Vascular Calcification in Diabetes: Mechanisms and Implications

Randa Salam[1],*Hemmat E .El Haddad* [2]

Abstract

Diabetes is associated with an increased prevalence of atherosclerotic vascular disease and cardiovascular mortality. In diabetic patients, medial calcification appears to be a strong independent predictor of cardiovascular mortality; it occurs particularly in those with neuropathy. Recent evidence suggests that medial calcification in diabetes is an active, cell mediated process, similar to that observed in patients with end-stage renal disease (ESRD), in which vascular smooth muscle cells (VSMCs) express a number of bone matrix proteins that act to either facilitate or regulate the calcification process. Several bone-associated proteins (eg, osteopontin, bone sialoprotein, alkaline phosphatase, type I collagen, osteocalcin) have been demonstrated in histologic sections of vessels obtained from patients with diabetes or ESRD. In in vitro experiments, high glucose induced cell proliferation and expression of osteopontin in cultured VSMCs. Hypoxia had additive effects of hyperglycemia on VSMCs. In addition, uremic serum upregulates osteoblast transcription factor Cbfa1 and osteopontin expression in cultured VSMCs. The pathogenesis of vascular calcification in diabetes is not completely understood, although high glucose and other potential factors may play an important role by transforming VSMCs into osteoblast-like cells.

Further understanding of the mechanism by which diabetes induces this complication is needed to design effective therapeutic strategies to intervene with this process.

Introduction

Vascular calcification (VC) is an important component of vasculopathy in type 2 diabetes mellitus (DM), leading to coronary artery disease (CAD) and peripheral vascular disease (PVD), therefore most causes of mortality and morbidity, respectively, in these subjects .
Although, chronic hyperglycaemia is the primary factor for initiation of vascular damage, the progression of vascular disease ,may be due to several associated factors downstream such as enhanced oxidative stress (OS) (1)
The increased OS in DM may be due to impaired antioxidant response and/or excessive production of free radicals in close approximation to the vessel wall [3].Persistent OS is detrimental to the endothelial lining of the vessel wall and has been demonstrated to promote endothelial cell dysfunction and apoptosis (2)
Endothelial cell dysfunction is a major intermediate event in the vascular pathology between OS and progressive vascular disease such as atherosclerosis and VC of the intimal layer (atherosclerotic calcification) and medial arterial calcification (MAC).
Chronic OS manifests its effects by promotion of endothelial cell dysfunction, modulation of calcifying vascular smooth muscle cells (VSMC) and influencing osteogenic transcription factors in the vessel wall (3)

Xanthine Oxidase and Oxidative Stress

Xanthine oxidase system is one of the major sources of reactive oxygen species, which includes free radicals such as superoxide (*O2-), hydroxyl (*OH) and non–radical molecules such as hydrogen peroxide (H2O2)(Fig 1) (4)
The superoxide (*O2-) generated by xanthine oxidase may react with nitric oxide (NO) in the vascular lumen to produce reactive nitrogen species - peroxynitrite (ONOO-), a highly reactive oxidant
Chronic hyperglycaemia-induced excess formation of peroxynitrite plays a major role in the pathogenesis of endothelial cell dysfunction and vascular damage(4)
Xanthine oxidase has been reported to be an important source of free radicals in human cultured aortic endothelial cells .Subjects with type 2 DM have been found to have significantly high levels of xanthine oxidase as compared to healthy controls .(5)

