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REVIEW

Fibroblast Growth Factor 23 and Muscle Wasting: A Metabolic Point of View

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Protein energy wasting (PEW), mostly characterized by decreased body stores of protein and energy sources, particularly in the skeletal muscle compartment, is highly prevalent in patients with moderate to advanced chronic kidney disease (CKD). Fibroblast growth factor 23 (FGF23) is an endocrine hormone secreted from bone and has systemic actions on skeletal muscle. In CKD, FGF23 is elevated and its coreceptor α-klotho is suppressed. Multiple lines of evidence suggest that FGF23 is interconnected with various mechanisms of skeletal muscle wasting in CKD, including systemic and local inflammation, exaggerated oxidative stress, insulin resistance (IR), and abnormalities in adipocytokine metabolism. Investigation of metabolic actions of FGF23 on muscle tissue could provide new insights into metabolic and nutritional abnormalities observed in patients with CKD.

Kidney Int Rep (2023) **8,** 1301–1314; https://doi.org/10.1016/j.ekir.2023.04.027
KEYWORDS: adipokines; chronic kidney disease; fibroblast growth factor; inflammation; insulin resistance; muscle wasting; oxidative stress

Patients with CKD display a certain form of nutritional and metabolic abnormality suitably called PEW.[1] Presence and severity of PEW is highly predictive of short-term and long-term morbidity and mortality among patients with all stages of CKD.[2] PEW of CKD is usually characterized by decreased body stores of protein and energy. Detailed studies of protein metabolism suggest that there is relatively increased protein breakdown relative to protein anabolism, particularly in the skeletal muscle compartment.[3] These abnormalities are observed in almost 20% of patients with stage 3 to 5 CKD who are not on maintenance dialysis, and the prevalence sharply increases to more than 55% once the patients initiate on maintenance dialysis, regardless of the dialytic modality. FGF23 belongs to the FGF family of polypeptides and is shown to play an important role in bone and mineral metabolism in patients with CKD. FGF23 and its coreceptor klotho deficiency or mutations are characterized by severe muscle wasting in animal models.[4-11] In this article, we review the metabolic actions of FGF23 on skeletal muscle tissue and explore the interconnections between FGF23 and known mechanisms of skeletal muscle wasting in the setting of CKD.

FGF23 Physiology

The FGF family is composed of polypeptides, which have critical biologic functions such as cell growth, differentiation, angiogenesis, embryonic development, wound healing, repair, and metabolic function. There are 18 mammalian FGFs (FGF1–FGF10 and FGF16–FGF23).[12] Majority of FGFs act as autocrine and paracrine proteins (canonical FGFs) with 4 tyrosine kinase receptors [FGF receptor (FGFR) 1–4)].[13] They bind FGFRs with quite low affinity and require transmembrane glycoproteins, α-klotho and β-klotho, as coreceptors in their respective tissues to activate their cognate FGFRs.[12-14] There are 2 known isoforms of membrane klotho, namely α-klotho, present in the kidney; and β-klotho, which is found in various peripheral metabolic tissues.[11,15,16] FGFs have a role in vitamin D and phosphate homeostasis, in bile acid, glucose, lipid metabolism, and metabolic adaptation.[13] In addtition, FGFR1, FGFR3, and FGFR4 are present in human skeletal muscle from 11 weeks of gestation and may play a role in skeletal muscle maturation.[17]

Human FGF23 is a 251 amino acid peptide with a molecular weight of 32-kDa. The source of FGF23 is the osteocyte, a cell derived from osteoblasts that becomes

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Received 19 December 2022; revised 13 April 2023; accepted 24 April 2023; published online 3 May 2023

embedded in mineralized bone. During secretion, it is proteolytically cleaved by subtilisin-like protein convertases.[13,18–20] The full-length protein is biologically active and its cleavage *in vivo* results in generation of C-terminal and N-terminal fragments. C-terminal FGF23 peptide retains the ability to bind to FGFR-α-klotho complex without inducing signaling, thus, functions as a naturally occurring competitive FGF23 antagonist.[14] Both biologically active full-length FGF23 and cleaved fragments exist in normal plasma.[14,21]

FGF23-Klotho Axis in CKD

FGF23 is a regulator of vitamin D metabolism and phosphate homeostasis.[12,13,19,20,22–27] Klotho protein exerts diverse effects on the physiological regulation of mineral ions (calcium and phosphate) and energy metabolism by influencing the endocrine activities of FGF23.[28] FGF23 has a feedback relationship with its coreceptor klotho; klotho deficiency increases FGF23 levels, and elevated FGF23 exacerbates klotho deficiency via low vitamin D.[29] FGF23 levels begin to rise as early as stage 2 to 3 CKD, dramatically reaching to 100-fold to 1000-fold higher serum concentrations as CKD progresses to end-stage kidney disease.[12,23,30,31] These changes in FGF23 biology and levels are known to play a major role in CKD-related mineral bone disease.[31–34] The functions and regulation of FGF23 are depicted in Figure 1.

The etiology of elevated FGF23 levels in moderate to advanced CKD is mostly because of decreased renal clearance and a feedback response to elevated serum phosphate to maintain phosphate balance. Furthermore,

