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KLOTHO, FGF21 AND FGF23: NOVEL PATHWAYS TO MUSCULOSKELETAL HEALTH?

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Abstract

Bone mineral density, muscle mass and physical function reach their peak between the second and fourth decade of life and then decline steadily with aging. The crucial question is: what factors contribute to or modulate this decline? The aim of this mini-review is to propose a theoretical framework for the potential role of emerging biomarkers such as klotho, fibroblast growth factors (FGF)21 and FGF23 on musculoskeletal health, with a particular focus on decline in muscle mass and function, and calls for future research to examine this proposed link. The identification of new physiological mechanisms underlying these declines may open a potentially important avenue for the development of novel intervention strategies aimed at preventing or reducing their potentially detrimental consequences.

Keywords

Klotho; fibroblast growth factors; aging; skeletal muscle

Musculoskeletal Changes with Aging and their Implications

Bone loss and the decline in muscle mass, strength and physical function that occur with aging are major risk factors for the development of adverse outcomes, including falls (1, 2), mobility limitation (3) and recurrent hospitalization (4), and often represent the early stage of a continuum leading to disability and dependency (3, 5, 6). Considering the projected demographic transition, with an estimate of 19% of Americans being 65 or older in 2030 (7), these aging-related conditions will dramatically increase in the next years, as well as their medical and health care costs (8, 9). Therefore, the identification of factors contributing to the exacerbation and progression of bone/muscle loss and functional decline represent an important public health concern, and a crucial step for the development of primary and secondary prevention strategies.

Bone mineral density, muscle mass and physical function reach their peak between the second and fourth decade of life and then decline steadily with aging (10–12). The crucial question is: what factors contribute to or modulate this decline? It is well-known that the

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level of physical activity is reduced with advanced age and that muscle disuse plays an important role in bone loss and the decline in muscle mass and physical function (13, 14). However, it has been shown that even highly active older persons, including master swimmers and athletes, still have significantly lower muscle mass and strength than their younger counterparts (15), suggesting that other factors contribute to this aging-related process.

The aim of this mini-review is to propose a theoretical framework for the potential role of emerging biomarkers such as klotho, fibroblast growth factors (FGF)21 and FGF23, on musculoskeletal health, with a particular focus on decline in muscle mass and function, and calls for future research to examine this proposed link. The identification of new physiological mechanisms underlying these declines may open a potentially important avenue for the development of novel intervention strategies aimed at preventing or reducing their potentially detrimental consequences.

Klotho, FGF21 and FGF23: Metabolism and Clinical Phenotypes

Klotho is a recently discovered protein (16) that was named after the Greek goddess, Klotho, who spins the thread of life. It is mainly expressed in the distal renal tubule and the choroidplexus in the brain (16) and is composed of a very short (10 amino acids) intracellular domain, a transmembrane, and a large extracellular domain which can act as a circulating hormone (17). It is released into the extracellular space and can be detected in sera (18). There are two forms of klotho protein: membrane klotho and secreted klotho.

Membrane klotho functions as a receptor for FGF21 and FGF23 and is required for their metabolic activity (19, 20). Because of the lack of a heparin-binding domain, these FGFs can leave the tissues of origin and serve as circulating hormones (21).

Secreted klotho functions as a humoral factor with a number of activities, including lowering intracellular oxidative stress and regulation of ion channel and transport (22, 23). Experimental studies have shown that klotho extends lifespan by 19–31% when overexpressed (24) and causes a phenotype of premature aging, including muscle atrophy and muscle weakness (16, 25), when its expression is disrupted. Furthermore, klotho deficient mice are osteopenic (16, 26) with low bone turnover, resulting in a decreased cortical bone thickness of femur, tibia and vertebrae by 20–40% when compared with wild-type mice (27). Although the underlying factors contributing to this premature aging phenomenon are unclear, putative mechanisms are its role in repressing insulin/IGF1 signaling through FGF21 (24), lowering intracellular oxidative stress (22) and regulating phosphate and calcium homeostasis through FGF23 (24, 28).

