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Review

Fibroblast growth factor 21; review on its participation in vascular calcification pathology

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ABSTRACT

Vascular calcification (VC) is an independent cardiovascular event and also a complication commonly found in chronic kidney disease (CKD) and diabetic patients. The mechanisms underpinning pathophysiology of VC is yet to be fully understood. Nevertheless, certain processes are generally believed to participate in its onset and progression. VC pathology is characterized by disequilibrium in the amount of natural inhibitors and active inducers of VC process. The imbalance may favor ectopic deposition of calcium-phosphate in form of hydroxyapatite in media or intima tunica compartments of blood vessels. This eventually could trigger phenotypic switch of smooth muscle cells to osteoblasts related cells. Thus, VSMC phenotypic trans-differentiation is currently considered as one of the hallmarks of VC. At the moment, there is no approved treatment.

Fibroblast growth factors (FGFs) are a protein family that participates in varieties of biological processes. More recently, FGF21 seems to be gaining more attention with recent findings showing its anti-calcifying efficacy. In this review, the aim is to point out specific processes involved in VC and also to highlight the participation of FGF21 in the pathology of vascular calcification.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of mortality worldwide [1]. Vascular calcification (VC) is a contributor to cardiovascular mortality observed in end-stage kidney disease [2], metabolic syndrome and type 2 diabetes mellitus [3]. Moreover, VC is a pointer to onset of CVD, it is therefore used as a prognostic marker for predicting risk of CVD exposure [4]. VC was thought to be a passive process involving vascular ageing and degeneration. But at the moment, it is more considered to be an actively driven process [5].

The vasculature is composed of the vascular smooth muscle cells which dictate vascular tones of blood vessels [6]. Increased expression of smooth muscle cells' makers is key to maintaining the normal phenotype of the vasculature and thus, ensuring the arterial wall compliance [7].

The pathophysiology underpinning VC is not fully understood. It is considered as a multifactoral condition involving pathways that could favor ectopic calcium-phosphate deposition [8]. A significant breakthrough in vascular calcification research is the discovery that smooth muscles produce certain Vasopeptides that play calcification inhibitory roles [9,10]. Thus, deficiency in these natural inhibitors is known to be the initiating step in calcification pathology [11].

Molecular manipulation of these inhibitors in animal models suggest their active participations in calcification process [9,12,13]. On the other hand, certain bio-molecules are also known as calcification inducers. These inducers ensure initiation and progression of VC process. They include Bone morphogenic protein 2 (BMP2) [14,15], Tissue non specific alkaline phosphatase (TNAP) [16], Matrix metalloproteinases 2 and 9 (MMP2 and MMP9) [17,18].

The pathology of VC is an interplay between the active inhibitors

Abbreviations: VC, Vascular calcification; FGF21, Fibroblast growth factors 21; FGFR1, Fibroblast Growth Factor Receptor 1; VSMC, Vascular Smooth Muscle Cell; ECM, Extracellular Matrix; MMP, Matrix Metalloproteinase; TGFβ-1, Transforming Growth factor beta-1; SMAD2, Similar to mother against decapentaplegic homolog 2; BMP 2, Bone morphogenic proteins 2; CKD, Chronic kidney disease; RUNX2, Runt related transcription factor 2; PPi, Inorganic pyrophosphate; TNAP, Tissue Non-specific Alkaline Phosphatase; MGP, Matrix Gla protein; BGP, Beta-glycerophosphate; TCF4, Putative transcription factor 4; LRP, Low-density lipoprotein receptor-related protein; MAPK, Mitogen-activated protein kinases; ERK, Extracellular signal-regulated kinases; pAkt, Phosphorylated protein kinase B; PI3K, Phosphatidylinositol 3-kinase; CHOP, CCAAT-enhancer-binding protein homologous protein

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and inducers of VC. Imbalance may favor ectopic hydroxyapatite deposition and vascular smooth muscle cells phenotypic switch [19,20]. VC could be intima or media. They are morphologically different. Intima calcification is also referred to as Atherosclerosis which involves patchy deposition of lipids or cholesterol in intima layer of the arterial wall. Media calcification on the other hand, it is commonly known as arteriosclerosis. Its pathology includes the deposition of hydroxyapatite on the media segment of the arterial wall which could lead to arterial wall stiffness. Thus, reduced compliance [21–23].

