PERIPHERAL VASCULAR DISEASE

Core Curriculum

Peripheral Arterial Calcification: Prevalence, Mechanism, Detection, and Clinical Implications

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Vascular calcification (VC), particularly medial (Mönckeberg's medial sclerosis) arterial calcification, is common in patients with diabetes mellitus and chronic kidney disease and is associated with increased cardiovascular morbidity and mortality. Although, the underlying pathophysiological mechanisms and genetic pathways of VC are not fully known, hypocalcemia, hyperphosphatemia, and the suppression of parathyroid hormone activity are central to the development of vessel mineralization and, consequently, bone demineralization. In addition to preventive measures, such as the modification of atherosclerotic cardiovascular risk factors, current treatment strategies include the use of calcium-free phosphate binders, vitamin D analogs, and calcium mimetics that have shown promising results, albeit in small patient cohorts. The impact of intimal and medial VC on the safety and effectiveness of endovascular devices to treat symptomatic peripheral arterial disease (PAD) remains poorly defined. The absence of a generally accepted, validated vascular calcium grading scale hampers clinical progress in assessing the safety and utility of various endovascular devices (e.g., atherectomy) in treating calcified vessels. Accordingly, we propose the peripheral arterial calcium scoring system (PACSS) and a method for its clinical validation. A better understanding of the pathogenesis of vascular calcification and the development of optimal medical and endovascular treatment strategies are crucial as the population ages and presents with more chronic comorbidities. © 2014 Wiley Periodicals, Inc.

Key words: vascular calcification; peripheral artery disease; atherosclerosis

BACKGROUND

Vascular calcification (VC) has been recognized, studied, and described for centuries. Historical records note the description of "ossification of the arteries" dating back to the early 16th century, a finding that has remained the focus of continued research [1,2]. However, despite centuries of study, the challenges surrounding the ideal treatment of VC remain uncertain. This is particularly pertinent as the field of endovascular medicine continues efforts to fully elucidate and define the optimal treatment strategies to address this vexing clinical problem. Chronic kidney disease (CKD) and diabetes mellitus (DM) are the leading causes of VC. In these disease states, there is an accumulation of calcium (Ca^{++}) and phosphate (P) in arteries with mineral deposits in the intimal or medial layer of the vessel wall [3–6]. The association between VC and chronic comorbidities, including coronary artery disease (CAD) [6,7], peripheral arterial disease

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(PAD) [8], DM [9,10], and CKD [4,11–13] is well established. In patients with CKD, VC is associated with an increased risk of cardiovascular morbidity and mortality [4,12] and when patients progress to chronic hemodialysis, intimal, and medial calcification develops rapidly [13]. When coronary arteries are affected with calcification, obstruction to myocardial perfusion may result with an increased risk of infarction. As the population ages, clinicians will increasingly place emphasis on chronic disease management and VC. Specifically, in treating patients with PAD, physicians will focus on less invasive endovascular treatments.

Calcium is an essential ion in many metabolic pathways, including the thrombosis cascade, the regulation of heart rate and contractility, neuronal activity, the endocrine system, and, paradoxically, in the genesis of VC. Although stored primarily in bones and teeth, calcium intake is only through diet where its uptake is proportional to dietary content. Therefore, excess Ca^{++} only results when dietary allowance is regularly surpassed or in diseased states, where its storage is compromised. Calcium may also accumulate in various organs: the spleen, liver, kidney, and the circulatory system, where it is deposited in the arterial intima and media and may eventually lead to obstructive atherosclerosis.

Currently, a comprehensive body of literature exists to describe calcification in different vascular beds; yet, there is a paucity of information specifically related to the peripheral arteries of the lower extremities. This review article will focus on the prevalence of VC in lower extremity PAD, proposed mechanisms of formation, clinical consequences, and the challenges it presents to the effectiveness and durability of currently available endovascular therapies.

MECHANISMS OF VASCULAR CALCIFICATION

Vascular calcification is a pathologic response to toxic stimuli involving metabolic substances and/or inflammatory cells [1,3,8,15,16]. Historically, VC was considered to be a passive process, the result of Ca^{++} and P ions exceeding solubility in tissue fluid, thereby inducing the precipitation and deposition of hydroxyapatite crystals. However, current thinking has shifted away from this passive theory; VC formation is now considered a complex, actively controlled intracellular molecular process, involving the differentiation of macrophages and vascular smooth muscle cells (VSMCs) into osteoclast-like cells, similar to that which occurs in bone formation [2–4,7].

