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CORONARY ARTERY DISEASE WITH PROSPECT OF FIBROBLAST GROWTH FACTOR-23 AND VARIOUS OTHER FACTORS -A NOVEL REVIEW PART III.

Medical Science

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ABSTRACT

In continuation of the second part, present review explains the relationship of CAD with FGF-23 levels in the blood. With a molecular weight of 32kda Fibroblast growth factor -23 (FGF-23), is a bone derived hormone mainly expressed in osteocytes. FGF-23 along with FGF-19 and FGF-21, is activated by using α-Klotho co-receptor complexes. Since FGF-23 is involved in phosphate homoeostasis changes in FGF-23 levels may also affect CAD.

KEYWORDS

Coronary Artery Disease, Fibroblast Growth Factor-23

INTRODUCTION

Increase in levels of FGF-23 in circulating blood can be an important marker in predicting the mortality and cardiovascular events in patients with chronic kidney disease [1-2]. Also, this relationship recently been observed in patients with normal renal function and recorded coronary disease in these patients [3]. Hence with the aid of coronary artery calcification (CAC) the risk of coronary atherosclerosis can be assessed. Coronary artery calcification (CAC) can also be associated with coronary artery disease even in asymptomatic individuals. whether FGF-23 provides a protective or as a detrimental role on vasculature [4, 5] is a matter of debate, since the clinical studies have shown discordant evidences.

FIBROBLAST GROWTH FACTOR-23(FGF-23)

FGF-23 is 32-kDa protein of 251 amino acids with 2 terminal region, where the FGF homology domain contains N-terminal region and C-terminal region with 71 amino acids that was initially discovered in embryonic mouse complementary DNA library [6]. it's a peptide bone derived hormone belong to FGFs family mainly secreted by osteocytes, in small quantities it's also expressed with the aid of osteoprogenitor cells, osteoblasts, cementoblasts, odontoblasts, and chondrocytes [7,8]. Its gene is located on chromosome 12 and is sorted along with FGF-19 and FGF-21 [9]. FGF-23 acts on kidneys where it decreases reabsorption of phosphate and promote excretion of it. Thus, acts as a phosphaturic effect, it also decreases expression of 1α-hydroxylase in proximal convoluted tubules, therefore decreasing production of active calciferol hormone [10]. Thus FGF-23 is additionally referred as Phosphatonin or Tumor-derived hypophosphatemia-inducing factor. The FGF-23 is regulated by 1, 25 dihydroxy vitamin D, parathormone, secreted klotho, glucocorticoids, calcium, phosphate and leptin[10]. Calcitriol in turn controls FGF23 production, creating a feedback loop [11].

The FGF group are further classified into 7 subgroups by phyletic and sequence locus analyses. These subgroups can be further divided on the basis of their mechanism of action into three groups, the intracellular subfamily, endocrine subfamily and canonical subfamily [6], where FGF-23 belongs to endocrine subfamily. This Endocrine subfamily function by reducing heparin-binding affinity and presence of a new COOH terminus that activates FGF receptor in absence of heparin [12], conformational change occurs mainly at the region of β10-β12 which contain the remnant for heparin affinity [13],weak binding prevents them from being taken in the extracellular matrix and so permits to function as endocrine and this additionally prevents direct interaction between endocrine FGFs FGFRs [14], this in turn require a cofactor to mediate their affects through FGFRs. The action of FGFs is determined on the expression of cofactor α- klotho. α-Klotho is a 130KDa single pass transmembrane protein [15] which helps in activation of FGF-23.

FGF-23 by Galnt3 is glycosylated. This glycosylation prevents FGF-23 proteolytic processing and allows FGF-23 secretion [16]. Any mutation of Galnt3 impairs secretion of FGF-23, resulting in faded serum FGF-23 levels and enhanced phosphate[17]. Missense mutations of FGF-23 leads to loss of function. Thus, mutations of FGF-23 disrupt the tertiary structure and is degraded [18]. This reduced FGF-23 signalling cause's metabolic disorders. Familial tumoral calcinosis (FTC) is characterized by high phosphate level and dystrophic calcification. Study show there's association between circulating FGF-23 and severity of CAD, [19,20] because of vascular calcification. It is also associated with obesity, bone mineral density and insulin sensitivity[21]. Since FGF-23 is inflammatory marker, thus in patients with normal renal function it is considered as a biomarker for decreased metabolic function [22].