Fibroblast growth factors are signaling proteins of about 22 family members. They are involved in various biological processes via fibroblast growth factor receptors and the co-receptor beta Klotho [24]. The family regulates processes such as arthritis [25], Inflammation [26] and Neurogenesis [27].

FGF21 is an essential class of FGF family but have not gained much attention in the past. Interestingly, FGF21 is recently coming to limelight. Serum concentration of FGF21 has a strong correlation with metabolic syndrome [28]. [29] Reported increased cardiac hypertrophy in FGF21 knockout mice which was reversed by exogenous administration of FGF21. Although the result might not have been consistent, it's expedient to fully understand the role of FGF21 in pathology of vascular calcification.

In this review, the aim is to highlight specific processes favoring VC pathology and also update knowledge on the participation of FGF21 in calcification process.

2. Processes favoring pathology of vascular calcification

Pathology of VC is not yet well understood due to its multifactoral pathology involving different signaling pathways. Nevertheless, certain processes are known to participate actively in the initiation and progression of VC. Its onset is more of an active process than being caused by traditional cardiovascular risk factors [30]. VC is an independent cardiovascular process and at the same time commonly found in end stage CKD and metabolic syndrome [31]. As earlier mentioned, genesis of VC process is the disequilibrium between endogenous inhibitors and inducers. However, there are other factors contributing to the onset of VC as an independent event or as a complication of CKD.

2.1. Disordered mineral metabolism

Mineral homeostasis is a hormone regulated interplay between organ systems, mainly the skeletal system, intestine, parathyroid gland and kidney [32]. Unregulated mineral metabolism is common in CKD resulting in mineral dysregulation. FGF23 increases during the course of CKD and as a result of this, Calcitrol synthesis declines. Decreased Calcitrol synthesis raises the parathyroid hormone level. This then induces calcium and phosphorus release. In CKD, there is decline in glomerular filtration rate. Thus, excessive serum accumulation of calcium, phosphate and parathyroid hormone; risk factors associated with onset of vascular calcification in CKD [33].

Hyperphosphatemia is a unique predisposing factor to VC due to its multifactoral involvement in VC pathology [34]. Type III sodium dependent phosphate co-transporter (Pit-1) participates actively in phosphate metabolism. This makes it a significant player in calcification pathology. Over expression of Pit-1 aids the influx of phosphate from the extracellular into the intracellular compartment of smooth muscle. Therefore translating to muscle calcification and phenotypic trans-differentiation in response to increased phosphate level [35].

Nutrients also influence homeostasis maintenance. Potassium itself is a mineral supplement that helps in regulating fluid and mineral balance. Increased interstitial potassium ion is associated with vasodilation and proper blood flow [36]. It has been experimentally validated that reduced potassium intake promotes vascular calcification in Apolipoprotein E deficient mouse [37]. Unfortunately, patients with CKD have difficulty in handling a severe amount of potassium due to decreased glomerular filtration rate. When potassium level is lower enough to trigger hypokalemia, it induces vascular and cardiac damage [38].

2.2. Uremia accumulation

The Kidney and heart works in concert inform of biological communication between the compartments. There is an overlap that exists between kidney and the heart functions. Impairment of normal kidney function is an independent risk factor for onset of cardiovascular diseases. On the other hand, impairment of heart function is also a critical risk factor to pathology of renal dysfunction. These are concepts referred to as renocardiac and cardiorenal syndrome respectively [39,40]. To buttress this concept of functional crosstalk, adenine model of renal failure is used to study vascular calcification as a complication of CKD [41]. The reduced glomerular filtration rate favors accumulation of uremic toxin. This increases the activity of renin angiotensin system with capability to initiate arterial remodeling and stiffening [42]. Uremia increases level of reactive oxygen species, promotes vasoconstriction, remodeling and reduced vascular compliance [43]. Clinically, positive correlation exists between aortic stiffening and uremia [44].