The alterations in serum Ca^{++} and P levels, in concert with the oxidative stress caused by locally generated hydrogen peroxide (H_2O_2), promote the differentiation of VSMCs in the vascular wall to an osteogenic phenotype. These alterations are also associated with the significant loss of endogenous VSMC calcification inhibitors (e.g., matrix Gla protein, a calcium-binding protein involved in bone formation, pyrophosphate, and the inducible inhibitor osteopontin) and circulating inhibitors, such as fetuin-A [2]. A detailed discussion of the intracellular interactions and molecular processes associated with VC is beyond the scope of this review; the reader is referred to excellent overview of the subject [2,3]. However, the underlying pathophysiological mechanisms resulting in VC can be broadly described as: (1) elevation in serum Ca^{++} and P levels, (2) the induction of osteogenesis, (3) the inadequate inhibition of the mineralization process, and (4) the migration and differentiation of macrophages and VSMCs into osteoclast-like cells [2–5] (Fig. 1). A potential genetic role in medial VC has been proposed whereby gene mutations that regulate VSMC extracellular matrix phosphate production and protein promoters of VC have been reported [17]. Regardless of the mechanisms involved, the ultimate result of VC is the formation of calcified deposits of hydroxyapatite crystals within the tissues that initiate the calcification process.

Two categories of VC have been described: intimal, medial (or Mönckeberg's medial sclerosis). Intimal calcification is associated with atherosclerotic plaques and thought to result from modified lipid accumulation, pro-inflammatory cytokines, and apoptosis within the plaque that induce osteogenic cell differentiation. The teleological function of intimal calcification may be to isolate and interrupt the progress of an abnormal cellular process, thereby protecting healthy adjacent intima [2]. However, obstructed blood flow by stenotic intimal lesions may lead to decreased organ perfusion and ischemia. Medial calcification is considered to be more widespread in the lower abdominal region, associated with PAD [18–21], and results from the osteogenic differentiation of VSMCs within the medial layer of the vessel wall [14]. Ca^{++} accumulation begins as an amorphous mineral deposit and undergoes progressive remodeling, ultimately mineralizing into mature bone. Although medial calcification is generally not associated with luminal obstruction, the decrease in the arterial vessel wall elasticity and compliance may ultimately lead to atherosclerosis, reduced perfusion, and eventually, CAD and PAD.

PREVALENCE OF VASCULAR CALCIFICATION

Aging is a major cause of VC [22] and, from age 20–90 years, its incidence may increase by 30% [1]. VC may occur throughout the vasculature, although prevalence estimates vary [22,23]. In an unselected
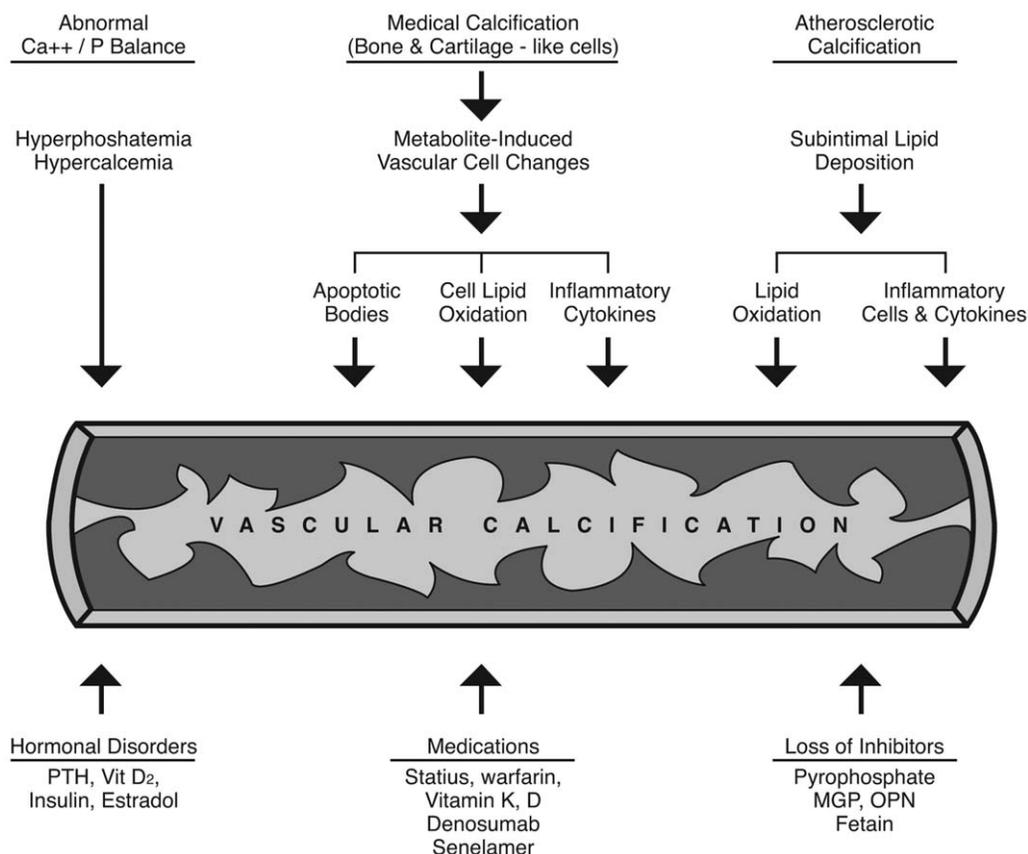
Fig. 1.   Schematic diagram depicting multiple mechanisms leading to vascular calcification.