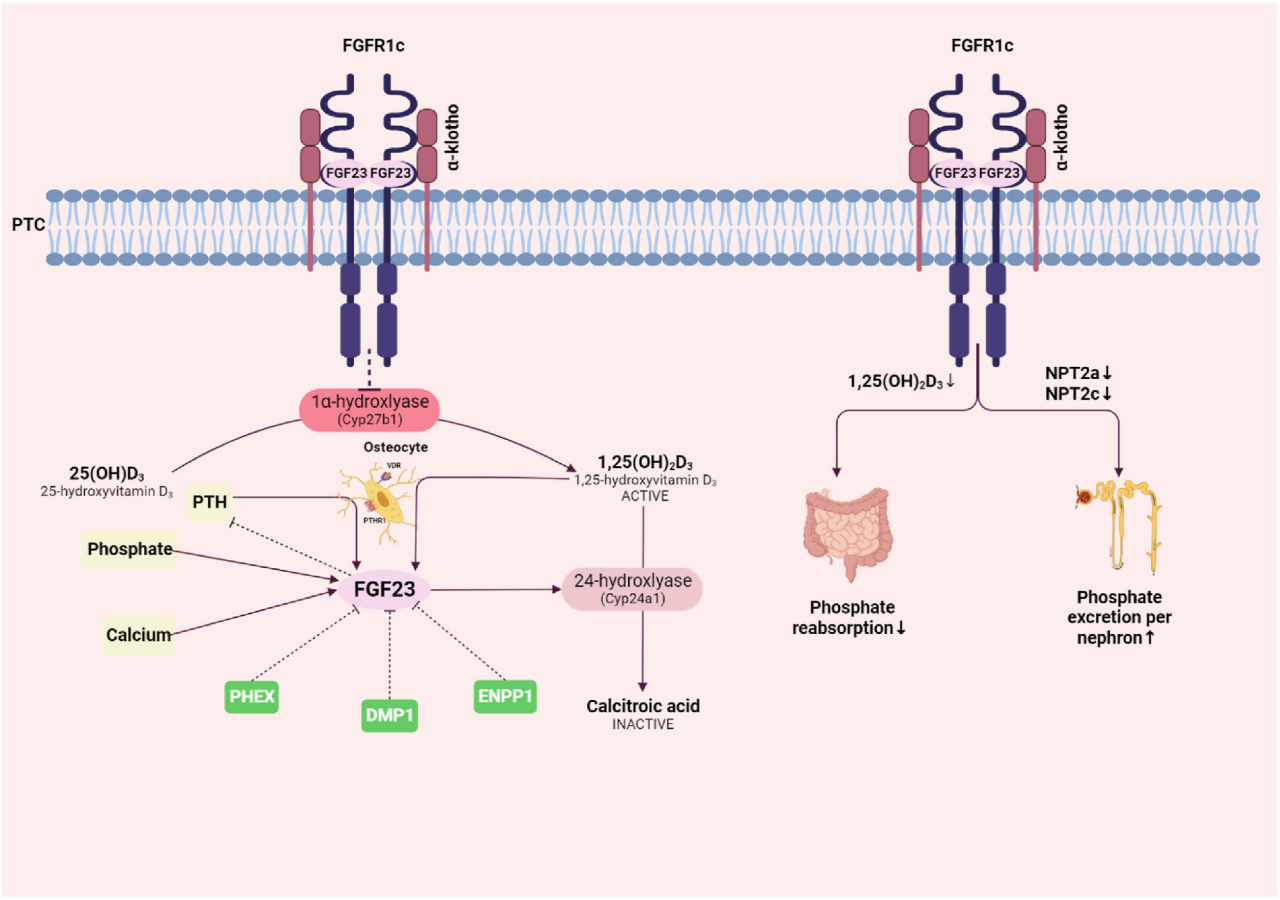

Figure 1. Functions and regulation of FGF23.
FGF23 and its coreceptor klotho protein inhibit renal 1-α hydroxylase and activate 24-hydroxylase in kidney proximal tubular cells.[12,19,20,22–24] FGF23 expression is induced by $1,25(OH)_2D_3$ through the activation of VDR.[13] Phosphorus and calcium also stimulate FGF23 synthesis.[12,13,25,26] In the intestine, via downregulation of 1α-hydroxylase and a reduction of vitamin D availability, FGF23 inhibits absorption of dietary phosphate.[12] In 3 classic feedback loops, FGF23 secretion is stimulated by elevated serum phosphate, vitamin D or PTH (via PTHR1), with corresponding negative feedbacks to maintain homeostasis.[12,19,20] FGF23 increases phosphate excretion per nephron via signaling through the FGFR1 and down-regulating proximal tubular expression of sodium-dependent phosphate cotransporters (NPT)2a and NPT2c.[19,22,23,27] PHEX, DMP1, and ENPP1 suppress synthesis and secretion of FGF23.[19] DMP1, dentin matrix protein 1; ENPP1, ectonucleotide pyrophosphatase/phosphodiesterase 1; FGF23, fibroblast growth factor 23; FGFR1, fibroblast growth factor receptor 1; NPT, sodium-dependent phosphate cotransporter; PHEX, phosphate-regulating protein with homology to endopeptidases on the X chromosome; PTC, proximal tubular cell; PTH, parathyroid hormone; PTHR1, parathyroid hormone receptor 1; VDR, vitamin D receptor. Created with BioRender.com. Published with permission.

in earlier stages of CKD, suppression of α-klotho might cause resistance to the actions of FGF23 and lead to elevated FGF23 levels. Overall, the rise in serum FGF23 concentrations in early CKD is mostly because of increased production by osteocytes, and it precedes any detectable increase in serum phosphate and decrease in vitamin D concentrations. As CKD progresses, secondary hyperparathyroidism and bone remodeling are pivotal to FGF23 elevations[12,13,19,20] along with erythropoietin, iron status, and inflammation.[26,35] The relationship between FGF23, erythropoiesis, and inflammation are bidirectional. Erythropoietin, iron deficiency, and inflammation induce FGF23 production and cleavage, whereas FGF23 affects erythropoiesis and regulates inflammatory responses.[26]

FGF23-Klotho, Inflammation, and Oxidative Stress

Systemic inflammation is commonly observed in patients with advanced CKD and is closely associated with presence and severity of PEW.[2,36,37] Whereas there is an inverse relationship between kidney function and markers of inflammatory response such as interleukin (IL)-6, tumor necrosis factor (TNF)-α, and IL-1β,[35] FGF23 levels and markers of systemic inflammation are directly associated across all stages of CKD.[35] FGF23 directly stimulates production of proinflammatory cytokines (via FGFR4 binding and activation on hepatocytes) and amplifies systemic inflammation, and in return, proinflammatory cytokines directly stimulate osteocyte production of FGF23.[26,35,38] In animal studies, infusion of TNF-α and IL-6 promotes muscle protein degradation and muscle wasting. Increased IL-6 expression in skeletal muscle enhances muscle catabolism by the ubiquitin-proteasome pathway, which is also induced by TNF-α. Both TNF-α and IL-6 enhance muscle protein degradation via the nuclear factor-kappa B (NF-κB) pathway. Similarly, IL-1β activates NF-κB signaling, induces expression of IL-6, and most effects of IL-1β are synergistically augmented by TNF-α. Zhang *et al.*[39] demonstrated that in mouse CKD model and in muscle biopsy specimens obtained from patients with CKD or those undergoing maintenance hemodialysis, both mRNA and protein expression of nucleolar protein 66 were increased, which is associated with decreased muscle mass. Furthermore, muscle-specific nucleolar protein 66 knockout in mice blocked CKD-induced loss of muscle mass and improved protein synthesis. C2C12 myotubes treated with cytokine mixture of IL-6, TNF-α and interferon gamma increased the expressions of both the nucleolar protein 66 mRNA and protein via NF-κB pathway suggesting a role of inflammation in protein synthesis.[39] Myostatin, a negative regulator of muscle growth, has also been linked to inflammation. Blocking of myostatin reduces circulating levels of IL-6 and TNF-α that are known to stimulate Janus protein tyrosine kinases. Janus protein tyrosine kinases mediate tyrosine phosphorylation of signal transducer and activator of transcription factors, especially signal transducer and activator of transcription-3 associated with cachexia. Recently, it was shown that in CKD, signal transducer and activator of transcription-3 activation occurs resulting in increased expressions of CCAAT/enhancer-binding protein δ with increased myostatin expression and muscle wasting.[40] In addition, both TNF-α and IL-6 suppress insulin and insulin-like growth factor-1 (IGF-1) signaling. Therefore, inflammation has both direct catabolic effects via the ubiquitin-proteasome and NF-κB pathways, and indirect catabolic effects via promoting IR in CKD.[37,41-44] The overlapping actions of FGF23 and inflammatory cytokines in CKD might potentially activate catabolic pathways and suppress anabolic pathways, resulting in skeletal muscle wasting (Figure 2).

