MEDIAL ARTERIAL CALCIFICATION (MONCKEBERG'S SCLEROSIS) IN DIABETIC AND NON-DIABETIC PATIENTS

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Abstract

Medial arterial calcification is an entity observed with high frequency in diabetic patients, but its clinical significance is relatively unknown. New data revealed that medial calcification of the arteries is an active process involving phenotypic differentiation of vascular smooth muscle cells. Epidemiological observations link medial sclerosis not only to diabetes, but also to other disease states commonly encountered in the population, such as osteoporosis and chronic kidney disease. Few prospective studies have been conducted in order to determine the role that medial arterial calcification plays as a prognostic indicator in diabetics or in other populations. This review tries to shed some light on this pathologic process and its presumed consequences for diabetic and non-diabetic patients.

Keywords: medial arterial calcification, diabetes, vascular smooth muscle cells, osteoporosis, chronic kidney disease, cardiovascular disease

Background

Monckeberg's sclerosis represents calcification of vascular media of small to medium size vessels without associated intimal thickening. Mineral deposition in arteries can occur either as a component of atheroma or in the absence of atherosclerotic plaque. In atherosclerotic plaque, calcification typically forms in the intima, most often near the base of the plaque adjacent to the medial layer of the artery and is associated with hyperlipidemia, macrophage recruitment and inflammation. Calcifications near the luminal surface may result in erosions and have been implicated in plaque disruption and thrombosis. In contrast, calcification of the medial layer of arteries occurs independently of atherosclerosis [29]. This type of calcification, known as Monckeberg's sclerosis, has radiographically a classic "railroad tracks" pattern (see Figure 1). It is a condition that leads to the stiffening of the elastic layer of the arterial wall, but in contrast to intimal artery calcification it does not lead to obstruction of the arterial lumen. Medial calcification can occur in otherwise normal young patients with no overt metabolic disease, increases linearly with age, and is common in elderly patients.

Far from being understood, medial calcification is related to disorders characterized by generalized metabolic,

electrolyte, or pH derangements, such as hypervitaminosis D, end-stage renal disease (ESRD), and diabetes mellitus. The cellular biology of medial arterial calcification (MAC) has been extensively studied, with some surprising new data in recent years. However, the clinical significance of this finding is largely unknown, with only a handful of trials that link medial calcification to hard clinical end-points.

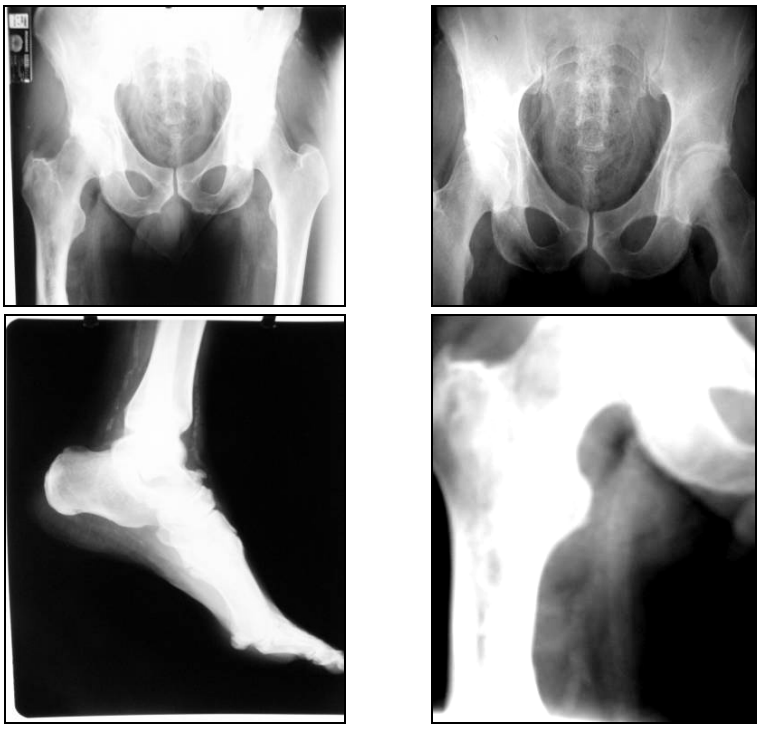

Figure 1. Radiographical images (with detail in the lower right corner) of a 48-years old, type 1 diabetic patient who presented for a femoral fracture, showing extensive medial calcification of intrapelvic, femoral and tibial arteries.

With Monckeberg's sclerosis remaining mainly an incident finding on plain radiological films, and no corresponding consequences in clinical approach, this review tries to shed some light on the mechanisms behind arterial medial calcification, its association with conditions mentioned above, and its presumed clinical importance in diabetics, as well as in other groups of patients.