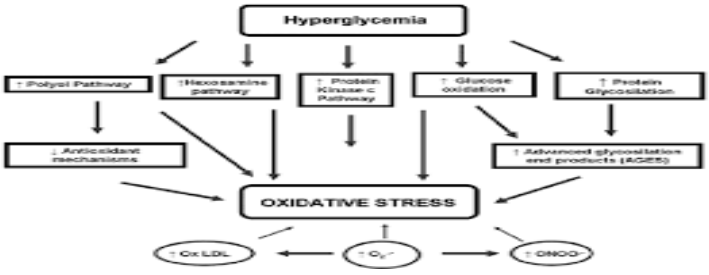

Figure 1: Generation of Oxidative stress in Diabetes Mellitus
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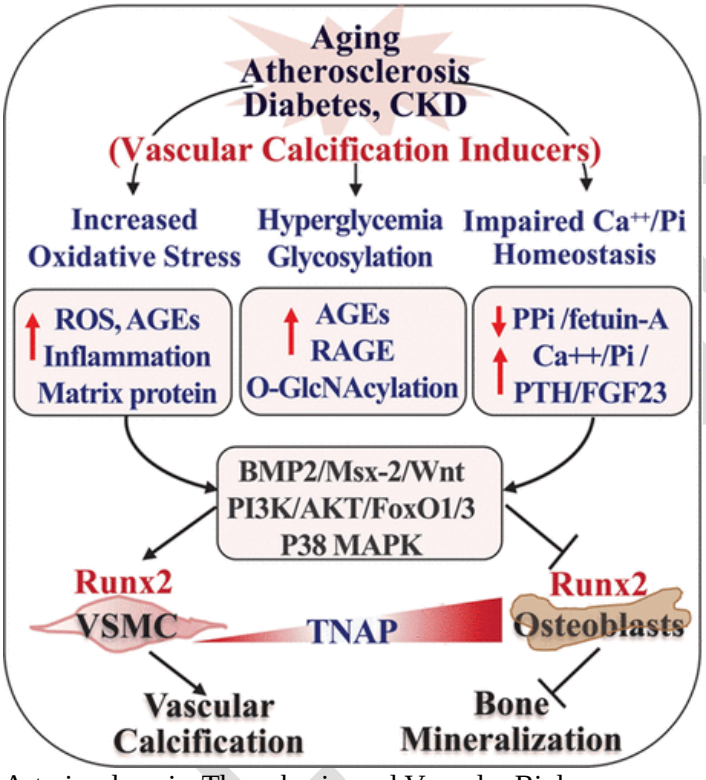
Oxidative Stress and Vascular Calcification

Enhanced OS plays a key role in the initiation and progression of vascular damage from endothelial cell dysfunction to atherosclerosis and finally VC .
MAC, the characteristic calcification in subjects with type 2 DM leads to compromised vessel compliance, as

a result of reduced elasticity (4) Traditionally, MAC has been considered as a benign process, usually related to the ageing process, however recent studies have deciphered this as a slow but dynamic process of vascular mineralization, with involvement and contribution from several cell types such as the endothelium, inflammatory cells and vascular smooth muscle cells (VSMC) amongst others, leading to significant cardiovascular functional compromise (6).
The manifestation and progression of MAC on the background of progressive OS is primarily an imbalance between inhibitors of VC in the vascular milieu such as inorganic pyrophosphate, matrix Gla protein, Fetuin A, Osteopontin and Osteoprotegerin, and the major promoters of VC such as endothelin-1, alkaline phosphatase, bone morphogenetic protein (BMP)-2, BMP-4, transforming growth
factor (TGF-β) and receptor activator of nuclear factor kappa β ligand (RANKL), favoring the latter (Figure 2) (6)



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The pathogenesis of VC in DM is multifactorial with different distinct processes working in a disconcerted manner as a result of complex metabolic, cytokine, inflammatory and ageing factors [4].
Chronic hyperglycaemia, on its own, may promote apoptosis of vascular cells (endothelial cells and VSMC) and in conjunction with increased oxidative stress, the impact may be enhanced (7) The apoptosis of the vascular cells may provide a trigger for TNF- α stimulation, which induces BMP-2 secretion from the remaining vascular cells (6)
BMP-2 is known to activate the homeobox homolog (Msx2) and Wnt signalling pathways in the vasa-vasorum, the concentric network of blood supply to the large arteries (7) These pathways promote the process and promoters of mineralisation in the vessel wall, by induction of osteogenic enzymes and matrix proteins at the site of activation, leading to MAC (8)
These pathways may be fuelled by progressive oxidative stress, which may facilitate enhanced progression of VC in subjects with DM (7)

Diabetic complication in relation to vascular calcification
medial artery calcification (MAC)is frequently observed in patients with diabetes and is associated with increased risk of n MAC tends to be concentric and symmetrical, and is a common feature of more distal arteries in diabetes nephropathy, retinopathy, major amputation, coronary artery disease and all-cause mortality (2,3)
Arterial calcification was noted in the feet of 15 of 20 patients with severe diabetic neuropathy (6)and was greater in patients with neuropathy than in controls (6). Neuropathy was also more prevalent in a Veterans Administration population with arterial calcification than in those without (7) Psyrogiannis and colleagues reported that calcification was present in 40% of people whose diabetes was complicated by neuropathy [7]. Arterial calcification is also increased in other conditions associated with DSN, although not to as great an extent as in diabetes.
The assessment of suspected coronary heart disease is more challenging in diabetic patients because of the atypical nature or absence of chest pain symptoms, more frequent inability to perform an exercise tests and less reliable stress imaging in the presence of obesity or multivessel disease (8). Moreover, among the patients referred after a non-conclusive stress test, diabetic patients were overrepresented. CT coronary angiography is considered complementary to stress testing, and for the mentioned reasons may be particularly useful in diabetic patients. While it lacks the diagnostic and prognostic value of the aerobic performance, it adds value in terms of (non-obstructive) plaque imaging. However, the higher calcium may complicate severity assessment of individual lesions.(9)
Since calcium deposition is related to the presence of atherosclerosis, coronary calcifications serve as a direct marker for CAD, and more severe plaques tend to have a greater amount of calcium(10)
Coronary artery calcification (CAC) is an independent risk factor of cardiovascular disease (CVD) regardless of CKD status, and the CAC score (CACS) may have clinical implications beyond an increased CVD risk. In a prospective cohort study from 1936 patients with