Another metabolic derangement that is well-documented in moderate to advanced CKD is oxidative stress. The primary reactive oxygen species responsible for oxidative stress are superoxides produced by nicotinamide adenine dinucleotide phosphate oxidase in phagocytes and endothelial cells. Superoxides are removed by manganese superoxide dismutase (MnSOD). In the setting of advanced kidney disease, nicotinamide adenine dinucleotide phosphate oxidase upregulation and MnSOD downregulation enhance oxidative stress, which could in turn promote muscle wasting.[47-51] FGF23 reduces the number of human skeletal muscle mesenchymal stem cells and induces senescence *in vitro* by enhancing oxidative stress via upregulation of nicotinamide adenine dinucleotide phosphate oxidase and suppression of MnSOD.[52] Increased reactive oxygen species production correlates with the increase in inflammatory mediators, such as TNF-α, IL-6, NF-κB and C-reactive protein, which further enhances muscle wasting via ubiquitin-proteasome proteolytic pathway.[47] On the contrary, klotho protein increases resistance to oxidative stress at the cellular and organismal level in mammals via activation of forkhead box protein O fork head transcription factors that are negatively regulated by insulin/IGF-1 signaling. By inducing expression of MnSOD, klotho facilitates reactive oxygen species removal and confers oxidative stress resistance.[53] Klotho is also downregulated by oxidative stress.[54] Therefore, FGF23-klotho axis has multiple interactions with oxidation/reduction process, which is also interconnected with

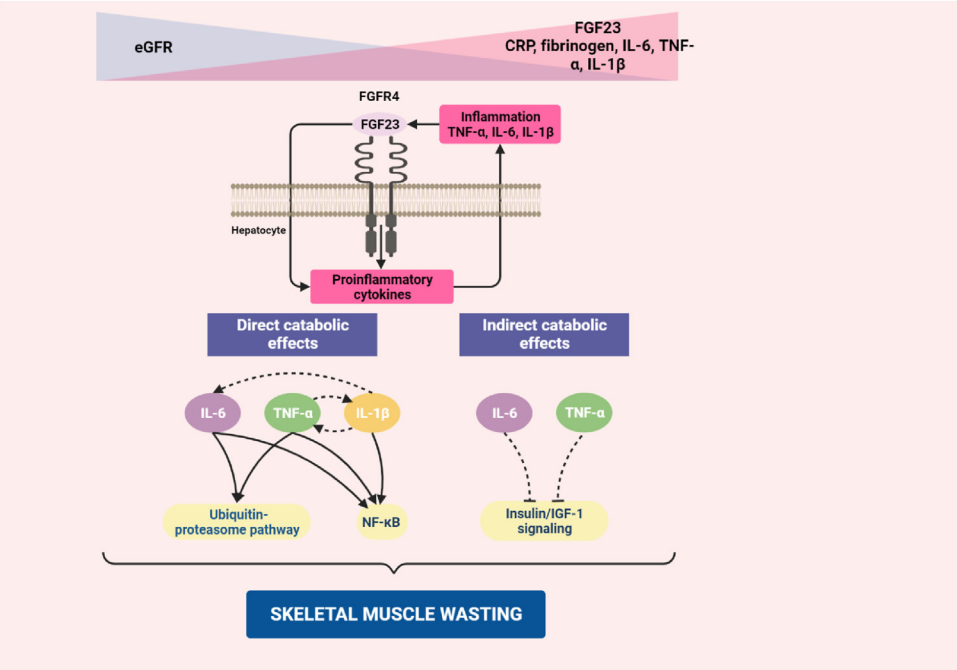

Figure 2. The reciprocal link between FGF23 and inflammation, and resultant catabolic state leading to skeletal muscle wasting in chronic kidney disease.
In chronic kidney disease, there is an inverse relationship between kidney function and levels of FGF23 and inflammatory parameters.[12,35,38,45] TNF-α, IL-6, and IL-1β trigger inflammatory cascades and mutually interact with FGF23 in a vicious cycle.[26,38] This interaction results in increased catabolism, both directly via activation of ubiquitin-proteasome (IL-6, TNF-α) and NF-κB pathways (IL-6, TNF-α, IL-1β), and indirectly via inhibition of insulin/IGF-1 signaling.[37,41-44] Increased catabolism results in skeletal muscle wasting in chronic kidney disease.[35,46] CRP, C-reactive protein; eGFR, glomerular filtration rate; FGF23, fibroblast growth factor 23; FGFR4, fibroblast growth factor receptor 4; IGF-1, insulin-like growth factor-1; IL-1β, interleukin IL-1β; IL-6, interleukin 6; NF-κB, nuclear factor-kappa B; TNF-α, tumor necrosis factor-α. Created with BioRender.com. Published with permission.

insulin/IGF-1 signaling and inflammatory pathways (Figure 3).