cohort of asymptomatic patients presenting for preventative care ($n = 650$), 61% of patients displayed atherosclerotic calcification in either carotid, coronary, proximal and distal aorta or iliac vascular beds [24]. These authors also found that calcification increased exponentially with age, noting that more than two thirds of patients over 70 years old manifested calcification in all vascular beds studied. Age and hypertension were the most important risk factors for systemic calcific atherosclerosis. In a similar large cohort study ($n = 4,291$), after a mean 7.8 years, the prevalence of calcification ranged from 31% to 55% in the carotid, coronary, iliac arteries and thoracic and abdominal aorta. Notably, the presence of calcium in the thoracic aorta, carotid, and iliac arteries was associated with total mortality; whereas, the presence of coronary calcium was associated with cardiovascular mortality. In another patient cohort study ($n = 4,450$), the same investigators assessed the association between renal artery calcification and mortality; renal artery calcification was present in 14% of the patients and conferred a 63% increased risk for all-cause mortality. However, due to the small number of cardiovascular deaths, a significant associa-

tion could not be established between renal artery calcification and cardiovascular mortality [23]. While it is difficult to extrapolate these results from a population pursuing preventative care, the results of these studies provide evidence that systemic VC may affect as many as 30–50% of asymptomatic patients in the United States [22,24]. Although lower extremity VC is commonly found in PAD and critical limb ischemia (CLI), clinical investigations are limited and severely calcified vessels are commonly excluded from investigational device trials. Therefore, true prevalence of VC in symptomatic PAD patients remains undefined.

DETECTION OF VASCULAR CALCIFICATION

A number of non-invasive imaging techniques, including computed tomographic (CT) and magnetic resonance (MR) imaging, duplex ultrasonography, measurement of pulse wave velocity, echocardiography, planar radiographs, and indirectly, the ankle-brachial index (ABI) are available for the detection of carotid, renal, and peripheral calcification. CT and MR imaging are highly sensitive methods to assess the degree and

extent of VC. However, both imaging modalities use contrast agents (iodinated for computed tomography and gadolinium-based for MR), which are associated with potential nephrotoxicity, and CT exposes patients to ionizing radiation. The highest-risk patient has baseline CKD, especially with concomitant DM, in which the risk of contrast-induced nephrotoxicity may be as high as 25% after angiographic procedures [25]. It is noteworthy that the arterial calcification scores generated by CT are a composite of both medial and intimal calcification, but still correlate with coronary angiographic findings [26]. Plain lateral abdominal radiography is a valuable, albeit semi-quantitative, tool for the detection of vascular calcification in patients with CKD patients. The latest iteration of the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend a lateral abdominal radiography or echocardiography for the detection of vascular or valvular calcification, especially for patients with stage 3–5 CKD [27]. Finally, when performing non-invasive vascular tests, specifically the ABI, the inability to compress the ankle arteries with a sphygmomanometer cuff suggests the presence of medial arterial calcification, defining PAD [28].

