kidney and dialysis

MDPI

Review

Vascular Calcification in Diabetic Kidney Disease

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Abstract: The pathogenesis of vascular calcification (VC) in diabetes mellitus (DM) has not been completely elucidated. VC often occur in patients with DM and chronic kidney disease (CKD). The incidence of VC in diabetic patients is more frequent than in nondiabetic patients, which is an important cause of cardiovascular (CV) morbidity and mortality. VC is a progressive transformation of the vascular wall; it results from an active and complex phenomenon affecting particularly the vascular smooth muscle cells (VSMCs). It leads to a change in the phenotype of the VSMCs towards an osteoblastic-like phenotype. DM is associated with specific risk factors in addition to hyperglycemia, such as increased oxidative stress, proinflammatory state, hypertension, and chronic kidney disease (CKD) promoting endothelial dysfunction. This article provides an overview and update of the pathophysiological data on the role of DM in VC progression.

Keywords: vascular calcification; diabetes; chronic kidney disease

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1. Introduction

DM is characterized by chronic hyperglycemia, impaired carbohydrate metabolism, and dyslipidemia caused by the partial or total failure of insulin secretion and/or insulin action. The overall prevalence of diabetes is increasing significantly, which is a cause for concern. The International Diabetes Federation counts 430 million people associated with DM, an estimated prevalence of 8.6% among adults; by 2030, 579 million people will develop DM according to this estimate [1]. VC can occur both in the intimal and medial layers of arteries. Intimal calcification occurs in the form of calcium crystals. The mechanism extends progressively from the intima to the media; intimal calcification develops specifically at sites of atheromatous plaques [2]. The medial calcification (Monckeberg's medial sclerosis) is most often associated with vascular stiffening and arteriosclerosis, as compared with intima calcification. Medial VC occurs more often in response to a metabolic imbalance of glucose in diabetes, phosphocalcic disorders associated with CKD, and ageing [3]. This leads to decreased arterial compliance and increased pulse wave velocity. VC is a critical cause of cardiovascular disease and death; peripheral arterial disease affects more than 8.5 million people in the United States. DM affects one-third of these patients [4]. DM is an important risk factor for myocardial infarction and ischemic stroke. The rate of stroke in patients older than 50 years old is estimated to be more than three times higher in patients with DM than in patients without DM [5]. Recently, it has become clear that VC is a complex, active, pathophysiological mechanism. Many of the risk factors of VC coincide in patients with DM. This review will examine the specific mechanisms of DM that are associated with the rapid progression of VC in this patient group, and it will focus on the pathophysiology of particular risk factors that are associated with both VC and diabetes [6].

2. Vascular Calcification—General Overview

Deposits of calcium-phosphate in hydroxyapatite form are characteristic of VC [7].

Under normal conditions, valves and vessels are protected from supersaturated concentrations of serum phosphate and calcium by a number of active inhibitors; these

inhibitors protect against abnormal mineral deposits in soft tissues and vessels. Several inhibitors of calcification have been identified, including pyrophosphate, matrix Gla protein (Gla-MGP), osteopontin, fetuin-A, and osteoprotegerin. Oxidative stress and high glucose levels stimulate VC, as well as the transformation/transition of VSMCs into an osteoblastic-like cell phenotype; these osteoblastic-like cells synthesize transcription factors regulating osteogenesis, such as core-binding factor a1 (Cbfa1), bone morphogenetic protein 2 (BMP-2), osteocalcin (OCN), and type I collagen; these proteins promote the deposition of calcium phosphate in the extracellular matrix and lead to VC formation [8].

3. Vascular Calcification Risk Factors in Patients with Diabetes

3.1. Advanced Glycosylated End Products (AGEs) and Hyperglycemia

Recently, the mechanism by which high plasma glucose levels promote VC has come to be partially understood. In a high glucose environment, cultured VSMCs synthesize BMP-2 and OCN at high levels and promote matrix calcification [9]. Decorin (DCN) is a stromal proteoglycan synthesized by VSMCs [10]. Recent studies in animals and humans with obesity or glucose intolerance have shown that DCN mRNA expression is increased in adipose tissue; these results suggest that hyperglycemia may promote the transformation of VSMCs into osteoblast-like cells [10,11]. In a study performed to characterize DCN expression in adipose tissue in male subjects, plasma DCN levels were measured while fasting and 2 h after an oral glucose loading test; DCN levels correlated with waist-to-hip ratio and glucose levels while fasting and 2 h after an oral glucose tolerance test ($p = 0.027$ and $p = 0.001$, respectively) [9]. DCN enhances matrix deposition and calcification while inhibiting the activity of extracellular matrix degradative enzymes and collagen degradation [11,12]. The hyperglycemic environment is even characterized by an increased production of advanced glycation end products (AGEs). During the hyperglycemic state of DM, glucose forms covalent adducts with plasma proteins through a nonenzymatic process known as glycation. AGEs play an important role in the pathogenesis of diabetic complications by settling in many tissues and organs, such as the kidney and the aortic wall [13]. AGEs and their receptors for advanced glycation end products (RAGEs) constitute the AGE/RAGE signaling pathway of reactive oxygen species (ROS) [14]. Hyperglycemia also stimulates the production of ROS, protein kinase C (PKC), and it leads to the activation of the polyol pathway and stimulates the production of cytokines, such as IL-6, IL-1β, and TNF-α, which contribute to VC development and endothelial damage [15]. The S100 family members' function is to regulate a wide range of cellular processes, including proliferation, differentiation, inflammation, apoptosis, and Ca^{2+} homeostasis [16]. S100A9, a member of the S100 family, is secreted by cells upon stimulation of hyperglycemia, exerting extracellular cytokine and chemokine activities through RAGEs, stimulating the release of calcified extracellular vesicles, and promoting microcalcifications in vessels [15]. After the binding of ligands to RAGEs, oxidative stress is increased; the over-expression of RAGEs contributes to an increase in the expression of BMP-2/4 proteins and the NF-κB pathway, inducing the osteogenic differentiation of VSMCs [17,18].

3.2. Hypertension and Diabetes

Hypertension is common in patients with DM, and it is thought to reflect the impact of underlying insulin resistance on the vascular system. Accumulating evidence suggests that disturbances in carbohydrate metabolism are also more prevalent in hypertensive patients [19]. Hypertension is present in more than two-thirds of patients with type 2 DM, and hypertension develops with an increasing risk of hyperglycemia [20]. Different mechanisms related to diabetes may explain the development of hypertension: (a) the effect of hyperglycemia on the renin-angiotensin-aldosterone system, (b) sodium and fluid retention, (c) the stimulatory effect of hyperinsulinemia on the sympathetic system, and (d) insulin resistance in the nitric oxide channel [21–23]. The renin-angiotensin-aldosterone system is involved in VSMC growth and differentiation, suggesting its potential implication in arterial calcification [24]. Osako et al., demonstrated that angiotensin II significantly promoted

VC in vitro and in vivo through the activation of the renin-angiotensin system, particularly the angiotensin II-converting enzyme and Ang II type 1 receptor, through activation of the receptor activator of nuclear factor kappa-B ligand (RANKL) [25]. In the obese population, insulin resistance is often accompanied by elevated plasma aldosterone [26]. This elevation of aldosterone, in turn, has a negative effect on blood vessel function and promotes inflammation, proliferation, and vascular stress [27]. Klotho protein is the receptor for fibroblast growth factor-23 (FGF23), which regulates calcium-phosphate homeostasis and vitamin D metabolism. Klotho-hypomorphic mice (kl/kl mice) exhibit rapid aging, severe growth development, accelerated VC via hyperphosphatemia, and hyperaldosteronism. When spironolactone is administered to these mice, it acts as a mineralocorticoid receptor antagonist: the calcification of vessels and soft tissues is reduced, and the life span of kl/kl mice is increased [28]. Recent studies suggest a crucial role of the tubular renal type III sodium-dependent phosphate transporter (Pit-1) in phosphate-induced calcification [6,29]. In calcified tissues of kl^{-}/kl^{-} mice, spironolactone decreased the expression of osteogenic transcription factors and Pit-1 mRNA formation [28]. In human aortic VSMCs, aldosterone stimulated Pit-1 mRNA expression in a dose-dependent manner and similarly increased the expression of osteogenic transcription factors. The effects of aldosterone are counteracted by both Pit-1 inhibition and spironolactone; this suggests that aldosterone may promote soft tissue and VC development, in part because of the activation of spironolactone-sensitive Pit-1-dependent osteo-inductive signaling; finally, spironolactone prevents Pit-1-dependent vascular osteo-induction, as in klotho-hypomorphic mice [28].