FGF23-Klotho, Carbohydrate Metabolism, and IR

Several *in vivo* studies suggest that FGF23-klotho axis plays a role in carbohydrate metabolism. Hesse *et al.*[4] reported that *Fgf23*$^{-/-}$ mice were hypoglycemic, had increased insulin sensitivity, and improved glucose tolerance. Compared to *ob*/*ob* mice, *klotho*$^{-/-}$ and *ob*/*ob-klotho* double-knockout mice had equally reduced fasting blood glucose levels and minimal abdominal fat tissue deposition, suggesting that elimination of klotho activity improved insulin sensitivity in *ob*/*ob* mice.[55] In study by Utsugi *et al.*,[56] klotho mutant (*kl*/*kl*) mice had decreased insulin content in the pancreas and increased insulin sensitivity compared to heterozygote mutant (*kl*/+) and wild-type mice. These mice showed abundance of glucose transporter type 4 mRNA in the skeletal muscle, which may partly explain increased insulin sensitivity.[56] Klotho overexpressing mice have higher blood insulin levels, require lower glucose infusion rates to maintain blood glucose levels, and show significant attenuation in hypoglycemic response to insulin and IGF-1 compared to wild-type mice.[8] There is also scarce evidence that FGF23 regulation of carbohydrate metabolism may be vitamin D receptor (VDR)-dependent.[22] For instance, in the study by Hesse *et al.*,[4] glucose tolerance curves and insulin secretory response of VDR mutant mice with a nonfunctioning VDR (VDR$^{\Delta/\Delta}$) closely matched those of double mutants (*Fgf23*$^{-/-}$/VDR$^{\Delta/\Delta}$), demonstrating that alterations of carbohydrate metabolism in *Fgf23*$^{-/-}$ mice may be caused indirectly through enhanced vitamin D signaling. In the study by Tsuji *et al.*,[57] leptin administration significantly increased bone FGF23 mRNA and decreased 1-α hydroxylase mRNA in *ob*/*ob* mice, without altering klotho mRNA expression. Interestingly, leptin administration did not alter serum FGF23 levels in leptin receptor-deficient *db*/*db* mice.[57]

The link between FGF23-klotho and IR has also been investigated in animal models other than *db*/*db* mice. Ellam *et al.*[58] showed that low dietary phosphate, associated with lower FGF23 levels, increased IR by 4-fold in apolipoprotein E$^{-/-}$ mice. Similarly, in *db*/*db*, leptin receptor-deficient mice (BKS.Cg-*Dock7*^{m} $^{+}$/$^{+}$ *Lepr*^{db}/J) with phosphate nephropathy, phosphorus-rich diet

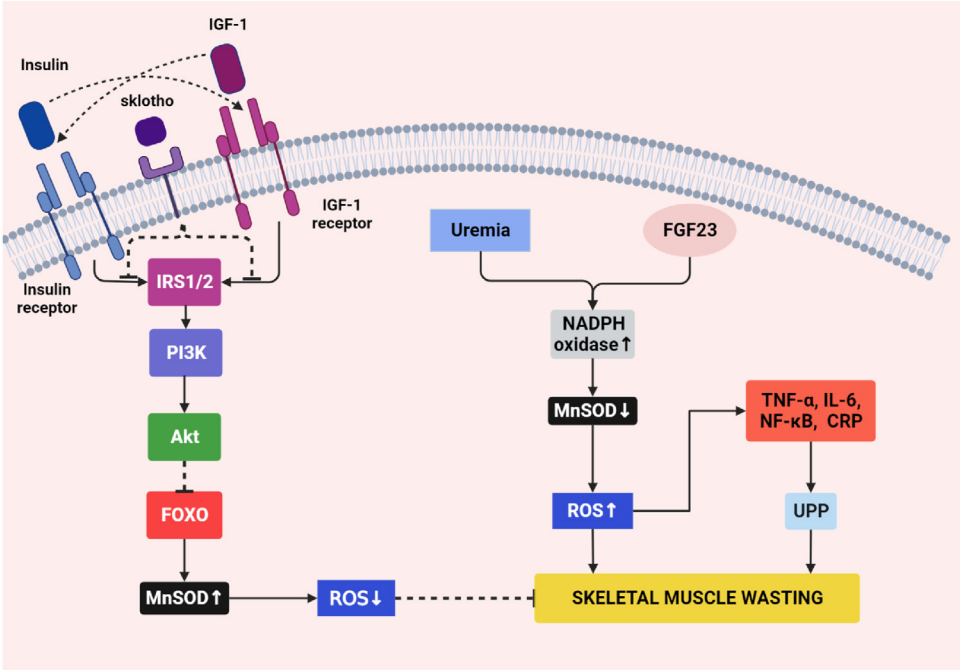

Figure 3. The interconnection between FGF23-klotho axis and oxidative stress, insulin/IGF-1 signaling, inflammation, and skeletal muscle wasting in chronic kidney disease.
sklotho activates PI3K/Akt/forkhead box protein O pathway, which is inhibited by insulin/IGF-1 signaling, induces MnSOD expression and decreases ROS generation.[53] Both uremia and FGF23 upregulate NADPH oxidase and suppress of MnSOD expression, enhance ROS generation, and increase oxidative stress.[50,52] Increased ROS production correlates with an increase in TNF-α, IL-6, NF-κB and CRP levels, which activate ubiquitin-proteasome proteolytic pathway.[47] Both increased oxidative stress and activation of ubiquitin-proteasome pathway result in skeletal muscle wasting in chronic kidney disease.
CRP, C-reactive protein; FOXO, forkhead box protein O; IGF-1, insulin-like growth factor-1; IL-6, interleukin-6; IRS, insulin receptor substrate; MnSOD, manganese superoxide dismutase; NADPH, nicotinamide adenine dinucleotide phosphate; NF-kB, nuclear factor-kappa B; PI3K, phosphatidylinositol 3 kinase; ROS, reactive oxygen species; sklotho, soluble klotho; TNF-α, tumor necrosis factor-α; UPP, ubiquitin-proteasome pathway. Created with BioRender.com. Published with permission.

strongly upregulated FGF23 levels and decreased HOMA-IR scores.[59] Contrarily, Hesse *et al.*[4] showed a positive association between FGF23 and IR. Collectively, these data suggest that there is an interconnection between FGF23-klotho and carbohydrate metabolism. The studies investigating the association of FGF23/klotho and carbohydrate metabolism in animals are summarized in Table 1.