PREVENTION AND MANAGEMENT

Because intimal VC is associated with atherosclerosis, the primary therapeutic goal is to prevent cardiovascular events through the control and/or elimination of risk factors, such as hypercholesterolemia, hypertension, diabetes, smoking, obesity, and physical inactivity. In patients with the metabolic syndrome, diabetes, and CKD, in whom media calcification is significantly more prevalent, treatment of VC is focused on the management of bone and mineral metabolism disorder [29]. However, because the mechanisms of bone formation and mineralized vessels are similar, unwanted effects on bone is an extremely important therapeutic issue and must be considered when targeting a vessel-specific therapy.

Secondary hyperparathyroidism (SHPT), a condition associated with progressive renal failure, cardiovascular disease and VC, develops when the serum P levels are too high and serum Ca^{++} levels too low, causing more Ca^{++} to be taken from the bones and reabsorbed by the intestines and kidney. Consequently, management of SHPT is central to the therapeutic strategies in bone and mineral metabolism disorders and has focused on minimizing hyperphosphatemia and hypocalcemia without producing hypercalcemia and suppressing PTH activity. This is achieved with oral phosphate binders, active vitamin D analogs and Ca^{++} mimetics.

Phosphate Binders

Calcium-based P binders are commonly used to treat hyperphosphatemia but, because a significant interaction has been observed between these drugs and bone metabolism, further increasing the Ca^{++} burden in patients with hypercalcemia or severe VC, it is recommended that Ca^{++}-free phosphate binders (e.g., sevelamer; Renvela™) be used [30,31]. Sevelamer produces a significant decrease in serum Ca^{++} levels without altering serum P levels, and the decrease in Ca^{++} levels has been suggested as the mechanism for the lower rates of VC. In addition, treatment with sevelamer decreases the levels of total and low-density lipoprotein cholesterol, apolipoprotein B, β2-microglobulin and C-reactive protein, while increasing the level of high-density lipoprotein.

Vitamin D Analogs and Calcium Mimetics

No clinical study has yet evaluated the effect of vitamin D supplementation on VC, but the results of studies in mice with CKD demonstrated that the administration of vitamin D receptor agonists at doses sufficient to correct SHPT were associated with a significant reduction in aortic calcification [32]. The authors suggested that the protective effect was likely due to the up-regulation of klotho and the anti-calcification factor osteopontin [32] or through a reduced osteoblastic gene expression in the aorta [33]. In patients with CKD, vitamin D therapy decreases serum PTH levels [34] and significantly reduces the incidence of cardiovascular events and improves survival. In patients with end-stage renal disease and SHPT, treatment with cinacalcet (Sensipar™), a synthetic G-protein coupled receptor that controls Ca^{++} homeostasis by regulating the release of PTH, results in fewer hospitalizations for cardiovascular complications compared with placebo [35]. Cinacalcet, in combination with low-dose vitamin D, also attenuates coronary and aortic calcification in hemodialysis patients [36].

CLINICAL CHALLENGES

The presence of VC, particularly in the infrainginual vasculature, represents a significant challenge to current endovascular device strategies. Currently, most ongoing U.S. Investigational Device Exemption (IDE) endovascular device protocols specifically exclude patients with "severe" calcification. The exclusion of this patient population is unfortunate, though understandable; given the desire to avoid lesion morphologies, which may be associated with increased device and/or procedure related adverse events (i.e., severe dissections, vessel perforations, atheroembolization)

and potential poor clinical outcomes. The presence of severe VC within a chronic total occlusion (CTO) presents a particular challenge; severe calcification at the CTO entry point, within the CTO core and/or medial calcification along its length may make the penetration of hydrophilic guidewires, passage of balloon catheters and CTO crossing devices (e.g., The Crosser[TM] CTO Recanalization Catheter; C. R. Bard, Murray Hill, NJ) and sub-intimal re-entry devices (e.g., Outback[TM] Re-entry Catheter, Cordis Corp., New Brunswick, NJ; Pioneer Plus[TM] Re-entry Catheter, Volcano, San Diego, CA). With the use CTO re-entry devices, severe medial calcium may make the sub-intimal passage of the device difficult or the penetration of the nitinol re-entry needle through the calcified media and/or intima and into the vessel lumen impossible. This situation may require the operator to seek a more distal, less calcified re-entry point, thereby functionally extending the length of the arterial segment that requires endovascular treatment.