3.3. Diabetes, Lipid Metabolism Disorder, and VC

As a result of hyperglycemia, oxidized low-density lipoprotein (Ox-LDL) further enhances medial VC and atherosclerosis [30]. By stimulating foam cell formation via increased CD36 expression on macrophages, increased plasma LDL concentrations become pro-atherogenic when oxidized to LDL (Ox-LDL) [31]. In addition, hyperglycemia, low HDL cholesterol, insulin resistance, and increased free fatty acid levels contribute to intimal VC associated with DM [32]. In aortic valves, in areas in which lipoproteins have been retained, progressive microscopic calcifications appear [33]. Using a model of VSMC calcification in which postconfluent VSMCs form nodules that calcify within 4 weeks, the authors demonstrated that lipid accumulation occurred spontaneously in the nodules; conversely, in the absence of lipoproteins, less lipid accumulated and fewer calcification nodules occurred [34]. Other studies have shown that HDL cholesterol which is not oxidized by free radicals could limit the phenomenon of vascular calcification in favor of an anti-atherogenic effect [35]. These results reinforce the hypothesis of a complex mechanism linking VC, osteogenic gene expression, and dyslipidemia. A low HDL cholesterol concentration is often associated with increased leptin serum concentration [36]. Adipokines, such as leptin, play an important role in the osteoblastic trans-differentiation and calcification of vascular cells [37]. A high concentration of leptin stimulates the action of BMP. BMP has an osteogenic function; it promotes ossification processes in bones, cartilage, and also in VSMC into osteoblast-like cells and increases VC [38,39]. Alkaline phosphatase activity (ALP) is a marker of osteoblast differentiation, and its concentration indirectly reflects its osteogenic activity. When VSMC are treated with HDL, a decrease in the concentration of APL is observed [40]. Prolonged treatment with HDL also inhibits calcification of VSMCs, further supporting the anti-osteogenic differentiation role of HDL on vascular cells. In addition, dyslipidemia increases oxidative stress and accelerates VC process [40,41]. Despite convincing data showing a link between triglycerides (TG) and VC, the extent to which TG mediates VC has not been fully elucidated. Hypertriglyceridemia is often associated with risk factors, such as obesity, hypertension, and insulin resistance, and it may increase the risk of developing VC. Epidemiological studies suggest that TGs independently predict the formation of coronary artery calcification in DM patients [42]. TG may be more appropriate to LDL-C in predicting diabetic nephropathy and cardiovascular complications [43,44]. The Wnt/β-catenin pathway plays a key role in VC pathogenesis via increased Runx2

transcription and facilitates the expression of osteoblastic markers and calcifications [45]. Recent studies also suggest that dyslipidemia is related to the Wnt/β-catenin pathway, which plays a central role in bone formation and calcification through the activation of an LDL-receptor-related protein in Wnt signal transduction [46,47].

3.4. Insulin Resistance, Diabetes, and VC

Insulin resistance can be defined as a stage prior to diabetes where the action of insulin on the muscles and liver decreases, reducing intracellular glucose uptake and promoting hyperglycemia. A few years ago, the Coronary Artery Calcification in Type 1 Diabetes study evaluated the progression of cardiovascular disease and the degree of coronary artery calcification (CAC) in a cohort of diabetic patients and nondiabetic controls using electron beam tomography (EBCT). Shauer et al., found that high levels of insulin resistance were associated not only with poorer glycemic control, but also with higher calcification scores [48]. Insulin resistance appears to predict the extent of CAC and may be associated with a higher risk of CVD, particularly in patients with diabetes; in contrast, insulin appears to exert a protective effect on CV [49]. In vitro, glucose promotes a phenotypic transition of VSMCs to osteogenic cells; numerous studies have suggested that NO decreases platelet activation and counteracts the proliferation and migration of VSMCs [50–52]. Under physiological conditions, insulin enhances the secretion of NO from the endothelium of arteries, leading to the oxidization of lipoproteins, reducing the mechanism of VC, and inhibiting the proliferation of VSMC [53]. The insulin-resistant state is associated with the migration of more free fatty acids into the liver, which stimulates hepatic TG uptake, as well as VLDL production and secretion. Thus, the risk of VC also increases. Higher states of insulin resistance are also associated with a higher risk of the accelerated formation of VC; this suggests that coronary plaque vulnerability may be associated with insulin resistance [54]. Other studies suggest that insulin resistance accelerates VC, inducing the inflammatory activity of immune cells and blood vessels [48]. Additionally, recent studies suggest a possible link between circulating VC, CVD, and osteoprotegerin (OPG), such that OPG appears to be a candidate marker for CVD [55]. In clinical studies, OPG appears to be a strong predictor of CV in dialysis patients [56,57]. OPG is a soluble receptor that binds to the nuclear factor kappa-B activating receptor RANK-ligand (RANKL) produced by osteoblasts. RANKL/RANK binding then stimulates osteoclast differentiation [58]. The RANKL/RANK/OPG system plays an active role in inflammation and pathological angiogenesis; insulin resistance is significantly correlated with OPG levels [59].

Plasma OPG concentration was elevated in DM patients with microvascular complications; hyperinsulinemia increases ALP and CBFA-1 concentrations and decreases MGP and OPG levels, resulting in the bone transformation of interstitial cells [60]. BMP is an osteogenic factor that promotes the differentiation of mesenchymal stem cells into chondroblasts and fibroblasts; MGP is produced by VSMC and endothelial cells and is considered as one of the major inhibitors of tissue and VC [61,62]. When hyperinsulinemia occurs, the clearance of Kupffer cells in the liver decreases [59]. Kupffer cells are resident macrophages in the liver and play an important function in maintaining liver function [63].

This change results in an increase in plasma insulin and glycolipid concentration due to a decrease in the clearance of glycolipids absorbed from the gastrointestinal tract [64].

3.5. Obesity and VC

Obesity is strongly associated with comorbidities, such as hypertension and insulin resistance [65]. Obesity is frequent in DM patients and is considered to be an independent risk factor for the development of CVD. Throughout the natural history of DM, endothelial dysfunction is accompanied with obesity/insulin resistance [66]. The prevalence of diabetes secondary to obesity will increase to 783 million people by 2045 according to the *International Diabetes Federation Atlas*, 10th edition, 2021 (IDF.org). The molecular mechanisms of obesity-induced vascular disease in the diabetic state are the subject of intense research. Several studies consider that cytokines and adipose-derived hormones express molecular

links between CVD and adiposity [67]. The volume of adipose cardiac tissue increases with obesity, especially around coronary arteries [68]. The effects of adipokines (resistin, adiponectin, and leptin) on atherosclerosis and vascular function/insulin sensitivity and inflammation (leptin, monocyte chemotactic protein 1, and IL-8) are under evaluation [69,70]. Recent studies have demonstrated that coronary calcifications are related to epicardial fat; epicardial tissue is located between the visceral layer of the pericardium and the myocardial surface. Epicardial adipose tissue interacts with the coronary artery via complex paracrine mechanisms involving adipokines and inflammatory markers, which may promote VC [71]. Other studies suggest that epicardial fat volume is correlated with VC, insulin resistance, dyslipidemia, and abdominal obesity [71–73]. It is possible in the future, that the presence of epicardial fat in the area of the coronary arteries could be considered as a predictive risk for CV.