2.3. Inhibitors and drivers imbalance

Disequilibrium between calcification inhibitors and drivers is considered a critical step in VC pathology. The imbalance favors hydroxyapatite's deposition which serves as template for ectopic mineralization thus, microenvironment needed to trigger trans-differentiation of smooth muscle cell is established [45]. Such inhibitors of VC include MGP, Fetuin-A, inorganic pyrophosphate, osteoprotegerin and alkaline phosphatase [12] [46] [47].

Bone morphogenic proteins 2 (BMP2) is an active inducer of vascular calcification [48] which enhances phosphate influx into the Smooth muscle cells via type III sodium-dependent phosphate co-transporter in other to induce phenotypic trans-differentiation [49]. MGP is the first inhibitor of calcification to be identified with the ability to bind BMP2 thereby preventing SMAD2 signaling pathway; a major route through which BMP2 is signaled [50]. Serum level of calcification inhibitors in CKD patients may give an insight into VC pathogenesis [9]. It is worthy of note that reports on exact roles of different calcification inhibitors have generated discordance. This is not in anyway disputing the validity of any report as difference maybe a reflection of different experimental models or origin of materials employed in their investigations (Figs. 1–3, Table 1)

2.4. Extracellular matrix degradation

The arterial wall is made up of extracellular matrix which is directly involved in maintaining vessel wall integrity thus, dictates mechanical properties [51]. Structurally, Extracellular matrix (ECM) is composed of elastin, collagen, proteoglycans, and structural glycoprotein. The ratio of collagen to elastin is a model used to infer vascular stenosis. During vascular disease development, ECM is degraded by the enzymatic activity of matrix metalloproteinases (MMPs). Activity of these ECM degradative enzymes in the absence of their inhibitors is a threat to vascular integrity. Once the vascular integrity is compromised, it gives room to excessive ECM deposition within the neointima in other to promote nucleation serving as template for mineralization [52] and also, pro-inflammatory macrophage infiltration into the vasculature [53] [54] [55]. MMPs have been said to participate in calcification. Neal et al. reported that inhibition of MMP-2 and 9 may be a possible therapeutic target for arterial calcification [17]. This report is in line with [56] where knockdown of MMP 2 and 9 blocked calcification of VSMC. Interestingly in this same report, recombinant MMP 2 and 9 aggravated induced calcification. Blockage of MMP 2 and 9 activity is a calcification preventive strategy [17] [56]. In addition, MMP12 is also