IR is a common and an early alteration in patients with CKD.[60-62] IR results in decreased insulin-stimulated protein synthesis and increased protein degradation in skeletal muscle, which plays a critical role in skeletal muscle wasting.[63] In IR, insulin signaling is impaired at the level of tyrosine phosphorylation of insulin receptor substrate (IRS)-1 leading to downregulation of the phosphatidylinositol 3 kinase (PI3K)/AKT pathway. Muscle wasting is linked to impaired IRS-1–associated PI3K/AKT activity in various catabolic conditions, including diabetes mellitus, uremia, sepsis, acidosis, or starvation. It is also shown that glucocorticoids activate glucocorticoid receptors, which results in increased glucocorticoid receptor activity along with decreased PI3K activity. This alteration further decreases the interaction of IRS-1/PI3K in catabolic conditions leading to activation of proteolytic pathways and accelerated muscle wasting. These findings suggest that glucocorticoid receptor activation results in competition between the glucocorticoid receptors and IRS-1 for PI3K.[64] In a mouse model of CKD (induced by subtotal nephrectomy) and in patients with CKD, upregulation of signal regulatory protein alpha occurs along with decreased insulin/IGF-1 signaling activity, impaired phosphorylation of AKT, impaired cardiac remodeling, and fibrosis.[65] Furthermore, signal regulatory protein alpha promotes IR in skeletal muscle and induces cachexia in CKD.[66] Therefore, the presumed mechanism relating FGF23-klotho with IR is the PI3K/AKT signaling pathway.[67,68]

Human klotho gene has 2 transcripts, namely a putative secreted soluble klotho protein (sklotho) and a membrane protein.[69] The sklotho has differential actions on IR, depending on the mechanism involved. The sklotho circulates as a hormone and binds to a cell-surface receptor through which it represses autophosphorylation of receptors for insulin and IGF-1. This, in turn reduces phosphorylation of IRS-1 and IRS-2, and

Table 1. Studies investigating the relationship between FGF23-klotho, carbohydrate metabolism, and insulin resistance in animals

Author, Ref.	Aim	Study design	FGF23 assay	Outcome
Ellam *et al.*,[58]	-To investigate impact of dietary phosphate on IR	-Eight-week-old male apolipoprotein $E^{-/-}$ mice were randomly assigned to atherogenic diets with low (0.2%), standard (0.6%), or high (1.6%) phosphate content	-iFGF23	-Low-phosphate diet decreased FGF23 and increased HOMA-IR
Eller *et al.*,[59]	-To investigate metabolic of hyperphosphatemia	-Five-week-old, male, *db/db* leptin receptor-deficient mice (BKS.Cg-Dock7^{m} / Lepr^{db}/J) and male C57BL/6J control mice underwent uninephrectomy and were afterward fed with either a standard chow or a phosphorus-rich diet	-iFGF23	-*db/db* mice on phosphorus-rich diet had higher serum FGF23 and lower HOMA-IR and smaller visceral adipocytes
Hesse *et al.*,[4]	-To clarify role of vitamin D in FGF23 signaling	-*Fgf23*$^{-/-}$ and VDR$^{\Delta/\Delta}$ mice were generated by embryonic stem cell technology - *Fgf23*$^{-/-}$/VDR$^{\Delta/\Delta}$ compound mutant mice were generated by mating *Fgf23*$^{-/-}$ and VDR$^{\Delta/\Delta}$ mice -All mouse were kept on a diet rich in calcium, phosphorus, and lactose (rescue diet) to prevent secondary hyperparathyroidism	-N/A	-*Fgf23*$^{-/-}$ mice had increased insulin sensitivity -Glucose tolerance and insulin secretion of *Fgf23*$^{-/-}$/VDR$^{\Delta/\Delta}$ mice closely matched those of VDR$^{\Delta/\Delta}$ mice -Alterations in carbohydrate metabolism in *Fgf23*$^{-/-}$ mice were caused indirectly through vitamin D axis
Streicher *et al.*,[22]	-To investigate relationship between FGF23 and carbohydrate metabolism in mice with a nonfunctioning VDR	-9-month-old male WT mice, VDR$^{\Delta/\Delta}$, and *Fgf23*$^{-/-}$/VDR$^{\Delta/\Delta}$ mice were fed with a standard rodent chow, or a rescue diet enriched with calcium, phosphorus, and lactose	-N/A	-VDR$^{\Delta/\Delta}$ mice had improved insulin sensitivity and glucose tolerance compared to WT mice - FGF23 deficiency did not alter peripheral insulin sensitivity in VDR$^{\Delta/\Delta}$ mice -FGF23 regulation of carbohydrate metabolism in vitamin D-dependent
Ohnishi *et al.*,[55]	-To study role of klotho in obesity *in vivo*	-Heterozygous klotho mutants were crossbred with heterozygous obese [C57BL/6J lep^{ob} (+/−)] mutants to obtain *ob/ob-klotho* DKO mice in a C57BL6 background -The WT and *klotho*-knockout mice were fed either a normal fat (20%) diet or a high-fat (60%) diet, starting at 3 weeks and continuing for ≥9 weeks	-N/A	- Both leptin-deficient *ob/ob* mice and *ob/ob-klotho* DKO mice had significantly higher serum insulin levels -*ob/ob* mice higher blood glucose levels than WT, *ob/ob-klotho* DKO and *klotho*$^{-/-}$ mice -*ob/ob-klotho* DKO mice had similar fasting blood glucose levels to klotho$^{-/-}$ mice -Insulin resistant *ob/ob* mice became insulin sensitive when klotho activity was eliminated
Utsugi *et al.*,[56]	-To determine whether mutation of the klotho gene was associated with IR	-The mice homozygote (*kl/kl*) and heterozygote (*kl/+*) for *klotho* mutation were used	-N/A	-During OGTT, blood glucose of *kl/kl* mice was significantly lower than WT mice, and plasma insulin of *kl/kl* mice was undetectable -*kl/kl* mice had significantly lower pancreas insulin content than *kl/+* and WT mice -During insulin tolerance test, *kl/kl* showed enhanced insulin sensitivity - GLUT4 mRNA was increased in skeletal muscle of *kl/kl* mice compared to *kl/+* and WT mice

DKO, double-knockout; FGF23, fibroblast growth factor 23; GLUT4, glucose transporter type 4. HOMA-IR, homeostatic model assessment of insulin resistance; iFGF23, intact fibroblast growth factor 23; IR, insulin resistance; N/A, not applicable; OGTT, oral glucose tolerance test; VDR, vitamin D receptor; WT, wild-type.