3.6. Chronic Kidney Disease-Bone Disorder (CKD-MBD), microRNAs, Calciprotein Particles, and Diabetes

Diabetic patients have a 30% risk of developing CKD, as compared to nondiabetic patients [74].

Several factors other than glycemic control influence the progression of CKD in diabetes, such as blood pressure control, dyslipidemia, degree of proteinuria, and certain genetic factors, such as the APOL1 variant [75]. The presence of renal failure in DM may therefore also be related to nephroangiosclerosis or other glomerulopathy. The study included a cohort of 371 diabetic patients with a renal biopsy and a median duration of DM of 10 years: 37% of patients had diabetic nephropathy (DN) alone, 36% had nondiabetic nephropathy (NDN), and 27% had both DN and NDN [76]. Patients with CKD and DM can have (1) true DN, (2) nondiabetic kidney disease with DM, or (3) a combination of both DN and NDN [77]. Compared to the general population, VCs in CKD patients are a strong predictor of increased cardiovascular mortality and morbidity [78,79]. As mentioned previously, media calcification is more prevalent in CKD patients; calcification of the intima is associated with atherosclerosis in particular, with the formation of atheroma plaques responsible for emboli and arterial stenosis [80]. In CKD patients, medial calcification is often compared to an osteogenic process similar to intramembranous ossification, which is independent of atherosclerosis and leads to a decrease in vessel wall elasticity and an increase in pulse wave velocity [81]. Arterial layers are more intensively and more frequently calcified in CKD patients than in nonuremic patients; medial calcification appears earlier in CKD patients compared to nonuremic patients [78,82]. CKD patients have a higher prevalence of VC as kidney function decreases, which results in increased morbidity and mortality [83]. The progressive loss of renal function is associated with the reduced clearance of toxic compounds, called uremic toxins, which play a crucial role in the progression of CKD and CVD pathophysiology; the uremic toxins stimulate multiple signaling pathways in different cell types, including VSMCs and endothelial cells [84]. Gradually, during chronic renal failure, phosphate clearance decreases, and phosphate, FGF23, and PTH increase, which is associated with a low vitamin D level. Disturbances of phospho-calcium balance secondary to chronic renal failure are grouped under the concept of chronic renal disease-mineral and bone disorder (CKD-MBD) [85]. These disturbances of the phospho-calcic balance lead to uremic osteopathy with a high risk of fracture characterized by rapid or slow bone turnover. In vitro and in vivo studies highlight the deleterious role of the disturbances of calcium phosphate metabolism and their impact on the differentiation of VSMCs into osteoblast-like cells [86,87]. There is probably a link between the pathophysiological process of VC and the degree of bone turnover (CKD-MBD) depending on the ability of the bone to bind or not circulate calcium, which accelerates the calcification process [84]. There is a state of micro-inflammation associated with CKD; this micro-inflammation results in the presence of other inflammation phase proteins, called cytokines, which aggravate endothelial dysfunction and also promote the transformation of VSMCs into osteoblast like cells [88,89].

This micro-inflammation state, similar to the disorders of phospho-calcium metabolism, thus promotes the process of VC [90].

MicroRNAs (miRNAs) are part of small noncoding RNAs; they seem to contribute both to bone pathophysiology and vascular damage [91]. In the case of renal insufficiency, the function of miRNAs seems to be disrupted. During VC, the initiation of VSMC apoptosis is partly regulated by the activity of mitochondria [92]. In case of overexpression, miRNAs, such as the miR-34 family, seem to stimulate the process of VSMC apoptosis [93]. On the contrary, hyperglycemia is reported to down-regulate the expression of miR-133a, and then it worsens the apoptotic susceptibility of VSMCs via the inhibition of insulin growth factor 1 receptor (IGFR-1R) activity and the activation of NF-κB. This suggests that miR-133a may have a protective function against VSMC apoptosis in DM [94]. The extracellular vesicles contain a different type of miRNA; they are considered to be mediators of cell-to-cell communication [95]. Extracellular vesicles from plasma uremic patients on hemodialysis stimulate the expression of certain mRNAs, such as miR-223, which stimulate the transformation of VSMCs into osteoblast-like cells compared with nonuremic controls [95].

Recently, a new player has been described in the assessment of VC severity in CKD patients with and without DM. Colloidal nanoparticles, called serum calciprotein particles (CPPs), are composed of calcification inhibitors (mainly Gla-MGP protein and fetuin-A) and Ca2+ compounds; CPPs regulate calcification process according to their concentrations, which vary from patient to patient [96,97]. There are two types of CPP nanoparticles; type I CCPs are composed of amorphous salt of calcium and phosphate, type II CCPs contains mainly phosphate calcium crystals [98]. The formation of these crystals is the origin of the process of the formation of tissue and vascular calcification. The transformation from CPP I to CPP II takes place under several mineral metabolism factors, such as the serum concentration of phosphorus, fetuin-A, Ca^{2+}, and Mg^{2+} [99]. The transition from CPP I to CPP II takes place naturally in serum, and the time needed for this transition can be evaluated. Additionally, in order to measure the risk of calcification for a given patient, Pash et al., established that half the time required for the transition in serum from CPP I to CPP II, designated by T50, could significantly predict this risk [100]. In addition, if the concentration of calcification inhibitors (such as fetuin-A or Gla-MGP protein) is high in the serum, or if the concentration of phosphate in the serum is low, the T50 should be high and may limit the risk of calcification. In renal insufficiency or in patients on hemodialysis, T50 is significantly lower than it is in the general population, probably due to hyperphosphatemia and to a lower level of fetuin-A/Gla-MGP protein concentration (Figure 1). T50 has been assessed in type 2 diabetes mellitus: A retrospective analysis could not establish an association between a history of macro-vascular events and T50, even if T50 were independently associated with glycemic control, suggesting that a lower HbA1c is associated with better cardiovascular outcomes [101]. The authors of another study examined T50 levels with abnormalities in phospho-calcium metabolism (APCM) and macro-vascular complications in DM patients with a follow-up period of more than 10 years [102]. T50 was associated with APCM, but not with the development of long-term macro-vascular complications. There are also some conflicting results regarding whether cardiovascular morbidity and/or mortality are associated with a lower T50; prospective studies will clarify the use of T50 to allow for the individualization of the therapeutic management of VC [103].