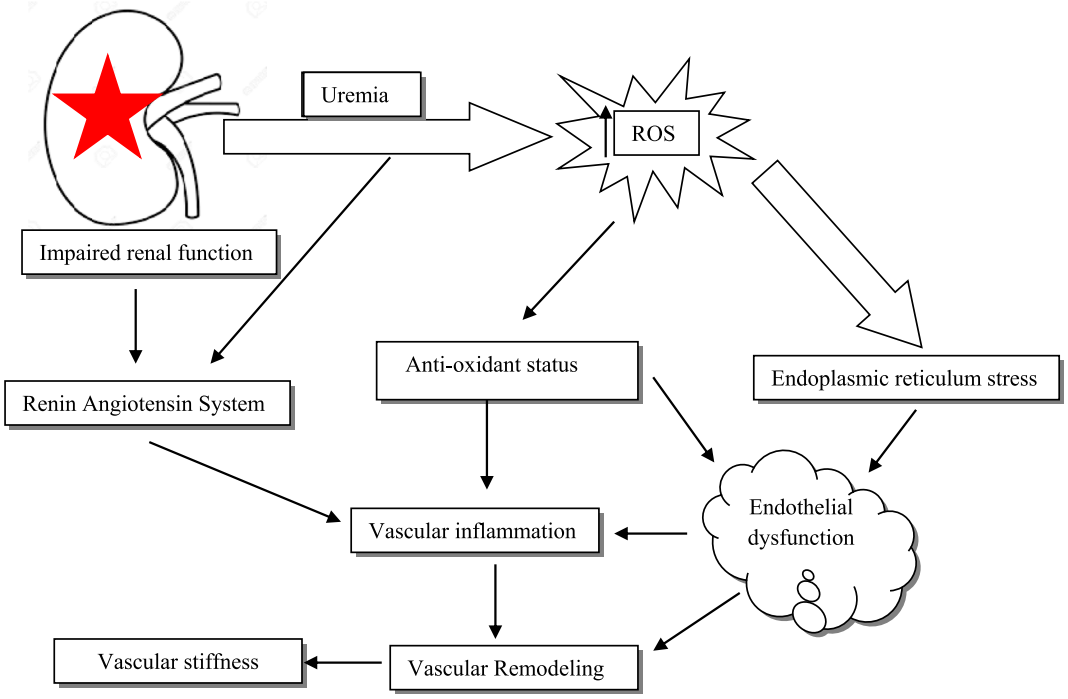

Fig. 1. Sketch showing the involvement of uremia in vascular stiffness

considered as a potent elastase playing pathogenic role in acute and chronic arterial wall stiffness [57]. MMP12 is associated with atherosclerotic plaque stability [58]. An interesting study by [59] found MMP 2, 9 and 12 to be upregulated in angiotensin II-induced abdominal aneurysm in mice. Using RXP470.1; a potent inhibitor of MMP12, [60] experimentally proved that selective inhibition of MMP12 is a possible anti-calcification strategy. These reports validate the involvement of MMPs in pathology of vascular calcification.

2.5. Vascular smooth muscle phenotypic switch

The embryonic vascular system development involves recruitment of vascular smooth muscle cells to form a principal component of blood vessels. Smooth muscle cells (SMCs) majorly maintain vascular tones conferring the ability to respond to external stimuli without affecting the primary structure [61]. Because SMCs and osteoblastic cells have common mesenchyma origin, SMCs have the potential to switch between the normal and its osteogenic counterpart. Phenotypic transdifferentiation of vascular smooth muscle cells (VSMC) to osteoblasts related phenotype reduces the expression of proteins linked with smooth muscle lineage and upregulates osteoblasts transcription factors.

These osteogenic transcription factors such as Cbfa1/Runx2 could then activate BMP, Notch, Wnt and other signaling pathways to over express bone-related proteins [52,62] [63,64]. Wnt/β-catenin signaling pathway has been reported as a pathway that is involved in progression of atherosclerosis [65]. This happens when Wnt protein activates the Frizzle receptor and its co-receptor LRP5/6. It eventually ensures intracellular translocation of β-catenin to form transcription complex [66]. Interestingly, Wnt/β-catenin was found to be over-expressed in Angiotensin II induced mouse model of heart failure. Its inhibition lowered blood pressure, cardiac hypertrophy and fibrosis [67].

The phenomenon of VSMC phenotypic switch is one of the most reported concepts in vascular biology and discovery of novel compounds or bimolecular with ability to inhibibit this process may be the long-awaited therapeutic headway.

3. Participation of FGF-21 in VC

FGF21 is involved in multiple physiological processes with the ability to serve as a paracrine or autocrine peptide [68]. FGF21 is considered to posses cardiac anti-inflammatory activity and prevents cardiac remodeling [69,70]. FGF21 involvement in vascular calcification is multifaceted. One of the latest research on understanding the role played by FGF21 in VC showed that exogenous administration of FGF21 could be promising therapeutic intervention [26]. Also, FGF21 had been observed to ameliorate CKD in calcification [71].