Cellular biology of Monckeberg's sclerosis

Monckeberg's sclerosis typically affects arteries that are less prone to develop atherosclerosis, such as the arteries supplying the extremities, the abdominal visceral arteries, arteries to the thyroid and breast, but it also is frequently encountered in the aorta. Medial calcification has not been reported to occur in the coronary arteries, so when

calcification is observed in the coronary arteries, it is almost certainly associated with intimal plaque.

In contrast to early theories stipulating the passive genesis of MAC by metastatic precipitation of apatite, newer research has unveiled that in fact Monckeberg's sclerosis is an active process of trans-differentiation of vascular smooth muscle cells (VSMCs). The presence of bone proteins in calcified vascular lesions has suggested that osteogenic mechanisms may play a role in vascular calcification. Several studies have reported differential expression of bone matrix proteins in MAC compared with normal arteries or to intimal calcification. For example, Shanahan et al. [36] compared mRNA and protein expression of bone matrix proteins in human peripheral arteries with and without medial calcification. Normal arteries expressed matrix Gla protein (MGP) and osteonectin in the media. In the medial layer of the arteries with medial calcification, there were decreased levels of expression of MGP and osteonectin, but increased expression of alkaline phosphatase, bone sialoprotein (BSP), bone Gla protein (BGP, or osteocalcin), and collagen II (a differentiation marker for chondrocytes) compared with normal vessels. There were no differences in expression of collagen I, which was variably expressed. MAC was noted to invariably occur directly adjacent to medial VSMCs expressing typical SMC markers such as SMCα actin, but was never seen in the vicinity of macrophages or lipid deposits. This contrasted with scattered, globular calcification of the intima, which was invariably associated with lipid and macrophages. This osteocytic/chondrocytic transformation with subsequent mineralization of VSMCs suggests that MAC is a regulated process that reflects either an adaptive response to limit mineralization or an osteogenetic response to facilitate it.

Further different mechanisms could be involved in vascular calcification. One of them is the lack of inhibitors of mineralization such as pyrophosphate, and matrix Gla protein, or fetuin/α2-HS-glycoprotein (fetuin is a major inhibitor of apatite found in the circulation and it's low level correlates with elevated cardiovascular mortality in hemodialysis patients). Another one is represented by deposition of circulating nucleational complexes released from bone turnover that may explain the link between vascular calcification and osteoporosis in postmenopausal women (see below). Phospholipid-rich membranous debris and apoptotic bodies provided by cell death may serve to nucleate apatite, especially in diseases with a high prevalence of necrosis and apoptosis, such as atherosclerosis. Elevated calcium, phosphate, and calcium-phosphorus product (CaxP) promote apatite nucleation and crystal growth and would be expected to exacerbate vascular calcification initiated by any of the other mechanisms described above [14].

Relation to diabetes mellitus

Numerous reports have reported the high prevalence of MAC commonly seen in patients with diabetes mellitus [4,9,13,20,25,31,43]. Medial calcification appears to be an indicator of the severity and/or duration of diabetes, because its association with many complications and

sequelae of diabetes, particularly autonomic neuropathy [10,12,13,41,43].

There also may be an independent association of medial calcification with nondiabetic neuropathies. Goebel and Fuessl [15] found, 6–8 years after bilateral lumbar sympathectomy that 93% (25 of 27) of patients exhibited MAC in both feet, and most of these patients were not diabetic. In the control group only 15% (4 of 27) of patients had MAC on X-ray films. Twenty patients had no evidence of medial calcification before surgery, but seven who underwent bilateral sympathectomy exhibited medial calcification in both feet, and 11 of 13 patients who received unilateral sympathectomy developed medial calcification only on the side of the operation, with no changes on contralateral side. In general, after unilateral sympathectomy, the incidence of calcified arteries on the same side as the operation was higher than that on the contralateral side (88 vs. 18%; $P<0.01$). Diabetic patients appear to have more extensive calcification than non-diabetic subjects, with no significant differences between groups. Thus, sympathetic denervation can cause Monckeberg's sclerosis regardless of whether diabetes mellitus is also present or not. MAC in diabetes may be related to destruction of sympathetic innervation as a part of diabetic neuropathy. Non-neuropathic diabetic patients and age-matched nondiabetic patients had a similar prevalence of MAC, with a moderate but significant correlation ($r=0.32$) between medial calcification and duration of diabetes (Young et al. [43]) Logistic regression showed that serum creatinine, vibration perception threshold, and duration of diabetes predicted the probability of vascular calcification.