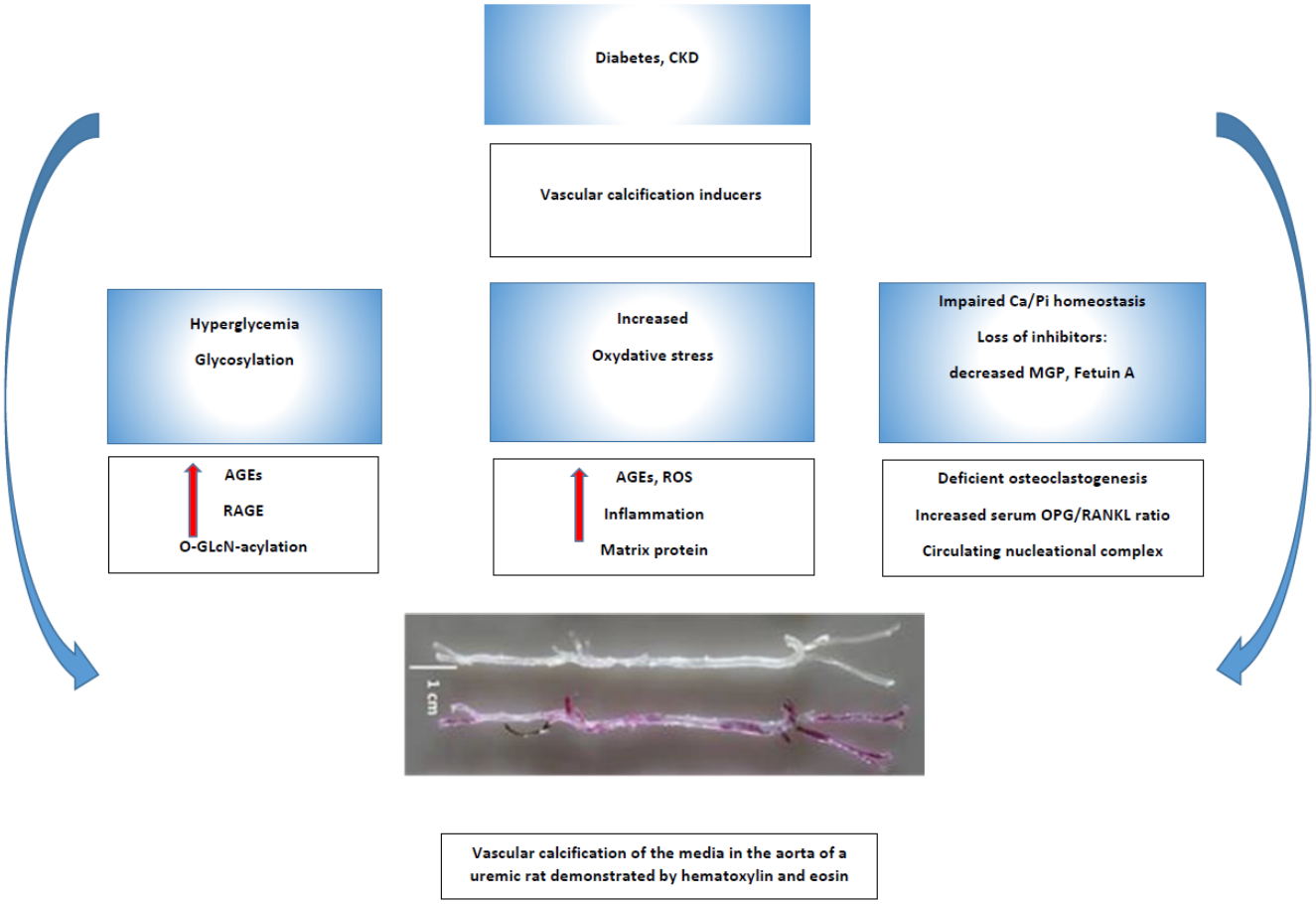

Figure 1. Factors involved in vascular calcification associated with diabetes mellitus (picture of aorta from the service of nephrology and hypertension, Lausanne).

4. Conclusions and Perspectives

Many pathways come together in DM patients with CKD, and they partially reinforce one another, which explains why DM patients are prone to both intimal and medial vascular calcifications. On the one hand, this multitude of pathways explains the extremely high CV risk of this population, but this interplay also offers treatment opportunities. An in-depth discussion on how to halt the process of accelerated VC is beyond the scope of this article, but new treatment options are arising, besides lifestyle interventions, diabetes treatment such as SGLT2 inhibitors, statins, and calcium-phosphate control, such as the use of a selective inhibitor of hydroxyapatite crystallization [7,104]. It has recently been reported that SNF472, an intravenous formulation of the hexasodium salt of myo-inositol hexaphosphate, is highly effective in vitro and in vivo in the inhibition of hydroxyapatite nucleation and crystal formation [104]. Moreover, SNF472 significantly reduced the progression of coronary calcification, as compared with placebo, in the phase 2b CaLIPSO trial of patients receiving maintenance hemodialysis [105]. Future studies will determine the impact of hydroxyapatite formation inhibitor on cardiovascular events in DM patients, with or without CKD.

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References

1. Zimmet, P.Z.; Magliano, D.J.; Herman, W.H.; Shaw, J.E. Diabetes: A 21st century challenge. *Lancet Diabetes Endocrinol.* **2014**, *2*, 56–64. [CrossRef] [PubMed]
2. Buse, J.B.; Pignone, M.P.; The ADA/AHA Primary Prevention Consensus Panel. Primary Prevention of Cardiovascular Diseases in People with Diabetes Mellitus: A Scientific Statement from the American Heart Association and the American Diabetes Association. *Diabetes Care* **2007**, *30*, e58. [CrossRef]
3. Chen, Y.; Zhao, X.; Wu, H. Arterial Stiffness: A Focus on Vascular Calcification and Its Link to Bone Mineralization. *Arterioscler. Thromb. Vasc. Biol.* **2020**, *40*, 1078–1093. [CrossRef] [PubMed]
4. Rabia, K.; Khoo, E.M. Peripheral arterial disease in people with diabetes. *Diabetes Care* **2003**, *26*, 3333–3341.
5. De Angelis, M.; Scrucca, L.; Leandri, M.; Mincigrucci, S.; Bistoni, S.; Bovi, M.; Calabrese, G.; Pippi, R.; Parretti, D.; Grilli, P.; et al. Prevalence of carotid stenosis in type 2 diabetic patients asymptomatic for cerebrovascular disease. *Diabetes Nutr. Metab.* **2003**, *16*, 48–55.
6. Jono, S.; McKee, M.D.; Murry, C.E.; Shioi, A.; Nishizawa, Y.; Mori, K.; Morii, H.; Giachelli, C.M. Phosphate Regulation of Vascular Smooth Muscle Cell Calcification. *Circ. Res.* **2000**, *87*, E10–E17. [CrossRef]
7. Schantl, A.E.; Verhulst, A.; Neven, E.; Behets, G.J.; D'Haese, P.C.; Maillard, M.; Mordasini, D.; Phan, O.; Burnier, M.; Spaggiari, D.; et al. Inhibition of vascular calcification by inositol phosphates derivatized with ethylene glycol oligomers. *Nat. Commun.* **2020**, *11*, 721. [CrossRef]
8. Moe, S.M.; Duan, D.; Doehle, B.P.; O'Neill, K.D.; Chen, N.X. Uremia induces the osteoblast differentiation factor Cbfa1 in human blood vessels. *Kidney Int.* **2003**, *63*, 1003–1011. [CrossRef]
9. Berezovska, O.; Yildirim, G.; Budell, W.; Yagerman, S.; Pidhaynyy, B.; Bastien, C.; van der Meulen, M.; Dowd, T. Osteocalcin affects bone mineral and mechanical properties in female mice. *Bone* **2019**, *128*, 115031. [CrossRef]
10. Bolton, K.; Segal, D.; McMillan, J.; Jowett, J.; Heilbronn, L.; Abberton, K.; Zimmet, P.; Chisholm, D.; Collier, G.; Walder, K. Decorin is a secreted protein associated with obesity and type 2 diabetes. *Int. J. Obes.* **2008**, *32*, 1113–1121. [CrossRef]
11. Zhang, J.; Wright, W.; Bernlohr, D.A.; Cushman, S.W.; Chen, X. Alterations of the classic pathway of complement in adipose tissue of obesity and insulin resistance. *Am. J. Physiol. Endocrinol. Metab.* **2007**, *292*, E1433–E1440. [CrossRef]
12. Zhang, W.; Ge, Y.; Cheng, Q.; Zhang, Q.; Fang, L.; Zheng, J. Decorin is a pivotal effector in the extracellular matrix and tumour microenvironment. *Oncotarget* **2018**, *9*, 5480–5491. [CrossRef]
13. Yamagishi, S.-I.; Fukami, K.; Matsui, T. Evaluation of tissue accumulation levels of advanced glycation end products by skin autofluorescence: A novel marker of vascular complications in high-risk patients for cardiovascular disease. *Int. J. Cardiol.* **2015**, *185*, 263–268. [CrossRef]
14. Tanikawa, T.; Okada, Y.; Tanikawa, R.; Tanaka, Y. Advanced Glycation End Products Induce Calcification of Vascular Smooth Muscle Cells through RAGE/p38 MAPK. *J. Vasc. Res.* **2009**, *46*, 572–580. [CrossRef]
15. Baxevanis, A.D.; Bryant, S.H.; Landsman, D. Homology model building of the HMG-1 box structural domain. *Nucleic Acids Res.* **1995**, *23*, 1019–1029. [CrossRef]
16. Bresnick, A.R.; Weber, D.J.; Zimmer, D.B. S100 proteins in cancer. *Nat. Rev. Cancer* **2015**, *15*, 96–109. [CrossRef]
17. Lavery, K.; Swain, P.; Falb, D.; Alaoui-Ismaili, M.H. BMP-2/4 and BMP-6/7 differentially utilize cell surface receptors to induce osteoblastic differentiation of human bone marrow-derived mesenchymal stem cells. *J. Biol. Chem.* **2008**, *28*, 20948–20958. [CrossRef]
18. Tóbon-Velasco, J.C.; Cuevas, E.; Torres-Ramos, M.A. Receptor for AGEs (RAGE) as mediator of NF-kB pathway activation in neuroinflammation and oxidative stress. *CNS Neurol. Disord. Drug Targets* **2014**, *13*, 1615–1626. [CrossRef]
19. Wei, G.S.; Coady, S.A.; Goff, D.C., Jr.; Brancati, F.L.; Levy, D.; Selvin, E.; Vasan, R.S.; Fox, C.S. Blood Pressure and the Risk of Developing Diabetes in African Americans and Whites: ARIC, CARDIA, and the Framingham Heart Study. *Diabetes Care* **2011**, *34*, 873–879. [CrossRef]
20. Kawamori, R.; Daida, H.; Tanaka, Y.; Miyauchi, K.; Kitagawa, A.; Hayashi, D.; Kishimoto, J.; Ikeda, S.; Imai, Y.; Yamazaki, T. Amlodipine versus angiotensin II receptor blocker; control of blood pressure evaluation trial in diabetics (ADVANCED-J). *BMC Cardiovasc. Disord.* **2006**, *6*, 39. [CrossRef]
21. Bendix, E.F.; Johansen, E.; Ringgaard, T.; Wolder, M.; Starup-Linde, J. Diabetes and Abdominal Aortic Calcification—A Systematic Review. *Curr. Osteoporos. Rep.* **2018**, *16*, 42–57. [CrossRef] [PubMed]
22. Nicoll, R.; Zhao, Y.; Ibrahimi, P.; Olivecrona, G.; Henein, M. Diabetes and Hypertension Consistently Predict the Presence and Extent of Coronary Artery Calcification in Symptomatic Patients: A Systematic Review and Meta-Analysis. *Int. J. Mol. Sci.* **2016**, *17*, 1481. [CrossRef] [PubMed]
23. Khurrami, L.; Møller, J.E.; Lindholt, J.S.; Urbonaviciene, G.; Steffensen, F.H.; Lambrechtsen, J.; Karon, M.; Frost, L.; Busk, M.; Egstrup, K.; et al. Cross-sectional study of aortic valve calcification and cardiovascular risk factors in older Danish men. *Heart* **2021**, *107*, 1536–1543. [CrossRef] [PubMed]
24. Bai, H.-Y.; Shan, B.-S.; Jiang, Y.-N. The protective effects of renin–angiotensin system compents on vascular calcification. *J. Hum. Hypertens.* **2020**, *35*, 410–418. [CrossRef] [PubMed]
25. Panizo, S.; Cardus, A.; Encinas, M.; Parisi, E.; Valcheva, P.; López-Ongil, S.; Coll, B.; Fernandez, E.; Valdivielso, J.M. RANKL Increases Vascular Smooth Muscle Cell Calcification Through a RANK-BMP4–Dependent Pathway. *Circ. Res.* **2009**, *104*, 1041–1048. [CrossRef] [PubMed]