CKD in South Korea, higher CACS (1–100 AU and >100 AU) was associated with an increased risk of CKD progression (1.29-fold and 1.42-fold, respectively) compared with a CACS of 0. This association was consistent even after adjustment of nonfatal cardiovascular events being treated as a time-varying covariate. Moreover, the slope of eGFR decline was significantly greater in patients with higher CACS. These findings suggest that CACS may represent potential risk of CKD progression and high odds for adverse CVD (11) (Fig 3)

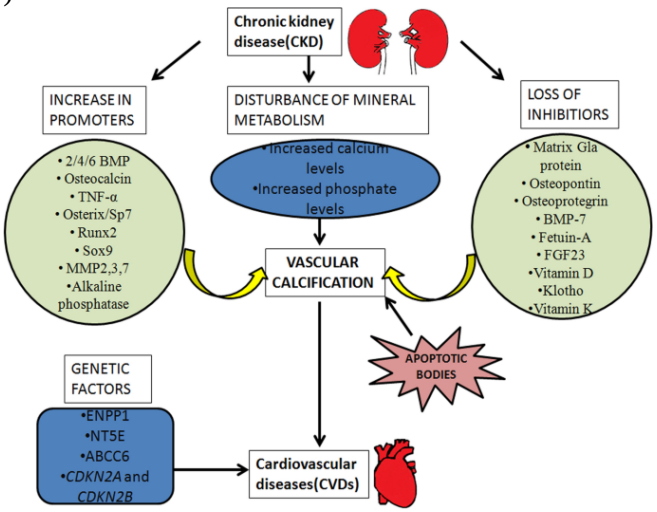

Fig 3:Overview of the influence of chronic kidney disease on various factors as key drivers of vascular calcification and its impact on cardiovascular diseases Update on vascular calcification and potential therapeutics https://link.springer.com/article/10.1007/s11033-020-06086-y

Measurement of vascular calcification

The evaluation of therapies for vascular calcification is problematic because of the lack of good methods to quantify it. The sensitivity of the various imaging modalities that have been used is unknown and the precision can be poor. Computed tomography of the aorta or coronary arteries is commonly used and is the only modality that can yield truly quantitative results, but different scoring systems can yield different results.(12)
In addition, the progression of vascular calcification is quite variable and has a much skewed distribution so that large numbers of patients are required and statistical analyses are not straightforward. Lastly, none of the methods can reliably distinguish between atherosclerotic and medial calcification and, therefore, measure the combined changes in two different pathophysiological processes. Calcification of coronary arteries, the site most commonly studied, is mostly atherosclerotic in ESRD patients, and any changes detected could be due to progression or regression of atherosclerosis rather than to changes in calcification.(13)

Therapeutic strategies

Unfortunately, till date, there is no comprehensive treatment which can cure or reverse vascular calcification in patients with CKD. The management of vascular calcification is based upon modulation of the key regulators of vascular calcification. Mainly, these include reduction of calcium-phosphorus complex precipitation by using phosphate binder, calcimimetics ,vitamin D , bisphosphonates ,vitamin K1, K2 However, the majority of these treatment options are under clinical investigation. Most common endogenous calcification inhibitors include fetuin-A, matrix Gla protein and pyrophosphates. However, these drugs have yet to prove their efficacy in patients with cardiovascular diseases.(14,15,16,17)

Conclusion

Subjects with type 2 DM harbor a great burden of vascular disease resulting in increased risk of cardiovascular and peripheral vascular disease in these subjects as compared to the rest of the population. Enhanced oxidative stress as a result of complex, metabolic, cytokine,inflammatory and ageing factors, on the background of chronic hyperglycaemia, predisposes these subjects to increased risk of vascular damage leading to atherosclerosis and vascular calcification

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1. *Faculty of Medicine, Internal Medicine, Endocrinology Department Cairo University*
2. *Faculty of Medicine, Internal Medicine, Endocrinology Department Cairo University*