A genetic component may be involved in MAC. Genetic analyses on a large group of Pima Indians supports the notion that medial calcification may have determinants that are independent of diabetes. These Pima Indians have a very high rate of MAC and they have been extensively studied because of one world's highest reported rates of obesity, insulin resistance, and type 2 diabetes, but nevertheless exhibit relatively low risk for atherosclerosis and the cardiovascular complications that are highly prevalent in other diabetic populations. Offspring of parents with medial calcification were significantly more likely to have medial calcification, even after adjusting for the effects of age, sex, diabetes, serum cholesterol, and blood pressure. Offspring of one parent with medial calcification had an odds ratio (OR) of 3.3 for having calcification [95% confidence interval (CI) 1.5 to 7.6], whereas if both parents manifested medial calcification, the OR increased to 8.1 (95% CI, 3.4 to 18.8). So, parental MAC increases the risk of MAC in offspring (Narayan et al. [24])

All of these studies are most consistent with the interpretation that medial artery calcification is associated with diabetes, particularly with autonomic neuropathy but in addition there is a genetic component that is independent of the determinants of diabetes and also of atherosclerotic disease.

Relation to cardiovascular disease

In patients with diabetes, MAC may be associated with increased risk of

cardiovascular complications. Lehto et al. [20] found that medial calcification was a strong independent predictor of total (risk factor-adjusted OR 1,6, and 95% CI, 1,2 to 2,2), cardiovascular (OR 1,6, 95% CI 1,1 to 2,2), and chronic heart disease mortality (OR 1,5, 95% CI 1,0 to 2,2) (see below for details). Others have similarly reported that medial calcification is associated with increased risk of future cardiovascular events in patients with diabetes [25].

Other studies did not find that MAC was an independent predictor of elevated cardiovascular risk (Maser et al. [22]). Also, Everhart et al. [11] found that nondiabetic subjects with MAC did not have higher mortality rates than subjects without medial arterial calcification. The reasons for these discordant results are unclear.

The harmful sequelae of medial calcification in patients with diabetes may be secondary to stiffening of arterial tone, increased systolic blood pressure, and impairment of endothelium-dependent relaxation, all of which can cause abnormal flow characteristics that may facilitate or synergize common complications of diabetes such as atherogenesis. (Edmonds, [9]). How this might occur is unclear at this point, particularly in view of evidence which suggests that in patients without diabetes mellitus, MAC may not predict increased cardiovascular risk.

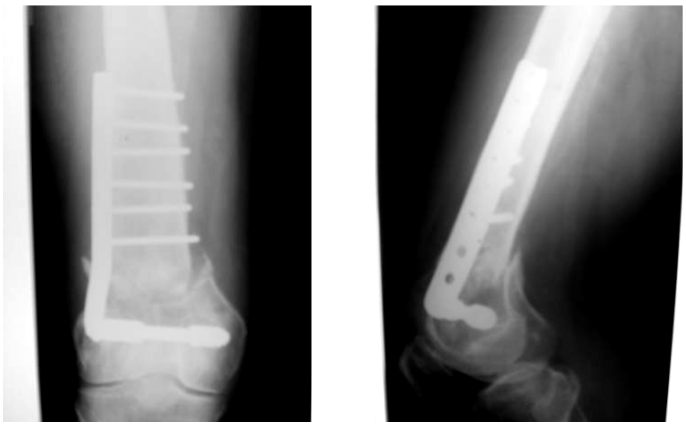

Figure 2. Arterial calcification of the deep femoral artery in the patient presented in figure 1, who underwent surgery for supracondylar femoral fracture on osteoporotic bone.

Relation to osteoporosis

Lots of population-based longitudinal studies in the recent years have demonstrated an intriguing association between osteoporosis and MAC or arterial stiffness [3,17,19,35,37-40] (see Figure 2). A strong association has been found between bone demineralization and progression of arterial calcification, with an increased risk for fractures, significantly higher for women with calcifications than for those without [35]. Osteoporosis and MAC are both influenced by common risk factors, such as aging, chronic inflammation, dyslipidemia, oxidative stress, estrogen deficiency, and vitamin D and K deficiencies, and so this epidemiological link now appears intuitive.