An added impediment to defining the appropriate role of endovascular therapies in patients with calcified peripheral arteries is the lack of a validated, quantitative calcium scoring system. Unlike the coronary circulation, where angiographic-derived calcium classification schemes have validated the presence of "heavy calcification" to procedural clinical outcomes [37], a similar calcium scoring system has not been established in the periphery. Ongoing regulatory peripheral device trials use a variety of subjective, semi-quantitative, angiographic, and fluoroscopic-based assessments of VC severity. These grading scales typically assess: the degree of vessel wall calcium based on a single AP or two orthogonal angiographic and/or fluoroscopic views (Fig. 2); the presence of one-sided versus circumferential vessel wall calcification; and define the length of VC relative to the length of the target atherosclerotic lesion. Given the absence of a validated peripheral arterial calcium scoring system (PACSS) (Table I). PACSS highlights the pathologic location of calcification (intima, media, combined) along with the length of the segment affected. We intend to validate PACSS based on angiographic core lab adjudicated assessment and correlate the objective assessment of VC with endovascular device-related acute procedural and 30-day major adverse events (MAEs).

Regardless, the lack of a uniform, validated peripheral artery calcium scoring system has not dampened investigator enthusiasm in evaluating endovascular devices to address this vexing problem, although the published experience reflect mixed results. Balloon angioplasty of "severely" calcified lesions is limited by early elastic recoil and poor acute and long-term outcomes [38]. Similarly, the high compressive forces applied against slotted tube femoropopliteal nitinol stents by rigid calcified plaques results in incomplete and/or eccentric stent expansion, a residual percent diameter stenosis frequently >30% which is, in turn, linked to inferior patency outcomes when compared to fully expanded stents [39]. The Supera® Stent (iDEV; Abbott Vascular, Mountain View, CA), a unique closed cell interwoven nitinol stent design, provides four times higher compression resistance force and the potential for superior stent expansion in severely calcified lesions. In an observational registry, this stent design resulted in superior vessel lumen preservation, particularly in severely calcified lesions, when compared to traditional nitinol stent designs [40].

Extractional atherectomy (Turbohawk[TM], Covidien, Minneapolis, MN) [41], orbital atherectomy (Diamondback360[TM], Cardiovascular Systems, Minneapolis, MN) [42], laser atherectomy [43] (TurboElite[TM], Spectranetics, Colorado Springs, CO), rotational aspiration atherectomy [44] (Jet Stream[TM], Bayer Medical, Kirkland, WA) and rotational atherectomy [45] (Rotoblator[TM], Boston Scientific, Natick, MA) have evaluated device efficacy in treating VC with varying degrees of procedural and near term success [46]. Unfortunately, to date, there have been no robust, prospective, independently core lab adjudicated evaluation of device related acute and/or 30-day MAEs and 12-month target lesion patency after treating severe VC. However, surgical bypass or endartectomy remains a very acceptable alternative to an endovascular approach (Fig. 3).

The DEFINITIVE Ca++ registry evaluated acute procedural and 30-day MAEs using the TurboHawk[TM] atherectomy catheter in moderate-severe to severe calcified superficial femoral artery (SFA) lesions in Rutherford 2–4 patients with mean lesion length of 3.9 cm. In this angiographic core laboratory adjudicated registry ($n = 133$), Claire et al., reported that the TurboHawk[TM] atherectomy catheter, used in conjunction with the Spider® distal protection device, appeared to be safe and provided adequate debulking of calcified SFA lesions (defined as ≤50% residual diameter stenosis post-plaque excision) in 150/162 lesions (92%) [41]. Adjunct/bailout stenting was required in 4.1% of lesions with a 30-day freedom from MAEs of 93.1%; three SFA perforations, one thrombosis, and three distal embolization events, all without clinical sequelae, were reported. Notably, the procedural duration (72 minutes) to treat relatively short lesions lengths and increased device costs associated with the required use of a distal protection device, highlight the challenges of treating severely calcified peripheral arteries.

