FETUIN A AS A THRESHOLD CONCEPT IN THE MINERAL TRAFFICKING AND DEPOSITION IN CASE OF CHRONIC KIDNEY DISEASES

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ABSTRACT

Calcification is a common problem in many pathologic and physiologic conditions, such as ageing, dyslipidemia, diabetes, genetic disorders, and illnesses with abnormalities in calcium metabolism. Vascular calcification is more prevalent, occurs early, and adds to the significantly higher cardiovascular risk in people with chronic kidney illnesses. One of the calcification inhibitors, fetuin A, has a reduced amount in CKD individuals. Therefore, in term of appreciated the importance of fetuin A as a circulating glycoprotein, in preventing ectopic calcium phosphate mineralisation, this review would aim to highlight the independent Fetuin A role associated factor to the risk of vascular inflammation.

Keywords: vascular inflammation, Vascular calcification, Fetuin A, chronic kidney disease

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INTRODUCTION:

(FA) is a negative severe phase glycoprotein that synthesis and secreted from the liver. In 1944 FA was determined by Kai Pedersen because of its behaviour in the ultracentrifuge as reported by (1). Between the years 1950s to 1954s, improvement fractionation methods were reported by Harold Deutsch (2), which organized a new purified fraction of FA that was more uniform than Pedersen' s (3), which was defined FA in human foetal blood. In 1960, Heremans and Schmidt defined α 2-HSG for the first time (4), (5). The protein was illustrated as an atomic mass equal to 49-60 KD, human plasma glycoprotein secreted into the circulation by the hepatocytes at a concentration of (0.4-0.85) gram /Litre. The name of fetuin (Latin; fetus) was proposed due to the prevailing component in the foetal serum, quickly declined, and lastly missing in the new-born calf (6).

(VC) or Vascular calcification is an ongoing process, which is prevalent in both CKD cases and the overall elderly. Researchers have shown that the degree and histoanatomic form of arterial calcification seem to be indicators of vascular fatalities in the future. VSMCs dedifferentiation into osteoblast-like tissues may be the first stage of arteries calcification (7). Studies conducted throughout vitro indicate that uremic toxicity and increased phosphorus may both cause differentiation. Such "osteoblast-like cells" can create proteins for bone, allowing them to control calcification. High calcium phosphorus production from

aberrant bone, extra hyperparathyroidism, as well as high calcium consumption may speed up the procedure already when mineralization has begun. Even though medical understanding of the numerous factors as well as molecular mechanisms in vascular calcification in kidney disease patients has significantly improved as a consequence of research efforts over the past ten years, so several questions remain because scientists no longer agree that "vascular calcification in CKD" is a passive process brought on by an increased calcium-phosphate (8).

Clinically substantial reductions in fetuin-A levels are seen in dialysis patients receiving calcimimetic treatment for secondary hyperparathyroidism. Moreover, in individuals with intractable renal hyperparathyroidism, blood fetuin-A levels clearly rose after parathyroidectomy. Treatment of glucose intolerance and a rise in insulin production were the results of medical therapy for hyperparathyroidism in CKD cases. PTH did not alter the tissue's receptivity to insulin in an animal model of CKD, and the stabilization of glucose metabolism in the lack of PTH was brought on by higher insulin secretion (9). Issues of mineral metabolism (abnormal amounts of blood calcium and phosphate), vascular calcification, and abnormal bone (kidney osteodystrophy) seem to be linked in CKD patients. Most people with CKD advance both parathyroid hormone (PTH) and phosphate levels (10).

A crucial modulator of the mineralization of the extracellular matrix is fetuin A (FA). Higher molecular weight "colloidal protein-mineral" compounds known as calciprotein particles are formed and stabilized in part by fetuin A. regardless of the lack of renal failure, inflammation seems to be linked to mineral distress (11).

FA was said to act as a systemic arterial calcification regulator. Amounts of blood FA can be gathered by VSMCs within internal membrane-bound matrix vesicles. These vesicles, as was previously mentioned, are discharged from VSMCs and serve as the nidus for mineral nucleation. These liberated vesicles lack normal "membrane-bound matrix vesicles'" capacity to make hydroxyapatite crystals and are rich in FA. However, extracellular P does not stimulate the absorption of FA by VSMCs like extracellular Ca does. This FA uptake, which is facilitated by "annexin Ca channel activity" and contributes to its inhibitory function in VSMC mineralization, raises the quantity of Ca that enters VSMCs. Vascular calcium causes cardiac ischemia and failure as well as the loss of arterial flexibility, an increase in pulse wave velocity, the formation of left ventricle hypertrophy, and a decline in coronary artery perfusion. The overwhelming majority of CKD cases have these changes as their primary reasons of mortality (12).