Yuchen Shi et al. in his recent publication reported exogenous

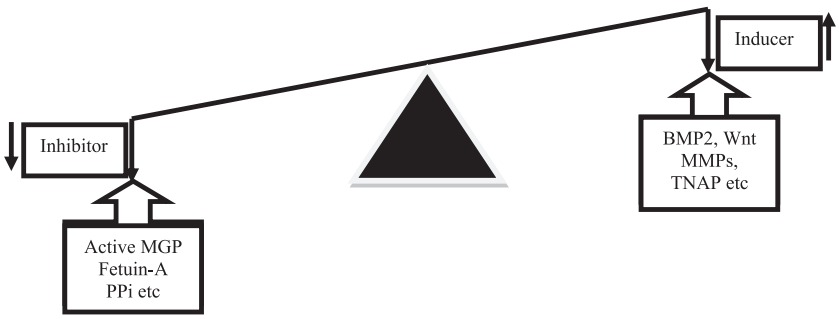

Fig. 2. Sketch showing imbalanced inhibitors to inducers ratio as an initiation factor for vascular calcification.

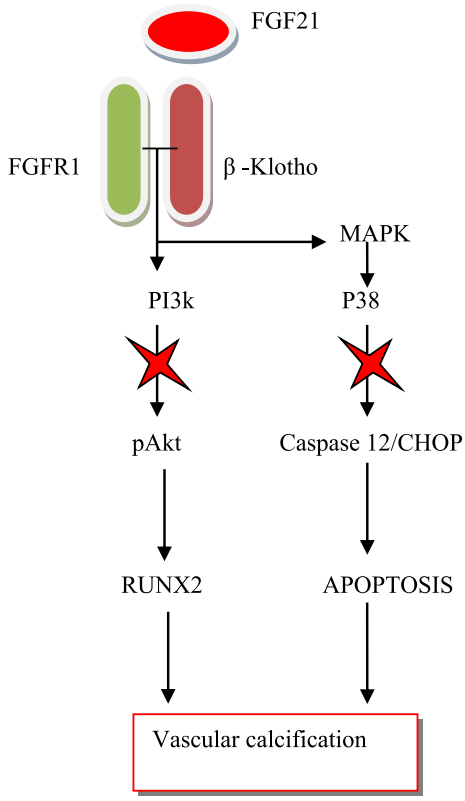

Fig. 3. FGF21 anti-calcifying molecular mechanisms of action.

administration of 70 μg/kg/day FGF21 using an osmotic pump infused in to VDN rats ameliorated aortic calcium deposition, aortic apoptosis and also reduced the hemodynamic alterations commonly found in VDN model of VC [26] with a similar result shown in [72]. In medium induced calcification In vitro model, published data showed In vitro bioactivity of recombinant FGF21 attenuated mineralization, down-regulated the expression of osteoblast related genes with reversal in the presence of FGF21 inhibitor [73].

As discussed previously, deposition of ECM as a process which favors initiation of calcification by serving as nucleation site. Transforming growth factor β-1 (TGFβ-1) is a significant pathway that underpins ECM deposition. This pathway controls SMAD2 dependent calcification mechanism in which its inhibition is a possible mechanism in calcification inhibition strategy. FGF21 shut-down enhances extracellular matrix deposit leading to organ hypertrophy [74]. In FGF21 knockout mice model, FGF21 deletion led to acceleration of diabetes-induced aortic aneurysm characterized by wall thickening via fibrosis and also reduced aortic pro-inflammatory macrophage infiltration [75]. FGF21 is already reported to have the potency to modulate BMP2/SMAD signaling pathway to attenuate beta-glycerophosphate induced VSMC mineralization [73]. In human subjects, serum level of FGF21 gave a positive correlation with carotid atherosclerosis in female subjects showing that it could be biomarker or therapeutic target [76] which is almost the same as the report of Zhang et al. on Chinese subjects [77].