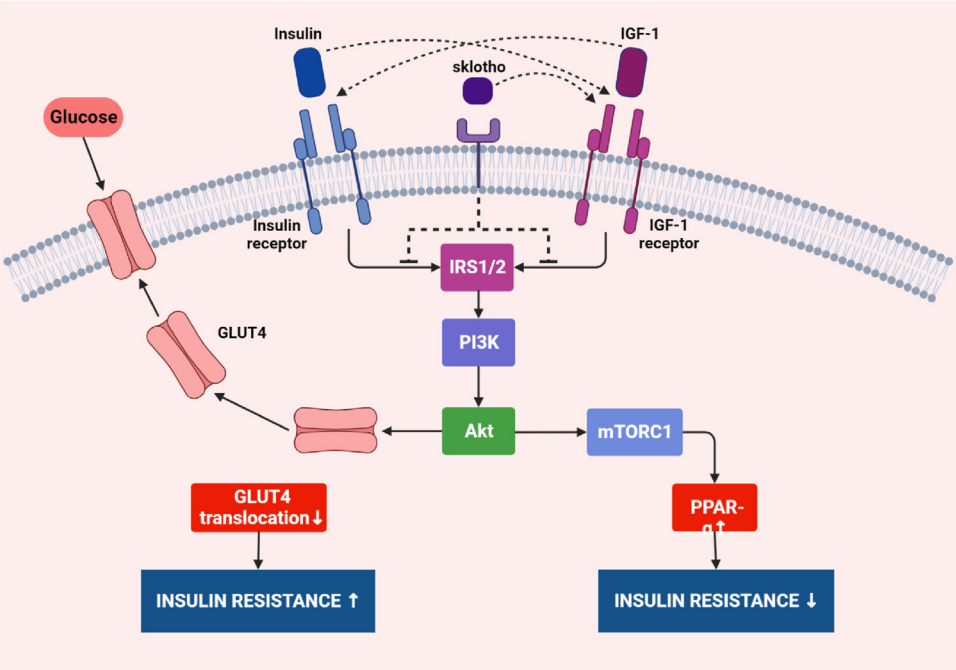

Figure 4. The putative interconnected mechanisms between FGF23/klotho axis and insulin resistance in chronic kidney disease.
sklotho binds to a cell-surface receptor through which it represses autophosphorylation of receptors for insulin and IGF-1. This, in turn reduces phosphorylation of IRS-1 and IRS-2, and their association with PI3K, inhibits insulin/IGF-1 signaling and induces insulin resistance.[8,70] Contrarily, sklotho also directly interacts with IGF-1 receptor and inhibits PI3K/AKT/mTORC1signaling pathway and upregulate PPAR-α and decreases insulin resistance.[72]
GLUT4, glucose transporter type 4; IGF-1, insulin-like growth factor-1; IRS, insulin receptor substrate; mTORC1, mammalian target of rapamycin complex 1; PI3K, phosphatidylinositol 3 kinase; PPAR-α, peroxisome proliferator-activated receptor; sklotho, soluble klotho.
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their association with PI3K, thereby inhibiting insulin and IGF-1 signaling and inducing IR.[8,70] A high ratio of sklotho to membrane protein potentiates development of IR.[71] In addition, Gu *et al.*[72] recently showed that sklotho also inhibited PI3K/AKT/mTORC1 signaling, upregulated peroxisome proliferator-activated receptor α by directly interacting with IGF-1 receptor, and decreased IR in mice with type 2 diabetes. IR suppresses glycogenesis, inhibits beta oxidation, increases supplies of free fatty acids, alters triglyceride transport, and results in accumulation of triglycerides in the skeletal muscle tissue. The resulting loss of skeletal muscle mass and intramuscular adipose tissue accumulation are hallmark findings of muscle wasting in the setting of CKD[61] (Figure 4).

The association between FGF23 and IR in humans is a novel research topic. Plasma FGF23 is positively correlated with homeostatic model assessment of IR (HOMA-IR) in the elderly,[73] in African American adolescents,[74] in obese subjects,[75] in patients with coronary heart disease[76] and in HIV-1-infected patients with highly active antiretroviral therapy-associated lipodystrophy syndrome.[77] In general, available data suggest that FGF23 is associated with IR in a diverse group of subjects with normal kidney function.

In patients with CKD, available data show that FGF23 is related with IR and IR-related conditions such as hyperlipidemia[73,78] and adiposity,[73,79] especially visceral adiposity[80] and intermuscular adipose tissue deposition.[81] In nondiabetic predialysis patients with CKD, Fayed *et al.*[82] showed that FGF23 was an independent predictor of HOMA-IR. In this study, because HOMA-IR was correlated with phosphorous, and the authors suggested that the rise in FGF23 that occurs in response to phosphorus retention was a risk factor of increased HOMA-IR.[82] In patients with stage 3 to 5 CKD not yet on dialysis, Garland *et al.*[83] reported that patients with higher FGF23 levels had higher HOMA-IR, and FGF23 was an independent predictor of HOMA-IR.[83] On the other hand, Hanks *et al.*[46] reported that CKD significantly modified the relationship between FGF23 and IR in community-dwelling adults. In their study, FGF23 was positively associated with HOMA-IR only in individuals without CKD.[46] However, patients with medical conditions that would prevent long-term participation were excluded in this study. Klotho is also independently associated with HOMA-IR in patients with type 2 diabetes who have stage 2 to 3 CKD.[84] Overall, data suggest that FGF23-klotho is associated with IR and related metabolic

Table 2. Studies investigating the relationship between FGF23/klotho, insulin resistance, and metabolic syndrome