Despite the lack of a uniform accepted calcium scoring system, several investigators have established the importance of "heavy" SFA calcification and its impact on long-term effectiveness of new evolving

Fig. 2. The fluoroscopic (panel A) and digital subtraction angiographic (panel B) appearance of severe calcification involving the SFA.

technologies, specifically drug coated balloons. Fanelli [47] described the impact of increasing degrees of SFA calcification on 12-month primary patency and late lumen loss (LLL) after the use of drug eluting balloon technology (IN.PACT Admiral™, Medtronic, Inc., Santa Rosa, CA) in 60 Rutherford Class 2–4 patients

TABLE I. Proposed Peripheral Arterial Calcium Scoring System (PACSS)

Proposed Fluroscopy/DSA based Peripheral Arterial Calcification Scoring Systems (**PACSS**): Intimal and medial vessel wall calcification at the target lesion site as assessed by high intensity fluoroscopy and digital subtraction angiography (DSA) assessed in the AP projection.

Grade 0: No visible calcium at the target lesion site

Grade 1: unilateral calcification < 5cm; a) intimal calcification; b) medical calcification; c) mixed type

Grade 2: unilateral calcification ≥ 5cm; a) intimal calcification; b) medical calcification; c) mixed type

Grade 3: bilateral calcification < 5cm; a) intimal calcification; b) medical calcification; c) mixed type

Grade 4: bilateral calcification ≥ 5cm; a) intimal calcification; b) medical calcification; c) mixed type

with a 6.1 cm mean calcified lesion length. Using lower extremity CT angiography, these investigators observed that circumferential calcification, defined as $270°$-$360°$ around the circumference of the SFA, was associated with a significant increase in 12-month LLL and a 50% increase in loss of primary patency when compared to lesser degrees of vessel wall calcium. These investigators hypothesized that despite clinical evidence of a biological effect of paclitaxel, vessel wall calcification appeared to present a barrier to its optimal effect. However, it is still unclear as to the mechanism(s) which might contribute to the increased loss of patency in this lesion cohort: suboptimal vessel expansion and delayed vessel recoil after balloon angioplasty as a result of the vessel non-compliance, a mechanical barrier of calcified vessel wall segments for sufficient drug penetration into the media/adventitia, or both. Paclitaxel is a lipophilic drug, which must be combined with a hydrophilic excipient or spacer [e.g., urea (FreePac™; Medtronic, Minneapolis, MN) to facilitate sufficient vessel wall penetration,
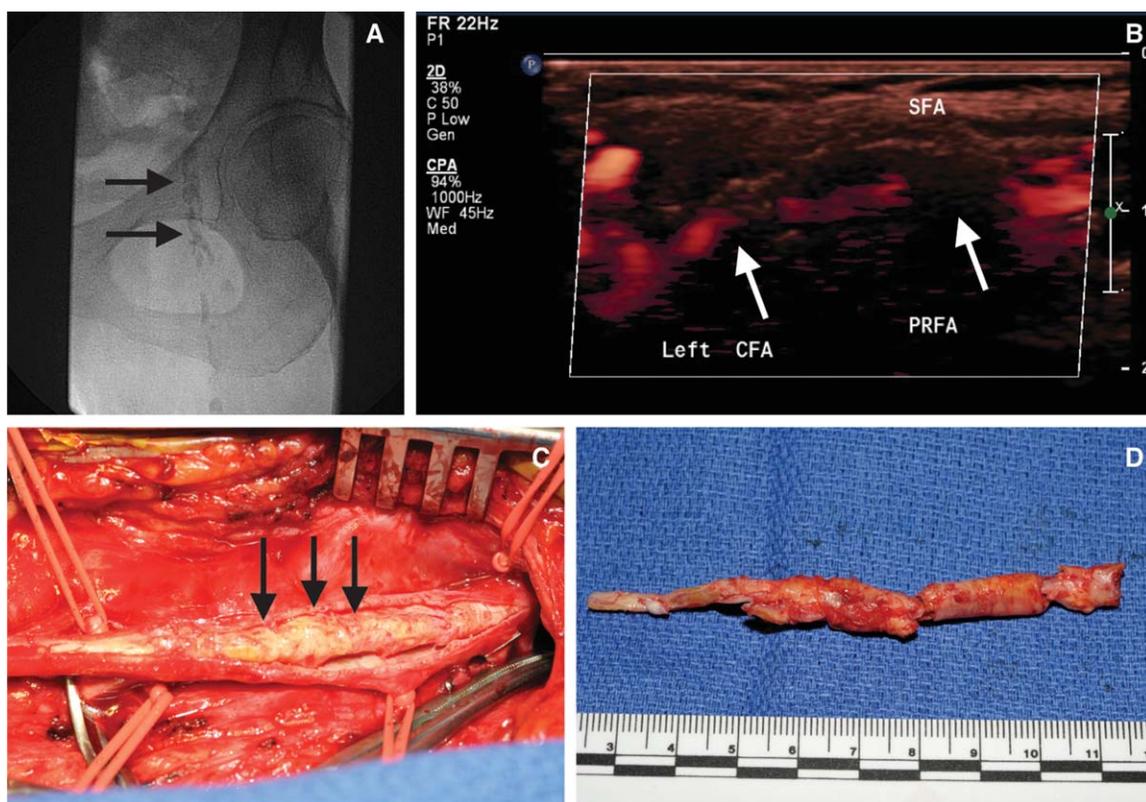
Fig. 3. The fluoroscopic (panel A), Duplex ultrasonographic (panel B) and surgical appearance (panels C,D) of severe vascular calcification in a 64 year old diabetic female with symptomatic peripheral arterial disease. Severe circumferential calcification involves the common femoral artery (panel A, black arrows). Sonographic "drop-out," seen as voids in the sonographic signal, is caused by dense calcification (panel B, white arrows). Common femoral artery incised during endarterectomy demonstrating densely calcified segment (black arrows, panel C) and after excision (panel D).