3.1. Anti-calcifying molecular mechanisms FGF21

FGF21 is a key regulatory protein with diverse transcriptional activities. FGF21 acts via the FGFR1 which works in concert with its co-receptor (β-Klotho) to activate FGFR1/β-Klotho complex [79]. Mineralization of VSMC cultured in a calcification medium was inhibited by FGF21 in a dose dependent manner through the activation of FGF21/FGFR1/3/β-Klotho/P38/MAPK/RUNX-2 signaling pathway [73]. Yuchen Shi et al. profiled the pharmacological involvement of FGF21 as an exogenous protein using vitamin D plus nicotine model of vascular calcification. His team reported ability of FGF21 as an anti-calcifying agent acting through endoplasmic reticulum stress inhibition. In addition, FGF21 inhibited CHOP and Caspase 12- induced smooth muscle apoptosis; a key factor favoring vascular calcification process [26].

FGF21 also plays a vital role in browning of white adipose tissue. Moreover, activation of browning process increases uncoupling proteins needed for thermogenesis [80]. It activates perixosome proliferator-activated receptor α (PPARα) to enhance lipid metabolism [69]. This prevents accumulation of excessive lipids in walls of blood vessel as seen in atherosclerosis [81].

4. Possible setbacks in FGF21 efficacy profiling and future perspectives

Participation of FGF21 has not been fully understood till date. Its role in serving as a possible therapeutic target in vascular calcification has been promising so far. Nevertheless, it is necessary to ascertain the bioactivity of FGF21 in various models of calcification to make necessary comparisons. Currently, there are no robust reports on FGF21 efficacy, especially in different models to ensure validity and reproducibility of results without any conflict of interest.

Discordance in reports on efficacy of FGF21 exists as certain researchers have reported elevation of serum FGF21 level in cardiovascular risk factors [82]. In this case, endogenous FGF21 level could increase as an anti-inflammatory response to vascular inflammation. Therefore, there should be clear distinction between the physiological and therapeutic roles of FGF21.

This in anyway does not dispute the efficacy of FGF21. The discordance in results could due to difference in experimental models, dose and route of FGF21 administration, source of experimental materials, difference in cell or animal species used and possibly, method of data analysis used.

It is high time female counterparts of experimental animals are given more consideration for preliminary exploration to prevent gender bias. This is important as hormonal difference could influence results. Interestingly, [76,77] Showed positive correlation in the serum level of FGF21 in female subjects with no correlation in the male subjects. To buttress this view on the need for gender consideration, available evidences support the concept of sexual hormonal protection against calcification pathology [83,84].

5. Conclusion

Based on reports we could lay our hands on so far, it is evident that

Table 1
FGF21 participation in vascular calcification.

Author	Effect	Model	Ref
Shi et al.	Amelioration of aortic apoptosis	Vitamin D3 and Nicotine induced VC	[26]
Cao et al.	Modulation of BMP2/SMAD pathway	BGP induced mineralization in VSMC	[73]
Yan et al.	Reversal of diabetic aortic collagen deposit	FGF21 Knockout diabetic mice model	[75]
Shi et al.	Down-regulation of aortic injury	Vitamin D3 and Nicotine induced VC	[71]
Cao et al.	Down-regulation of osteoblast related proteins	VSMC culture in calcification medium	[78]

more investigation is required to ascertain the efficacy of FGF21 as a therapeutic inhibitor of VC. In summary, distinction between the physiological and the therapeutic role of FGF21 would be a necessity. Interestingly, different models are already established which are explorable to study the pathology of VC and efficacy of bioactive compounds in this respect. Therefore, more vascular calcification experimental models should be employed in other to ascertain the anti-calcifying pharmacological claims of FGF21.

Author's contribution

Olapoju Samuel searched the literature and drafted the review while Adejobi Oluwaniyi Isaiah and Le Thi Xoan contributed to final editing and revision of the manuscript.

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Declaration of Competing Interest

The authors declared no conflict of interest.

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