26. Bender, S.B.; McGraw, A.P.; Jaffe, I.Z.; Sowers, J.R. Mineralocorticoid receptor-mediated vascular insulin resistance: An early contributor to diabetes-related vascular disease? *Diabetes* **2013**, *62*, 313–319. [CrossRef]
27. Hwang, M.-H.; Yoo, J.-K.; Luttrell, M.; Kim, H.-K.; Meade, T.H.; English, M.; Segal, M.S.; Christou, D.D. Mineralocorticoid receptors modulate vascular endothelial function in human obesity. *Clin. Sci.* **2013**, *125*, 513–520. [CrossRef]
28. Voelkl, J.; Alesutan, I.; Leibrock, C.B.; Quintanilla-Martinez, L.; Kuhn, V.; Feger, M.; Mia, S.; Ahmed, M.S.; Rosenblatt, K.P.; Kuro-o, M.; et al. Spironolactone ameliorates PIT1-dependent vascular osteoinduction in klotho-hypomorphic mice. *J. Clin. Investig.* **2013**, *123*, 812–822. [CrossRef]
29. Li, W.; Feng, W.; Su, X.; Luo, D.; Li, Z.; Zhou, Y.; Zhu, Y.; Zhang, M.; Chen, J.; Liu, B.; et al. SIRT6 protects vascular smooth muscle cells from osteogenic transdifferentiation via Runx2 in chronic kidney disease. *J. Clin. Investig.* **2022**, *132*, e150051. [CrossRef]
30. Okui, T.; Iwashita, M.; Rogers, M.A.; Halu, A.; Atkins, S.K.; Kuraoka, S.; Abdelhamid, I.; Higashi, H.; Ramsaroop, A.; Aikawa, M.; et al. CROT (Carnitine O-Octanoyltransferase) Is a Novel Contributing Factor in Vascular Calcification via Promoting Fatty Acid Metabolism and Mitochondrial Dysfunction. *Arter. Thromb. Vasc. Biol.* **2021**, *41*, 755–768. [CrossRef]
31. Chen, Y.; Yang, M.; Huang, W.; Chen, W.; Zhao, Y.; Schulte, M.L.; Volberding, P.; Gerbec, Z.; Zimmermann, M.T.; Zeighami, A.; et al. Mitochondrial Metabolic Reprogramming by CD36 Signaling Drives Macrophage Inflammatory Responses. *Circ. Res.* **2019**, *125*, 1087–1102. [CrossRef]
32. Gautam, S.; Banerjee, M. The macrophage Ox-LDL receptor, CD36 and its association with type II diabetes mellitus. *Mol. Genet. Metab.* **2011**, *102*, 389–398. [CrossRef]
33. Farzaneh-Far, A.; Proudfoot, D.; Shanahan, C.; Weissberg, P.L. Vascular and valvar calcification: Recent advances. *Heart* **2001**, *85*, 13–17. [CrossRef]
34. Proudfoot, D.; Davies, J.; Skepper, J.; Weissberg, P.; Shanahan, C. Acetylated Low-Density Lipoprotein Stimulates Human Vascular Smooth Muscle Cell Calcification by Promoting Osteoblastic Differentiation and Inhibiting Phagocytosis. *Circulation* **2002**, *106*, 3044–3050. [CrossRef]
35. Vergeer, M.; Holleboom, A.G.; Kastelein, J.J.P.; Kuivenhoven, J. The HDL hypothesis: Does high-density lipoprotein protect from atherosclerosis? *J. Lipid Res.* **2010**, *51*, 2058–2073. [CrossRef]
36. Tsao, C.W.; Preis, S.R.; Peloso, G.M.; Hwang, S.-J.; Kathiresan, S.; Fox, C.S.; Cupples, L.A.; Hoffmann, U.; O'Donnell, C.J. Relations of Long-Term and Contemporary Lipid Levels and Lipid Genetic Risk Scores with Coronary Artery Calcium in the Framingham Heart Study. *J. Am. Coll. Cardiol.* **2012**, *60*, 2364–2371. [CrossRef]
37. Parhami, F.; Tintut, Y.; Ballard, A.; Fogelman, A.M.; Demer, L.L. Leptin enhances the calcification of vascular cells: Artery wall as a target of leptin. *Circ. Res.* **2001**, *88*, 954–960. [CrossRef]
38. Ebisawa, T.; Tada, K.; Kitajima, I.; Tojo, K.; Sampath, T.K.; Kawabata, M.; Miyazono, K.; Imamura, T. Characterization of bone morphogenetic protein-6 signaling pathways in osteoblast differentiation. *J. Cell Sci.* **1999**, *112*, 3519–3527. [CrossRef]
39. Hruska, K.; Mathew, S.; Lund, R.; Fang, Y.; Sugatani, T. Cardiovascular risk factors in chronic kidney disease: Does phosphate qualify? *Kidney Int.* **2011**, *79121*, S9–S13. [CrossRef]
40. Parhami, F.; Basseri, B.; Hwang, J.; Tintut, Y.; Demer, L.L. High-density lipoprotein regulates calcification of vascular cells. *Circ. Res.* **2002**, *91*, 570–576. [CrossRef]
41. Varma, B.; Ogunmoroti, O.; Ndumele, C.E.; Zhao, D.; Szklo, M.; Sweeney, T.; Allison, M.A.; Budoff, M.J.; Subramanya, V.; Bertoni, A.G.; et al. Higher leptin levels are associated with coronary artery calcium progression: The multi-ethnic study of atherosclerosis (MESA). *Diabetes Epidemiol. Manag.* **2021**, *6*, 100047. [CrossRef] [PubMed]
42. Reiner, Ž. Hypertriglyceridaemia and risk of coronary artery disease. *Nat. Rev. Cardiol.* **2017**, *14*, 401–411. [CrossRef] [PubMed]
43. Rutledge, J.C.; Ng, K.F.; Aung, H.H.; Wilson, D.W. Role of triglyceride-rich lipoproteins in diabetic nephropathy. *Nat. Rev. Nephrol.* **2010**, *6*, 361–370. [CrossRef] [PubMed]
44. Kaze, A.D.; Santhanam, P.; Musani, S.K.; Ahima, R.; Echouffo-Tcheugui, J.B. Metabolic Dyslipidemia and Cardiovascular Outcomes in Type 2 Diabetes Mellitus: Findings From the Look AHEAD Study. *J. Am. Heart Assoc.* **2021**, *10*, e016947. [CrossRef] [PubMed]
45. Cheng, S.-L.; Shao, J.-S.; Behrmann, A.; Krchma, K.; Towler, D.A. Abstract 222: Dkk1 and Msx2-Wnt7b Signaling Reciprocally Regulate the Endothelial-Mesenchymal Transition in Aortic Endothelial Cells. *Arter. Thromb. Vasc. Biol.* **2013**, *33*, 1679–1689. [CrossRef] [PubMed]
46. Yao, L.; Sun, Y.-T.; Sun, W.; Xu, T.-H.; Ren, C.; Fan, X.; Sun, L.; Liu, L.-L.; Feng, J.-M.; Ma, J.-F.; et al. High Phosphorus Level Leads to Aortic Calcification via β-Catenin in Chronic Kidney Disease. *Am. J. Nephrol.* **2015**, *41*, 28–36. [CrossRef]
47. Guo, C.; Yang, R.-J.; Jang, K.; Zhou, X.-L.; Liu, Y.-Z. Protective Effects of Pretreatment with Quercetin Against Lipopolysaccharide-Induced Apoptosis and the Inhibition of Osteoblast Differentiation via the MAPK and Wnt/β-Catenin Pathways in MC3T3-E1 Cells. *Cell. Physiol. Biochem.* **2017**, *43*, 1547–1561. [CrossRef]
48. Schauer, I.E.; Snell-Bergeon, J.K.; Bergman, B.C.; Maahs, D.M.; Kretowski, A.; Eckel, R.H.; Rewers, M. Insulin resistance, defective insulin-mediated fatty acid suppression, and coronary artery calcification in subjects with and without type 1 diabetes: The CACTI study. *Diabetes* **2011**, *60*, 306–314. [CrossRef]
49. Dabelea, D.; Kinney, G.; Snell-Bergeon, J.K.; Hokanson, J.E.; Eckel, R.H.; Ehrlich, J.; Garg, S.; Hamman, R.F.; Rewers, M. Effect of type 1 diabetes on the gender difference in coronary artery calcification: A role for insulin resistance? The Coronary Artery Calcification in Type 1 Diabetes (CACTI) Study. *Diabetes* **2003**, *52*, 2833–2839. [CrossRef]