Insulin activation induces stimulation of protein kinase B(PKB), serum- and glucocorticoid-inducible kinase isoforms, further resulting in the glycogen synthase kinase 3 suppression. Experiment revealed that as the sympathetic nervous system activity increases, glycogen synthase kinase was involved in the regulation of FGF-23 release [23]. Hu *et al.* found that increase in FGF--23 was associated with raise in insulin levels and insulin resistance, suggesting that hyperinsulinemia and insulin resistance might lead to the elevated levels of serum FGF-23 levels in diabetes population [24].

Vitamin D and FGF-23 are associated with cardiovascular disorder[25]. FGF-23 is a phosphaturic hormone and indirectly decreases Calcium level through its action on parathormone and vitamin D. FGF-23 is a major regulator of Calcium phosphate product that is usually monitored in chronic renal disease patients owed to predisposition to induce vascular calcification[26]. Serum levels of calcitriol raises when there is defect within the FGF-23 klotho system leading to dysregulation of expression of the enzymes action and inactivation of calcitriol in the kidney. Despite high levels of serum phosphate, calcium and Vitamin D, FGF-23 deficient mice show inappropriately renal expression of the Cyp27b1 gene that encodes 1α-hydroxylase, the catalyst that converts inactive vitamin D to active form [27].

They may also show inappropriate low renal expression of Cyp24 gene that encodes 24-hydroxlase, the enzyme that inactivates calcitriol. So, any defect in FGF-23 activity causes increased serum level of calcitriol due to increased synthesis and remittent inactivation. In contrast overexpression of FGF-23 decreases serum calcitriol level. Moreover, expression of FGF-23 is stimulated by calcitriol in bone. Thus FGF-23 could be target gene of Vitamin D. calcitriol binds with its high affinity nuclear Vitamin D receptor, this leads to formation of heterodimer between the ligand bound Vitamin D receptor and retinoid X receptor, which binds to vitamin D responsive elements in the FGF-23 gene promoter region and Trans-activates its expression[28,29]. In fact, the expression of FGF-23 in bone is enhanced on vitamin D administration. The increased FGF-23 decreases synthesis and promotes inactivation of calcitriol and closes a feedback loop in homeostasis of vitamin D. FGF-23 is a component of bone- kidney fgf-23 axis that maintains vitamin D homeostasis, because of defect in FGF-23 that disrupts this feedback loop and lead to high serum vitamin D levels. Since calcitriol synthesis takes place in proximal convoluted tubules, it is reasonable to speculate that FGF-23 binds to the FGF receptor complex expressed on the proximal convoluted tubular cells and activates FGF signalling pathway, which can cause down regulation of the Cyp27bi gene and up regulation of Cyp24 gene. The inhibitory effect of FGF-23 on expression and function of sodium-phosphate IIa and sodium-potassium IIc cotransporter may also

activate FGF signal in proximal convoluted tubules. The proximal tubular cells primarily express FGFR-3, these suggest that the ability of FGF-23 to regulate reabsorption of phosphate and Vitamin D is freelance of FGF signalling activation within the proximal convoluted tubules[30]. Vitamin D promotes dietary phosphate and calcium absorption from the intestine, thus increased Vitamin D level cause increase calcium and phosphate in FGF-23 deficient mice. Elevation of calcium and phosphate in the blood predisposition to ectopic calcification. Previous animal studies suggest increased Vitamin D causes vascular calcification in FGF-23 deficient mice. Vitamin D deficiency has been related with high blood pressure, coronary artery disease and stroke[31,32]. However, there is less data available regarding the possible influence of the relationship between these molecules on the prognosis of patients with CAD. Hence this review is an enlightens the relationship between circulating FGF-23 concentration, vitamin D and insulin level to the extent and severity of the coronary artery disease in individuals with and without obstructive atherosclerosis as may be determined by coronary angiography.

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