Author, Ref.	Aim	Study design	FGF23 assay	Outcome
Mirza *et al.*,[73]	- To investigate relationship between FGF23 and metabolic cardiovascular risk factors in the community	-2 community-based, cross-sectional cohorts of elderly whites ($n = 964$ men, and $n = 946$ men and women, respectively)	-iFGF23	-FGF23 was positively correlated with leptin levels -Higher FGF23 was associated with higher HOMA-IR -Elderly subjects with MetS had higher FGF23 levels than those without MetS
Ali *et al.*,[74]	-To determine whether FGF23 levels are greater in obese compared with normal-weight adolescents -To determine relationship between FGF23 and IR	-Cross-sectional study -Normotensive African American adolescents aged 13–18 years without CKD ($n = 130$)	-ctFGF23	-Plasma FGF23 was higher in obese than in normal-weight subjects -LogFGF23 was positively correlated with HOMA-IR -LogFGF23 was negatively correlated with adiponectin -LogFGF23 correlated with measures of adiposity, including BMI and waist circumference
Fernández-Real *et al.*,[75]	-To evaluate relationship between FGF23 levels and metabolic parameters	-Cohort 1; Middle-aged men with BMI <40 kg/m^2 ($n = 133$) -Cohort 2; Subjects with BMI >30 kg/m^2 ($n = 314$)	-iFGF23 and ctFGF23	-In cohort 1, both iFGF23 and ctFGF23 increased linearly with IR -In cohort 2, ctFGF23 increased linearly with HOMA-IR
Song *et al.*,[76]	-To investigate relationship between FGF23 and clinical characteristics in patients with coronary heart disease	-Prospective, single center, observational study - Patients with coronary heart disease treated by percutaneous coronary intervention with drug-eluting stent ($n = 214$)	-FGF23 (not specified)	-FGF23 was positively correlated with fasting blood glucose and IR index
Wojcik *et al.*,[88]	-To investigate correlation of serum FGF23 and glucose, insulin, and fat metabolism in obese adolescents	-Prospective study -Adolescents with simple obesity ($n = 68$)	-iFGF23	-FGF23 was negatively correlated with HOMA-IR -FGF23 was independently associated with HOMA-IR
Gateva *et al.*,[89]	-To investigate relationship between calcium-phosphate metabolism markers and glucose disturbances in obese patients with prediabetes	-Cross-sectional study -Group 1; Obese patients without glycemic disturbances ($n = 41$) -Group 2; Obese patients with prediabetes ($n = 39$)	-FGF23 (not specified)	-FGF23 was higher in obese patients with prediabetes than those with normal glucose tolerance -FGF23 levels were higher in patients with IR than their counterparts
Domingo *et al.*,[77]	-To determine relationship between FGF23 and metabolic alterations	-Cross-sectional study -Group 1; HIV-1-infected patients with HIV/HALS ($n = 60$) -Group 2; HIV-1-infected, antiretroviral-treated patients without HALS ($n = 43$) -Group 3; Naive HIV-1-infected patients ($n = 49$) -Group 4; Healthy controls ($n = 34$)	-iFGF23 and ctFGF23	-FGF23 was positively correlated with HOMA-IR -FGF23 was increased in HIV-1- infected patients, especially in those with HALS
Hanks *et al.*,[46]	-To examine associations of FGF23 and markers of inflammation, IR, and anthropometrics	-Cross-sectional study -Cohort of community-dwelling adults ≥45 years of age ($n = 1040$)	-ctFGF23	-FGF23 was positively correlated with IL-6, hsCRP, IL-10, HOMA-IR, BMI, and waist circumference in individuals without CKD, but not among individuals with CKD -FGF23 was associated with resistin irrespective of CKD status
Fayed *et al.*,[82]	-To investigate association between IR and mineral metabolism in predialysis nondiabetic patients with CKD	-Cross-sectional study -Patients with CKD ($n = 100$) and controls ($n = 20$)	-iFGF23	-Patients with CKD had higher HOMA-IR than controls -FGF23 and serum phosphorus were the only parameters significantly correlated with HOMA-IR -FGF23 was an independent predictor of HOMA-IR
Nakashima *et al.*,[90]	-To analyze relationship between resistin and FGF23 in patients with T2D who have CKD	-Cross-sectional study - Patients with T2D who have CKD ($n = 422$)	-iFGF23	-FGF23 levels were positively correlated and independently associated with resistin levels -Resistin levels were positively associated with FGF23 levels in older patients (≥64years) and in patients with a low BMI (<23.9 kg/m^2)
Silva *et al.*,[84]	-To evaluate the relationship between klotho and IR in patients with T2D who have CKD	-Cross-sectional study -Patients with T2D who have stage 2–3 CKD ($n = 107$)	-ctFGF23	-Klotho levels were inversely correlated with HOMA-IR and FGF23 levels, and directly correlated with vitamin D levels -FGF23 and HOMA-IR were independently associated with klotho levels
Garland *et al.*[83]	-To determine relationship between IR, FGF23, and coronary artery calcification in patients with CKD	-Cross-sectional study -Predialysis patients with stage 3–5 CKD (not receiving insulin therapy) ($N = 72$)	-ctFGF23	-FGF23 was significantly correlated with HOMA-IR, waist circumference, and BMI -HOMA-IR was independently associated with increased FGF23 levels -FGF23 levels were significantly higher as number of MetS components increased

(Continued on following page)

Table 2. (Continued) Studies investigating the relationship between FGF23/klotho, insulin resistance, and metabolic syndrome

Author, Ref.	Aim	Study design	FGF23 assay	Outcome
Kerr *et al.*,[85]	-To determine associations between epicardial fat, and kidney related CV risk factors including obesity and IR	-Cross-sectional study -Predialysis patients with stage 3–5 CKD ($n = 94$)	-cFGF23	-Epicardial fat deposition was higher in patients with MetS, in diabetic patients and in patients with HOMA-IR greater than the median value -LogFGF23 and HOMA-IR were correlated with epicardial fat deposition
Da Silva Martins *et al.*,[86]	-To investigate association between obesity, and MetS, and CKD-BMD	-Cross-sectional study -Hemodialysis patients ($n = 55$)	-cFGF23	-Patients with normal bone volume had higher FGF23, phosphorus and fasting insulin levels, higher BMI, and higher prevalence of MetS
Chen *et al.*,[87]	-To investigate relationship between FGF23 levels and MetS in kidney transplant recipients	-Retrospective study -Patients undergoing kidney transplantation ($n = 74$)	-cFGF23	-FGF23 levels were higher in recipients with MetS -FGF23 is an independent predictor of MetS in kidney transplant recipients

BMI, body mass index; CKD, chronic kidney disease; CKD-BMD, chronic kidney disease-mineral and bone disorder; ctFGF23, C-terminal fibroblast growth factor 23; CV, cardiovascular; FGF23, fibroblast growth factor 23; HALS, highly active antiretroviral therapy-associated lipodystrophy syndrome; HIV-1, human immunodeficiency virus-1; HOMA-IR, homeostatic model assessment of insulin resistance; iFGF23, intact FGF23; IL, interleukin; hsCRP, high sensitivity C-reactive protein; IR, insulin resistance; MetS, metabolic syndrome; T2D, type 2 diabetes.

derangements in CKD, even in the absence of type 2 diabetes.

There is also evidence to suggest that FGF23 is related to metabolic syndrome (MetS). Elderly subjects with MetS have higher FGF23 levels than those without MetS.[73] In patients with stage 3 to 5 CKD not yet on dialysis, Garland *et al.*[83] showed that FGF23 levels were significantly higher as the number of MetS components increased. In a study with relatively small sample size, Kerr *et al.*[85] reported that FGF23 was associated with epicardial fat deposition, which is a correlate of IR and MetS. Interestingly, bone volume may be an important factor in the interaction between FGF23 and MetS. In patients on maintenance hemodialysis with normal bone volume, FGF23 levels and prevalence of MetS is higher, supporting the role of bone as an endocrine organ in advanced CKD.[86] In kidney transplant recipients, high FGF23 independently predicts presence of MetS.[87] The studies investigating the association of FGF23-klotho, IR, and MetS are summarized in Table 2.