50. Suzuki, L.A.; Poot, M.; Gerrity, R.G.; Bornfeldt, K.E. Diabetes accelerates smooth muscle accumulation in lesions of atherosclerosis: Lack of direct growth-promoting effects of high glucose levels. *Diabetes* **2001**, *50*, 851–860. [CrossRef]
51. Mizutani, K.; Ikeda, K.; Ito, T.; Tamaki, K.; Nara, Y.; Yamori, Y. Protective effect of inducible type nitric oxide synthase against intracellular oxidative stress caused by advanced glycation end-products in vascular smooth muscle cells from stroke-prone spontaneously hypertensive rats. *J. Hypertens.* **2000**, *18*, 1071–1079. [CrossRef]
52. Hirafuji, M.; Tsunoda, M.; Machida, T.; Hamaue, N.; Endo, T.; Miyamoto, A.; Minami, M. Reduced expressions of inducible nitric oxide synthase and cyclooxygenase-2 in vascular smooth muscle cells of stroke-prone spontaneously hypertensive rats. *Life Sci.* **2002**, *70*, 917–926. [CrossRef]
53. Sagris, M.; Theofilis, P.; Antonopoulos, A.S.; Oikonomou, E.; Paschaliori, C.; Galiatsatos, N.; Tsioufis, K.; Tousoulis, D. Inflammation in Coronary Microvascular Dysfunction. *Int. J. Mol. Sci.* **2021**, *22*, 13471. [CrossRef]
54. Iguchi, T.; Hasegawa, T.; Otsuka, K.; Matsumoto, K.; Yamazaki, T.; Nishimura, S.; Nakata, S.; Ehara, S.; Kataoka, T.; Shimada, K.; et al. Insulin resistance is associated with coronary plaque vulnerability: Insight from optical coherence tomography analysis. *Eur. Heart J. Cardiovasc. Imaging* **2014**, *15*, 284–291. [CrossRef]
55. Tavintharan, S.; Pek, L.T.S.; Liu, J.; Ng, X.W.; Yeoh, L.Y.; Chi, L.S.; Fang, S.C. Osteoprotegerin is independently associated with metabolic syndrome and microvascular complications in type 2 diabetes mellitus. *Diab. Vasc. Dis. Res.* **2014**, *11*, 359–362. [CrossRef]
56. Ávila, M.; Mora, C.; Zavala, M.; Prado, M.D.C.; Paniagua, R. Osteoprotegerin Is the Strongest Predictor for Progression of Arterial Calcification in Peritoneal Dialysis Patients. *Am. J. Nephrol.* **2017**, *46*, 39–46. [CrossRef]
57. Ávila, M.; Prado, M.d.; Romero, R.; Córdova, R.; Rigo, M.d.; Trejo, M.; Mora, C.; Paniagua, R.; for The Mexican Nephrology Collaborative Study Group. Osteoprotegerin Is a Better Predictor for Cardiovascular and All-Cause Mortality than Vascular Calcifications in a Multicenter Cohort of Patients on Peritoneal Dialysis. *Biomolecules* **2022**, *12*, 551. [CrossRef]
58. Park, J.H.; Lee, N.K.; Lee, A.S.Y. Current Understanding of RANK Signaling in Osteoclast Differentiation and Maturation. *Mol. Cells* **2017**, *40*, 706–713. [CrossRef]
59. Yaturu, S.; Rains, J.; Jain, S.K. Relationship of elevated osteoprotegerin with insulin resistance, CRP, and TNF-α levels in men with type 2 diabetes. *Cytokine* **2008**, *44*, 168–171. [CrossRef]
60. Knudsen, S.T.; Foss, C.H.; Poulsen, P.L.; Andersen, N.H.; Mogensen, C.E.; Rasmussen, L.M. Increased plasma concentrations of osteoprotegerin in type 2 diabetic patients with microvascular complications. *Eur. J. Endocrinol.* **2003**, *149*, 39–42. [CrossRef]
61. Calvier, L.; Chouvarine, P.; Legchenko, E.; Hoffmann, N.; Geldner, J.; Borchert, P.; Jonigk, D.; Mozes, M.M.; Hansmann, G. PPARγ Links BMP2 and TGFβ1 Pathways in Vascular Smooth Muscle Cells, Regulating Cell Proliferation and Glucose Metabolism. *Cell Metab.* **2017**, *25*, 1118–1134.e7. [CrossRef] [PubMed]
62. Marulanda, J.; Gao, C.; Roman, H.; Henderson, J.E.; Murshed, M. Prevention of arterial calcification corrects the low bone mass phenotype in MGP-deficient mice. *Bone* **2013**, *57*, 499–508. [CrossRef] [PubMed]
63. Nguyen-Lefebvre, A.T.; Horuzsko, A. Kupffer Cell Metabolism and Function. *J. Enzymol. Metab.* **2015**, *1*, 101. [PubMed]
64. Barchetta, I.; Ceccarelli, V.; Cimini, F.A.; Bertoccini, L.; Fraioli, A.; Alessandri, C.; Lenzi, A.; Baroni, M.G.; Cavallo, M.G. Impaired bone matrix glycoprotein pattern is associated with increased cardio-metabolic risk profile in patients with type 2 diabetes mellitus. *J. Endocrinol. Investig.* **2019**, *42*, 513–520. [CrossRef] [PubMed]
65. Ward, Z.J.; Bleich, S.N.; Cradock, A.L.; Barrett, J.L.; Giles, C.M.; Flax, C.; Long, M.W.; Gortmaker, S.L. Projected U.S. state-level prevalence of adult obesity and severe obesity. *N. Engl. J. Med.* **2019**, *381*, 2440–2450. [CrossRef]
66. Vasim, I.; Majeed, C.N.; DeBoer, M.D. Intermittent Fasting and Metabolic Health. *Nutrients* **2022**, *14*, 631. [CrossRef]
67. Koenen, M.; Hill, M.A.; Cohen, P.; Sowers, J.R. Obesity, Adipose Tissue and Vascular Dysfunction. *Circ. Res.* **2021**, *128*, 951–968. [CrossRef]
68. Greif, M.; Becker, A.; von Ziegler, F.; Lebherz, C.; Lehrke, M.; Broedl, U.C.; Tittus, J.; Parhofer, K.; Becker, C.; Reiser, M.; et al. Pericardial Adipose Tissue Determined by Dual Source CT Is a Risk Factor for Coronary Atherosclerosis. *Arter. Thromb. Vasc. Biol.* **2009**, *29*, 781–786. [CrossRef]
69. Noblet, J.N.; Goodwill, A.G.; Sassoon, D.J.; Kiel, A.M.; Tune, J.D. Leptin augments coronary vasoconstriction and smooth muscle proliferation via a Rho-kinase-dependent pathway. *Basic Res. Cardiol.* **2016**, *111*, 25. [CrossRef]
70. Owen, M.K.; Witzmann, F.A.; McKenney, M.L.; Lai, X.; Berwick, Z.C.; Moberly, S.P.; Alloosh, M.; Sturek, M.; Tune, J.D. Perivascular adipose tissue potentiates contraction of coronary vascular smooth muscle: Influence of obesity. *Circulation* **2013**, *128*, 9–18. [CrossRef]
71. Yerramasu, A.; Dey, D.; Venuraju, S.; Anand, D.V.; Atwal, S.; Corder, R.; Berman, D.S.; Lahiri, A. Increased volume of epicardial fat is an independent risk factor for accelerated progression of sub-clinical coronary atherosclerosis. *Atherosclerosis* **2011**, *220*, 223–230. [CrossRef]
72. Shibasaki, I.; Nishikimi, T.; Mochizuki, Y.; Yamada, Y.; Yoshitatsu, M.; Inoue, Y.; Kuwata, T.; Ogawa, H.; Tsuchiya, G.; Ishimitsu, T.; et al. Greater expression of inflammatory cytokines, adrenomedullin, and natriuretic peptide receptor-C in epicardial adipose tissue in coronary artery disease. *Regul. Pept.* **2010**, *165*, 210–217. [CrossRef]
73. Kerr, J.D.; Holden, R.M.; Morton, A.R.; Nolan, R.L.; Hopman, W.M.; Pruss, C.M.; Garland, J.S. Associations of epicardial fat with coronary calcification, insulin resistance, inflammation, and fibroblast growth factor-23 in stage 3–5 chronic kidney disease. *BMC Nephrol.* **2013**, *14*, 26. [CrossRef]

