*. Article ID 364890

Saito, Fukumoto, 2009 – *Saito T, Fukumoto S.* (2009). Fibroblast growth factor 23 and disorders of phosphate metabolism. *Int J Ped Endicronology*, Article ID 496514, doi: 10.1155/2009/496514

Schnedl et al., 2015 – *Schnedl C, Fahrleitner-Pammer A, Pietschmann P, Amrein K.* (2015). FGF23 in Acute and Chronic illness. *Dis Markers*. 358086.

Shah, 2015 – *Shah NH, Dong C, Elkind MS, Sacco RL, Mendez AJ, Hudson BI, Silverberg S, Wolf M, Rundek T, Wright CB.* (2015). Fibroblast Growth Factor 23 Is Associated With Carotid Plaque Presence and Area: The Northern Manhattan Study. Arterioscler Thromb Vasc Biol. 35(9): 2048-2053.

Shimada et al., 2004 – *Shimada T, Kakitani M, Yamazaki Y, Hasegawa H, Takeuchi Y, Fujita T, Fukumoto S, Tomizuka K, Yamashita T (2004).* Targeted ablation of Fgf23 demonstrates an essential physiological role of FGF23 in phosphate and vitamin D metabolism. *J Clin Invest*. 113: 561–568.

Söderholm, Engström, 2015 – *Söderholm M, Engström G* (2015). Fibroblast Growth Factor 23 and Incidence of Subarachnoid Hemorrhage: Nested Case-Control Study. *Stroke*. 46(11): 3260-3262.

Tebben et al., 2005 – *Tebben PJ, Kalli KR, Cliby WA, Hartmann LC, Grande JP, Singh RJ, Kumar R.* (2005). Elevated fibroblast growth factor 23 in women with malignant ovarian tumors. *Mayo Clin Proc*. 80(6): 745-751.

Tsai et al., 2016 – *Tsai MH, Leu JG, Fang YW, Liou HH.* (2016). High Fibroblast Growth Factor 23 Levels Associated With Low Hemoglobin Levels in Patients With Chronic Kidney Disease Stages 3 and 4. *Medicine (Baltimore)*. 95(11): 3049.

Turan et al., 2010 - *Turan S, Aydin C, Bereket A, Ackay T, Guran T, Yaralioglou BA, Basteppe M, Murat H.* (2010). Identification of a novel dentin matrix protein-1 (DMP-1) mutation and dental anomalies in a kindred with autosomal recessive hypophosphatemia. *Bone*. 46(2): 402-409.

Urakawa, 2006 – *Urakawa I, Yamazaki Y, Shimada T, Iijima K, Hasegawa H, Okawa K, Fujita T, Fukumoto S, Yamashita T.* (2006). Klotho converts canonical FGF receptor into a specific receptor for FGF23. *Nature*. 444: 770–774.

Wahl, Wolf, 2012 – *Wahl P, Wolf M.* (2012). FGF23 in chronic renal disease. *Adv Exp Med Biol*. 728: 107-125.

Wolf, 2012 – *Wolf M.* (2012). Update on Fibroblast growth factor 23 in chronic kidney disease. *Kidney Int*. 82(7): 737-747

Wright et al., 2016 – Wright CB, Shah NH, Mendez AJ, DeRosa JT, Yoshita M, Elkind MS, Sacco RL, DeCarli C, Rundek T, Silverberg S, Dong C, Wolf M. Fibroblast Growth Factor 23 Is Associated With Subclinical Cerebrovascular Damage: The Northern Manhattan Study. Stroke. 47(4):923-928.

Wright, 2014 – *Wright CB, Dong C, Stark M, Silverberg S, Rundek T, Elkind MS, Sacco RL, Mendez A, Wolf M*. (2014). Plasma FGF23 and the risk of stroke: the Northern Manhattan Study (NOMAS). Neurology. 82(19): 1700-1706.

Yamashita et al., 2000 – *Yamashita T, Yoshioka M, Itoh N*. (2000). Identification of a novel fibroblast growth factor, FGF-23, preferentially expressed in the ventrolateral thalamic nucleus of the brain. Biochem Biophys Res Commun 2000; 277: 494–498.

Yu et al., 2005 – *Yu X, Ibrahimi OA, Goetz R, Zhang F, Davis SI, Garringer HJ, Linhardt RJ, Ornitz DM, Mohammadi M, White KE* (2005). Analysis of the biochemical mechanisms for the endocrine actions of fibroblast growth factor-23. Endocrinology 146: 4647–4656.

Zhang et al., 2011 – *Zhang M, Hsu R, Hsu CY, Kordesch K, Nicasio E, Cortez A, McAlpine I, Brady S, Zhuo H, Kangelaris KN, Stein J, Calfee CS, Liu KD*. (2011). FGF-23 and PTH levels in patients with acute kidney injury: A cross-sectional case series study. *Ann Intensive Care*. 4;1(1): 21.