FGF21 is a recently discovered endocrine factor that is emerging as a regulator of glucose and lipid metabolism. It is mostly expressed in the liver but also in the pancreas, white adipose tissue and muscle (29, 30). FGF21 expression in the liver is primarily induced by prolonged fasting through peroxisome proliferator-activated receptor (PPAR)-α activation and in white adipose tissue by feeding through activation of PPAR-y, a master transcriptional regulator of adipogenesis (31). The preferred receptor for FGF21 (FGFR1c) is abundantly

expressed in adipose tissue (19, 20, 32) where FGF21-regulated genes are involved in lipogenesis, lipolysis, and fatty acid oxidation (33, 34). When administered to rodents and monkeys with obesity and diabetes, recombinant FGF21 causes weight loss, and reduces plasma glucose, triglycerides, insulin resistance, and hepatic steatosis (33, 35, 36). Experimental studies suggest that FGF21 also regulates skeletal homeostasis, by potentiating PPAR-y activity and inhibiting osteoblastogenesis (37). However, little is known on the functional role of FGF21 in humans, where its role in glucose metabolism is controversial (38–43).

FGF23 was first identified in the ventrolateral thalamic nucleus of the brain in mice (44) and its importance was discovered when its mutation lead to the development of autosomal dominant hypophosphatemic rickets (ADHR) (45). FGF23 is a bone-derived hormone that acts on the kidney to modulate bone mineralization by regulating phosphate excretion, and the synthesis of 1,25-dihydroxyvitamin D3 [1,25-$(OH)_2D_3$] and parathyroid hormone (PTH) (46). In particular, when phosphate is in excess, FGF23 acts on kidney to promote phosphate excretion into urine. FGF23 also reduces serum 1,25-$(OH)_2D_3$ levels to suppress phosphate absorption from intestine. Thus, FGF23 functions as a hormone that induces negative phosphate balance (47, 48) and it has been shown to play a causative role in the development of several hypophosphatemic rickets/osteomalacia. Furthermore, FGF23 functions as an inhibiting factor of PTH synthesis (49, 50) and has been associated with PTH levels in humans as well (51). Mice knock-out for FGF23 show a clinical phenotype resembling aging, including growth retardation, skin atrophy, decreased bone density and decreased longevity (46). Patients with hypophosphatemic rickets/osteomalacia often report muscle weakness and bone pain that severely affects their daily life activities (52).

Novel Pathways to Musculoskeletal Health?

FGF21 and FGF23 share common structural and biological features (53) and both require klotho to bind their cognate FGF receptors and exert their biological activities (19, 54). Therefore, they likely act systemically and synergistically and may affect musculoskeletal health through different pathways. For example, klotho contributes to phosphate and calcium homeostasis (28) by affecting FGF23 (54), which is considered a putative cornerstone for bone mineralization, and also FGF21 might contribute to skeletal homeostasis not only in mice (37) but also in humans.

The main functions of FGF23 signaling in the kidney are the reduction of 1,25$(OH)_2D_3$ synthesis and of renal tubular phosphate reabsorption (55). Consequently, FGF23 is directly involved in the regulation of the active form of vitamin D and of serum phosphate levels. Extracellular phosphate is necessary to allow mineralization of bone matrix, while intracellular phosphate plays an important role in energy stores and production (e.g. in the form of phosphocreatine and ATP) (77), which are needed for muscles to function. Consequently, klotho and FGF23 may play an important role not only in bone mineralization but also in the maintenance of muscle mass and function given their interplay with vitamin D and the critical role of phosphate in energy (ATP) and protein production. In line with this hypothesis, a number of studies have shown that low levels of vitamin D are associated with decline in muscle mass (56), muscle strength (57) and physical function (58, 59).

Furthermore, skeletal muscle is a major user of ATP (60) to power the movement of the myosin heads and to allow muscle contractions. Interestingly, experimental studies have shown that injections of FGF23 antibodies increased serum phosphate and 1,25-$(OH)_2D_3$ levels as well as grip strength and spontaneous movements in hypophosphatemic mice (61).

FGF21 may play a role in muscle mass and function with its involvement in energy metabolism as well. Indeed, during starvation and intense physical activity the levels of FGF21 increase through the PPAR-α pathway in order to enhance energy production (ketogenesis) and utilization (oxidation) of free fatty acids. Chau et al. (62) demonstrated that FGF21 regulates energy homeostasis in adipocytes through activation of adenosine monophosphate (AMP)-activated protein kinase, sirtuin 1, and PPAR g co-activator-1a leading to enhanced mitochondrial function and oxidative capacity. FGF21 also causes growth hormone resistance, and therefore, plays a key role in orchestrating the adaptive starvation response (21). Finally, circulating levels of FGF21 are positively associated with insulin resistance (43, 63) and with type II diabetes (64), conditions associated with musculoskeletal-related outcomes (65, 66).