74. Cannata-Andía, J.B.; Martín-Carro, B.; Martín-Vírgala, J.; Rodríguez-Carrio, J.; Bande-Fernández, J.J.; Alonso-Montes, C.; Carrillo-López, N. Chronic Kidney Disease—Mineral and Bone Disorders: Pathogenesis and Management. *Calcif. Tissue Res.* **2020**, *108*, 410–422. [CrossRef]
75. Kruzel-Davila, E.; Wasser, W.G.; Aviram, S.; Skorecki, K. *APOL1* nephropathy: From gene to mechanisms of kidney injury. *Nephrol. Dial. Transplant.* **2015**, *31*, 349–358. [CrossRef]
76. Sharma, S.G.; Bomback, A.S.; Radhakrishnan, J.; Herlitz, L.C.; Stokes, M.B.; Markowitz, G.S.; D'Agati, V.D. The Modern Spectrum of Renal Biopsy Findings in Patients with Diabetes. *Clin. J. Am. Soc. Nephrol.* **2013**, *8*, 1718–1724. [CrossRef]
77. Anguiano Gómez, L.; Lei, Y.; Devarapu, S.K.; Anders, H.-J. The diabetes pandemic suggests unmet needs for 'CKD with diabetes' in addition to 'diabetic nephropathy'-implications for pre-clinical research and drug testing. *Nephrol. Dial Transplant.* **2018**, *33*, 1292–1304. [CrossRef]
78. Goodman, W.G.; Goldin, J.; Kuizon, B.D.; Yoon, C.; Gales, B.; Sider, D.; Wang, Y.; Chung, J.; Emerick, A.; Greaser, L.; et al. Coronary-Artery Calcification in Young Adults with End-Stage Renal Disease Who Are Undergoing Dialysis. *N. Engl. J. Med.* **2000**, *342*, 1478–1483. [CrossRef]
79. Tomiyama, C.; Higa, A.; Dalboni, M.A.; Cendoroglo, M.; Draibe, S.A.; Cuppari, L.; Carvalho, A.B.; Neto, E.M.; Canziani, M.E.F. The impact of traditional and non-traditional risk factors on coronary calcification in pre-dialysis patients. *Nephrol. Dial. Transplant.* **2006**, *21*, 2464–2471. [CrossRef]
80. Hunt, J.L.; Fairman, R.; Mitchell, M.E.; Carpenter, J.P.; Golden, M.; Khalapyan, T.; Wolfe, M.; Neschis, D.; Milner, R.; Scoll, B.; et al. Bone formation in carotid plaques: A clinicopathological study. *Stroke* **2002**, *33*, 1214–1219. [CrossRef]
81. Lanzer, P.; Boehm, M.; Sorribas, V.; Thiriet, M.; Janzen, J.; Zeller, T.; St Hilaire, C.; Shanahan, C. Medial vascular calcification revisited: Review and perspectives. *Eur. Heart J.* **2014**, *35*, 1515–1525. [CrossRef] [PubMed]
82. Phan, O.; Burnier, M.; Wuerzner, G.; Nephrology, S.O. Hypertension in Chronic Kidney Disease—Role of Arterial Calcification and Impact on Treatment. *Eur. Cardiol. Rev.* **2014**, *9*, 115–119. [CrossRef] [PubMed]
83. Krasniak, A.; Drozdz, M.; Pasowicz, M.; Chmiel, G.; Michalek, M.; Szumilak, D.; Podolec, P.; Klimeczek, P.; Konieczynska, M.; Wicher-Muniak, E.; et al. Factors involved in vascular calcification and atherosclerosis in maintenance haemodialysis patients. *Nephrol. Dial. Transplant.* **2007**, *22*, 515–521. [CrossRef] [PubMed]
84. Moe, S.; Drüeke, T.; Cunningham, J.; Goodman, W.; Martin, K.; Olgaard, K.; Ott, S.; Sprague, S.; Lameire, N.; Eknoyan, G. Definition, evaluation, and classification of renal osteodystrophy: A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int.* **2006**, *69*, 1945–1953. [CrossRef] [PubMed]
85. Hsu, C.-Y.; Chen, L.-R.; Chen, K.-H. Osteoporosis in Patients with Chronic Kidney Diseases: A Systemic Review. *Int. J. Mol. Sci.* **2020**, *21*, 6846. [CrossRef] [PubMed]
86. Perneger, T.V.; Whelton, P.K.; Klag, M.J. Race and end-stage renal disease. Socioeconomic status and access to health care as mediating factors. *Arch. Intern. Med.* **1995**, *155*, 1201–1208. [CrossRef]
87. Phan, O.; Ivanovski, O.; Nguyen-Khoa, T.; Mothu, N.; Angulo, J.; Westenfeld, R.; Ketteler, M.; Meert, N.; Maizel, J.; Nikolov, I.G.; et al. Sevelamer Prevents Uremia-Enhanced Atherosclerosis Progression in Apolipoprotein E–Deficient Mice. *Circulation* **2005**, *112*, 2875–2882. [CrossRef]
88. Bessueille, L.; Magne, D. Inflammation: A culprit for vascular calcification in atherosclerosis and diabetes. *Cell. Mol. Life Sci.* **2015**, *72*, 2475–2489. [CrossRef]
89. Vaziri, N.D.; Norris, K. Lipid Disorders and Their Relevance to Outcomes in Chronic Kidney Disease. *Blood Purif.* **2011**, *31*, 189–196. [CrossRef]
90. Gisterå, A.; Hansson, G.K. The immunology of atherosclerosis. *Nat. Rev. Nephrol.* **2017**, *13*, 368–380. [CrossRef]
91. Cordes, K.R.; Sheehy, N.T.; White, M.P.; Berry, E.C.; Morton, S.U.; Muth, A.N.; Lee, T.-H.; Miano, J.M.; Ivey, K.N.; Srivastava, D. miR-145 and miR-143 regulate smooth muscle cell fate and plasticity. *Nature* **2009**, *460*, 705–710. [CrossRef]
92. Cory, S.; Adams, J.M. The Bcl2 family: Regulators of the cellular life-or-death switch. *Nat. Rev. Cancer* **2002**, *2*, 647–656. [CrossRef]
93. Chen, Z.; Wang, M.; Huang, K.; He, Q.; Li, H.; Chang, G. MicroRNA-125b Affects Vascular Smooth Muscle Cell Function by Targeting Serum Response Factor. *Cell. Physiol. Biochem.* **2018**, *46*, 1566–1580. [CrossRef]
94. Casella, S.; Bielli, A.; Mauriello, A.; Orlandi, A. Molecular Pathways Regulating Macrovascular Pathology and Vascular Smooth Muscle Cells Phenotype in Type 2 Diabetes. *Int. J. Mol. Sci.* **2015**, *16*, 24353–24368. [CrossRef]
95. Cavallari, C.; Dellepiane, S.; Fonsato, V.; Medica, D.; Marengo, M.; Migliori, M.; Quercia, A.D.; Pitino, A.; Formica, M.; Panichi, V.; et al. Online Hemodiafiltration Inhibits Inflammation-Related Endothelial Dysfunction and Vascular Calcification of Uremic Patients Modulating miR-223 Expression in Plasma Extracellular Vesicles. *J. Immunol.* **2019**, *202*, 2372–2383. [CrossRef]
96. Viegas, C.S.B.; Santos, L.; Macedo, A.L.; Matos, A.A.; Silva, A.P.; Neves, P.L.; Staes, A.; Gevaert, K.; Morais, R.; Vermeer, C.; et al. Chronic Kidney Disease Circulating Calciprotein Particles and Extracellular Vesicles Promote Vascular Calcification: A Role for GRP (Gla-Rich Protein). *Arterioscler. Thromb. Vasc. Biol.* **2018**, *38*, 575–587. [CrossRef]
97. Heiss, A.; DuChesne, A.; Denecke, B.; Grötzinger, J.; Yamamoto, K.; Renné, T.; Jahnen-Dechent, W. Structural Basis of Calcification Inhibition by α2-HS Glycoprotein/Fetuin-A. *J. Biol. Chem.* **2003**, *278*, 13333–13341. [CrossRef]
98. Heiss, A.; Eckert, T.; Aretz, A.; Richtering, W.; van Dorp, W.; Schäfer, C.; Jahnen-Dechent, W. Hierarchical Role of Fetuin-A and Acidic Serum Proteins in the Formation and Stabilization of Calcium Phosphate Particles. *J. Biol. Chem.* **2008**, *283*, 14815–14825. [CrossRef]