FGF23-Klotho and Adipokines

Resistin is an adipokine secreted from adipose tissue[91] and has shown to induce IR in mice.[92] Resistin increases secretion of inflammatory cytokines (TNF-α, IL-6, and IL-12) via NF-κB dependent pathway[93]; and C-reactive protein, TNF-α, IL-1, IL-6, and IL-12 enhance resistin secretion, suggesting a circulatory pathway.[94] In addition, resistin significantly increases serine phosphorylation of IRS-1 in the skeletal muscle, further enhancing IR.[93] In community-dwelling adults and in patients with type 2 diabetes who have CKD, FGF23 is independently associated with resistin levels.[46,90]

Leptin is an adipocyte-secreted 16-kDa polypeptide hormone and plays a pivotal role in regulating lipid metabolism in skeletal muscle. It stimulates downstream targets, including AMP-activated protein kinase and Janus kinase 2 signaling pathways, and activates lipid oxidation in skeletal muscle by binding to its receptors.[95,96] Leptin induces IR in CKD, which is mediated by reduced fat oxidation and activation of the IRS/PI3K signaling pathway.[60] Furthermore, leptin acts directly on bone and enhances FGF23 expression, with no effect on klotho.[57,97] Treatment with leptin leads to elevation in serum FGF23 concentrations and suppresses vitamin D levels in leptin-deficient *ob/ob* mice.[57] Adiponectin is another adipocytokine and is almost exclusively secreted by the adipose tissue.[96,98] Adiponectin lowers hepatic glucose production and increases glucose uptake and fatty acid oxidation in skeletal muscle.[99] In contrast to leptin, adiponectin has a potent insulin sensitizing activity.[100] FGF23 levels are positively associated with leptin and negatively

Table 3. Phenotypes of different mouse models

Mouse model	Skeletal muscle wasting
Fgf23$^{-/-}$	+
klotho$^{-/-}$	+
Fgf23$^{-/-}$/*klotho*$^{-/-}$	+
kl/kl	+
Fgf23$^{-/-}$/*1α(OH)ase*$^{-/-}$	−
klotho$^{-/-}$/*1α(OH)ase*$^{-/-}$	−

associated with adiponectin in an elderly community with normal kidney function.[73] Adiponectin directly inhibits FGF23 production and klotho expression.[97] Both leptin and adiponectin levels are elevated in patients with CKD because of their decreased renal clearance and adipose tissue dysfunction. However, the extent of leptin accumulation is higher than that of adiponectin, creating a high leptin-adiponectin ratio, favoring IR.[101] Therefore, the association of FGF23 with increased resistin levels and differential interaction of FGF23 with leptin and adiponectin are also potential mechanisms by which FGF23 could contribute to development and worsening of IR and muscle wasting in patients with CKD.

FGF23, Klotho, and Muscle Wasting

Animal models consistently demonstrate that FGF23 and/or klotho deficiency are closely linked with severe skeletal muscle wasting (Table 3). In animal models, *Fgf23*$^{-/-}$ mice with normal klotho expression, have lower body weight and severe skeletal muscle wasting, compatible with premature aging and with a lifespan markedly shorter than wild-type mice.[4,9,10] Similarly, klotho knock out (*klotho*$^{-/-}$) mice show growth retardation apparent from 3 weeks onward. These rats also have severe muscle wasting, with reduced fat tissue and generalized tissue atrophy.[5,7] The phenotype of *Fgf23*$^{-/-}$/*klotho*$^{-/-}$ mice are identical to that of either *Fgf23*$^{-/-}$ or *klotho*$^{-/-}$ mice, all of which have severe skeletal muscle wasting.[6] Similarly, mice homozygous for klotho mutant allele (*kl*/*kl*) appear to be normal until 3 to 4 weeks of age but begin to manifest skeletal muscle atrophy and eventual premature death.[8]

FGF23 has regulatory actions on vitamin D metabolism. Interestingly, although FGF23 knock out (*Fgf23*$^{-/-}$) mice exhibit severe muscle wasting,[10] this effect is seen only in mice with a functioning VDR,[22] which is fully rescued by ablation of VDR activity.[4] This suggests that severe muscle wasting because of inactivation of the FGF23-klotho axis, either alone or in combination, may occur indirectly through VDR-dependent vitamin D signaling.[4–7,22] The potential VDR-dependent actions of vitamin D that may lead to skeletal muscle wasting are discussed in detail elsewhere.[102–110]

FGF23-Klotho and Nutritional Status

Given that nutritional derangement is associated with skeletal muscle wasting,[36] the link between FGF23 and nutritional parameters in CKD deserves mention. Along with mineral metabolism, age, and nutritional status are significant determinants of serum FGF23 in hemodialysis patients. Mizuiri *et al.*[30] showed that hemodialysis patients in the lowest FGF23 quartile displayed the lowest body mass index, normalized protein catabolic rate (nPCR), normalized protein equivalent of nitrogen appearance, geriatric nutritional risk index and were at risk for muscle wasting. Similarly, Ashikaga *et al.*[111] reported that FGF23 was positively correlated with normalized protein catabolic rate and geriatric nutritional risk index, and negatively with cholesterol and non-high density lipoprotein cholesterol in patients on maintenance hemodialysis. Patients in the higher FGF23 tertile had better nutritional status, as assessed by normalized protein catabolic rate, and higher muscle mass than their counterparts. Interestingly, in the study by Fukasawa *et al.*,[1] FGF23 was an independent predictor of muscle mass after adjustment for normalized protein catabolic rate. Nonetheless, FGF23-klotho axis seems to be linked with nutritional status, which may be a potential mechanism interconnecting FGF23, klotho, and muscle wasting.

Future Perspectives and Conclusion

FGF23 is an endocrine hormone secreted from the bone and has multiple systemic actions, including the skeletal muscle and adipose tissue. CKD is a state of progressive FGF23 elevation, resistance to actions of FGF23, and concurrent skeletal muscle wasting. Multiple studies suggest that the actions of FGF23 have overlapping involvement of the well-established metabolic pathways that are also deranged in patients with CKD. These include, but are not limited to, systemic inflammation, oxidative stress, IR, and adipocytokines. The emergent data highlight the importance of FGF23 as a potential modifiable risk factor for PEW and as a target for treatment in patients with CKD.

DISCLOSURE

Dr. Ikizler has consulted for Abbott Nutrition and Fresenius Kabi.

AUTHOR CONTRIBUTIONS

REA contributed to conceptualization, data acquisition, investigation, and writing the original draft. BA

contributed to conceptualization, writing original draft, review, and editing, TAI contributed to the final review and editing, and supervision.

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