Additional potential pathways that may link these novel biomarkers with musculoskeletal health are their involvement in the regulation of systemic inflammation and oxidative stress, as these conditions are associated with decline in muscle mass and strength (67–70). Indeed, Lee et al. recently showed that FGF21 plays a role in inhibiting the activation of the transcription factor nuclear factor-kappa B (NF-kB) (71), the master regulator of inflammation that can be activated in skeletal muscle cells under inflammatory conditions (72). Finally, NF-kB activation is tightly linked to increased oxidative stress, which alters the balance between protein synthesis and degradation and, consequently, may affect the rate of protein degradation in skeletal muscle (73, 74). Interestingly, klotho has been shown to be a cytoprotective protein that defends against oxidative stress (75) and, in turn, may contribute to reduce protein degradation and muscle loss. Therefore, as simplified in the conceptual framework (figure), these novel biomarkers may play a role in musculoskeletal health through different mechanisms, and are likely to function in an interaction network rather than in an additive fashion. However, despite this strong theoretical basis, there is a gap in the current scientific knowledge on the effect of klotho, FGF21 and FGF23 on muscle mass and function in humans. Indeed, there are only two studies in humans published to date on this topic, and they show that one standard deviation increase in plasma klotho was significantly associated with muscle strength (β=1.20, standard error=0.35, p=0.0009)(76) and with reduced risk of developing Activities of Daily Living disability (odds ratio=0.57, 95% confidence interval=0.35–0.93)(77) in Italian older persons. In conclusion, this mini-review provides a theoretical basis for the potential role of these emerging biomarkers on musculoskeletal health, with a particular focus on muscle mass and function. This could represent an interesting opportunity for the development of novel intervention strategies aimed at reducing muscle and functional decline with aging and their detrimental consequences.

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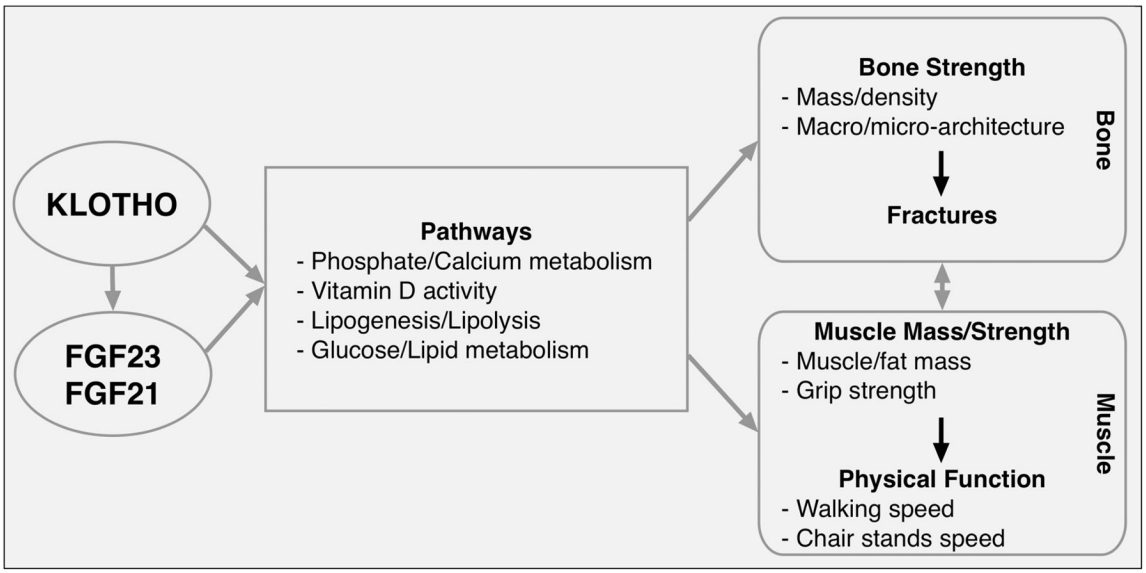

Figure 1.
Simplified conceptual framework