concentration, and retention. These hydrophilic spacers create a porous coating with a high contact surface between the lipophilic drug molecules and the vessel wall resulting in a uniform and efficient release of paclitaxel after a single balloon inflation, which guarantees high bioavailability of paclitaxel in the vessel wall. Localized plaque and vessel wall retention of paclitaxel serves as a reservoir for sustained drug delivery and diffusion into the deeper vessel wall layers such as adventitia where the target cells for the drug release, the smooth muscle cells, are located [48,49]. Therefore, three potential scenarios that might negatively affect the biological drug effect in severely calcified lesions exist: (1) intimal bone like calcified plaques might prevent the drug particles from forming drug reservoirs with sufficient concentration and might promote an increased secondary wash off of the released drug, (2) circumferential vessel wall calcification might negatively affect drug penetration into the adventitia, and (3) circumferential calcification in Mönckeberg's medial sclerosis interferes and/or prevents positive arterial remodeling in presence of atherosclerosis as described by Glagov [50].

In a small ($n = 30$), single-center evaluation of SFA lesions in Rutherford 3–6 patients, Cioppa et al., offered a potential solution to the presence of severe VC [51]. These investigators noted that an endovascular strategy to first debulk severe VC, defined as calcification >1 cm on both sides of the vessel wall under fluoroscopy, with the TurboHawk® catheter before drug coated balloon (IN.PACT Admiral™) deployment, was associated with a 90% 12-month primary patency rate. These investigators hypothesize that severe VC is an impediment to the diffusion of the lipophilic drug paclitaxel molecule.

CONCLUSION

Vascular calcification is recognized as an active cellular process that occurs in response to metabolic insults that is intimately entwined with aging, atherosclerosis, and other related chronic diseases (i.e., DM,

CKD). The prevalence of VC in lower extremity PAD is inadequately defined, but data extrapolated from other vascular beds provide evidence that 30–50% of patients may manifest some degree of VC. Minimizing traditional atherosclerotic risk factors, together with the avoidance of hypercalcemia, hyperphosphatemia and secondary hyperparathyrodism, are important preventive measures for the development and progression of VC. Because the pathophysiologic mechanisms associated with VC are poorly characterized and there are few effective pharmacotherapeutic options to prevent VC, the debulking of lower extremity VC as an adjunct to balloon angioplasty or drug delivery, may improve vascular remodeling and/or enhance drug diffusion into the vessel wall and promote drug effect. This may reduce restenosis and improve tissue perfusion with the potential beneficial effect of promoting walking distance in claudicants and accelerate wound healing and promote limb salvage in CLI patients. Understanding the true prevalence of peripheral VC, its metabolism, and the potential role of medical devices to modify calcified plaques, is central to defining endovascular strategies to successfully manage these complex PAD patients.

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