99. Wald, J.; Wiese, S.; Eckert, T.; Jahnen-Dechent, W.; Richtering, W.; Heiss, A. Formation and stability kinetics of calcium phosphate–fetuin-A colloidal particles probed by time-resolved dynamic light scattering. *Soft Matter* **2011**, *7*, 2869–2874. [CrossRef]
100. Pasch, A.; Farese, S.; Gräber, S.; Wald, J.; Richtering, W.; Floege, J.; Jahnen-Dechent, W. Nanoparticle-Based Test Measures Overall Propensity for Calcification in Serum. *J. Am. Soc. Nephrol.* **2012**, *23*, 1744–1752. [CrossRef]
101. Mencke, R.; van der Vaart, A.; Pasch, A.; Harms, G.; Waanders, F.; Bilo, H.J.G.; van Goor, H.; Hillebrands, J.-L.; van Dijk, P.R. Serum calcification propensity is associated with HbA1c in type 2 diabetes mellitus. *BMJ Open Diabetes Res. Care* **2021**, *9*, e002016. [CrossRef] [PubMed]
102. Van Dijk, P.R.; Hop, H.; Waanders, F.; Mulder, U.J.; Pasch, A.; Hillebrands, J.; van Goor, H.; Bilo, H.J.G. Serum calcification propensity in type 1 diabetes associates with mineral stress. *Diabetes Res. Clin. Pract.* **2019**, *158*, 107917. [CrossRef] [PubMed]
103. Chen, W.; Fitzpatrick, J.; Monroy-Trujillo, J.M.; Sozio, S.M.; Jaar, B.G.; Estrella, M.M.; Serrano, J.; Anokhina, V.; Miller, B.L.; Melamed, M.L.; et al. Associations of Serum Calciprotein Particle Size and Transformation Time with Arterial Calcification, Arterial Stiffness, and Mortality in Incident Hemodialysis Patients. *Am. J. Kidney Dis.* **2021**, *77*, 346–354. [CrossRef] [PubMed]
104. Ferrer, M.D.; Ketteler, M.; Tur, F.; Tur, E.; Isern, B.; Salcedo, C.; Joubert, P.H.; Behets, G.J.; Neven, E.; D'Haese, P.C.; et al. Characterization of SNF472 pharmacokinetics and efficacy in uremic and non-uremic rats models of cardiovascular calcification. *PLoS ONE* **2018**, *13*, e0197061. [CrossRef]
105. Raggi, P.; Bellasi, A.; Bushinsky, D.; Bover, J.; Rodriguez, M.; Ketteler, M.; Sinha, S.; Salcedo, C.; Gillotti, K.; Padgett, C.; et al. Slowing Progression of Cardiovascular Calcification with SNF472 in Patients on Hemodialysis: Results of a Randomized Phase 2b Study. *Circulation* **2020**, *141*, 728–739. [CrossRef]