In terms of inhibitory variables, the reduced amount of FA plays a significant part in the development of vascular calcification. FA, a versatile protein, could prevent the creation of 50% of calcium phosphate ions, which is a key factor in vascular calcification (13). Various organs calcify in FA defective rodents, but noticeably not the vasculature. The security provided by an intact endothelium, that is seriously weakened in the presence of atherosclerosis, could be the cause of the lack of vascular calcification. Created "fetuin-A/apolipoprotein E (ApoE)-deficient" animals were contrasted to ApoE-deficient as well as wild-type mice regarding atheroma development and additional osseous calcification in order to verify this theory. The degree of aortic lipid accumulation, neointima development, and coronary sclerosis seen with ApoE deficiency was not affected by fetuin-A insufficiency, but the interaction of fetuin-A deficiency, hyperphosphatemia, and CKD resulted in a 15-fold rise in vascular calcification (14).

Almost solely, instead of medial, calcification of atheromatous areas, fetal-A deficit encouraged it. Even in the presence of atherosclerosis, FA prevents pathologic calcification in the soft tissue and arteries. By quickly forming "soluble colloidal FA calcium phosphate" compounds, also referred as

calcipotriene particles, the suppression is accomplished (CPPs), It is enticing to assume that the vicious circle of phagocytosis, apoptosis, and ongoing accumulation of calcified detritus in the lack of FA may induce apoptosis in macrophages just like in smooth muscle cells. Vascular calcification (VC), which has negative clinical effects in those who have persistent kidney disease, is much more common than usual due to problems of bone and mineral metabolism; however, the pathogenesis of VC is not completely known (15).

Importance of Study FA and Knowledge Gap:

Depending on the vessel type (large elastic versus smaller muscle type artery) and the central versus distant locations of the arterial branch, calcification may vary. Determining the difference among intimal and medial calcification is also important for the clinical appearance, therapy, and prognosis since each variety has unique clinical effects, according to clinical research. Animal models used in in vivo research gave proof that vascular calcification and atherosclerosis share similar path mechanisms. Cases with CKD have extremely high levels of atherosclerosis as well as arteriosclerosis, and the results (cardiovascular events) pose a significant therapeutic issue for such patients (16). Experimental results supported an increase of atherosclerosis, that is defined by median and intimal calcification and appears to begin very early in the development of CKD. As for media calcification by now evident in early phases of CKD, the kinds of calcifications could develop independently of one another and vary in pathogenesis and clinical result. Although various kinds of calcifications may frequently be found in severe stages of CKD (17).

Based on the location, connection with plaque, as well as method of development, four kinds of calcification could be differentiated: Three morphologic forms of actively controlled calcification (occurring in the lack of elevated Ca/P levels) and dystrophic (passive) calcification, a weak form of pervasive nonspecific organ as well as soft tissue calcification, are also mentioned. heart valve calcification, both calcification in the blood vessel medial layers caused by elastin fibre mineralization, VSMC degradation, as well as upregulation of osteogenic programs just like in chronic kidney disease (CKD) or diabetes, and calcification in the arterial intimal layers associated with macrophages, VSMC, lipids as in classical atherosclerosis. This theory states that instead of a passive Ca inflow into the arterial wall or media because of Ca flow or tissue degeneration, the three newest types of vascular calcification are now considered to be an actively regulated process.

Soft tissue calcium, atherosclerotic “i.e., intimal or plaque calcification”, as well as medial calcification, as demonstrated by Abedin et al., have some variations but also prominent parallels. While all three kinds share cytokine release and inflammation, Sub-intimal lipid build up and macrophage aggregation are features of intimal calcification. In contrast, it is believed that in “medial calcification, metabolite-induced (toxic) vascular” changes in the absence of lipid deposits particularly cause the increase in the levels of osteogenic regulatory genes, which then cause mesenchymal cells to differentiate into osteogenic forms, which lead to the formation of matrix mineralization, cartilage, bone (19). Additionally, Lee et al. noted how vascular calcification and bone formation both have closely controlled processes for mineral deposition as well as mineral resorption. It should be noted that medial calcium of peripheral arteries frequently exhibits osteogenic differentiation with metaplastic bone formation, so although intimal calcification infrequently exhibits this phenomenon (20).

Therefore, as a knowledge deficit, a better grasp of the mechanism through which vascular calcification happens ought to give a chance of creating therapeutic methods to stop this process. Also, it might be a good idea to look for some relation between FA level and other marked biochemical changes in serum

patients of end stage CKD. Lastly, a full understanding of the prevention and/or reversal of the life-limiting calcifying vasculopathies seen in CKD patients are really needs for such cases.

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