Imbalance between bone resorption and bone repair results in bone loss. Calcium and phosphate, and other regulatory factors released from bone matrix with increased resorption play important roles in VSMC trans-differentiation (VSMC differentiation into osteoblast-like cells and their subsequent mineralization). These proteins include osteopontin, osteoprotegerin (OPG), the receptor activator of nuclear factor (NF)-kappa B ligand (RANKL) and the receptor activator of NF-kappa B (RANK) system [2,6,16,18,28,30,32,33]. RANKL is expressed by osteoblastic lineage cells and T lymphocytes and acts by binding to its physiological receptor, RANK, which is expressed on osteoclasts. Ligation of the receptor stimulates all aspects of osteoclast function, such as differentiation, maturation, fusion, survival, and activity.

By contrast, OPG seems to be a protective factor against both osteoporosis and MAC. It is produced by a variety of tissues, including the cardiovascular system, and acts as a soluble decoy receptor by neutralizing RANKL. OPG-deficient mice develop osteoporosis with severe cortical and trabecular bone porosity, high fracture rates, exhibit medial calcification of the aorta and large arteries and develop other vascular anomalies, like dissections. OPG inhibits arterial calcification induced by vitamin D and warfarin. By binding to RANKL, OPG inhibits osteoclastogenesis and bone resorption, may also limit local inflammatory responses and in vitro OPG acts as an antiapoptotic factor, prolonging endothelial cell survival.

This is in contrast to the fact that, in a recent study, OPG was linked to silent myocardial ischemia (SMI) in asymptomatic diabetic patients. Avignon et al. [1] found that OPG is an independent predictor of SMI for both sexes, type 1 and type 2 diabetic patients, with or without diabetic nephropathy. No significant correlation between peripheral arterial disease and high levels of OPG has been found in this study. Other risk factors besides OPG, such as hs-CRP, lipoprotein [a], fibrinogen, homocysteine, and adiponectin were not predictors of SMI.

Relation to chronic kidney disease

Vascular calcification is highly prevalent and often severe in patients with chronic kidney disease. More than half the deaths in patients with end-stage renal disease (ESRD) are due to cardiovascular events. The risk of cardiovascular mortality in adult patients with ESRD is 20 to 30 times higher than that of the general population.

In chronic kidney disease (CKD) or ESRD patients, the relationships between MAC and bone disorders were associated with deterioration of mineral and bone metabolism caused by changes in serum phosphate and calcium and disruption of endocrine and humoral pathways. It was thought that hyperphosphatemia by increasing the Ca×P was responsible for passive calcium-salt precipitation, but experimental and clinical data indicate that hyperphosphatemia and high Ca×P intervene directly in osteoblast-like transformation of VSMCs via the up-regulation of Runx2/Cbfa1 and transcription factors [7,8,23,34,42].

In hyperparathyroidism, the increased bone resorption is frequently associated with MAC. In addition to the possible role of

regulatory factors secreted by the bone matrix, the release of endogenous phosphate and calcium from bone probably plays an important role. Chronically elevated parathyroid hormone (PTH) up regulates RANKL and down regulates OPG gene expression and raises the RANKL/OPG ratio.

Recent observations in ESRD showed a negative association between bone activity and aortic calcification and stiffness [21]. Bone remodeling is regulated by multiple hormones, including adiponectin or leptin. Leptin is a powerful inhibitor of bone formation in vivo and favors MAC [27]. In ESRD patients, serum leptin is elevated and associated with low PTH [5], suggesting that leptin might reduce bone activity and promote MAC in these patients.

Clinical relevance in diabetic patients

An unique study from Finland has shed some light on the importance of MAC as a prognostic factor. Seppo Lehto et al [20] investigated the predictive value of medial artery calcification in relation to 7-year cardiovascular mortality, coronary heart disease (CHD) events, stroke, and amputation of lower extremity in 1059 patients (581 men and 478 women) with non-insulin-dependent diabetes mellitus (NIDDM). Radiologically detectable MAC in femoral arteries was present at baseline in 439 patients (41.5%) and intimal-type (atherosclerotic) calcification in 310 patients (29.3%) Patients with MAC were older and the mean duration of diabetes was somewhat longer than in those without MAC. In women, plasma glucose and glycated hemoglobin A_{1c} levels were higher in patients with MAC than in those without MAC. Baseline cardiovascular risk factors were also analyzed in relation to intimal artery calcification in the study population. Diabetic patients with intimal artery calcification were older, had lower HDL-cholesterol, and had a longer duration of diabetes than those without intimal calcification. Frequency of smokers among diabetic men with intimal artery calcification was significantly higher than among those without intimal artery calcification. During the 7-year follow-up, 305 diabetic patients (28.8%) died: 158 (14.9%, 97 men and 61 women) from CHD and 34 (3.2%, 13 men and 21 women) from stroke. During the follow-up, altogether 256 diabetic patients had a fatal or nonfatal myocardial infarction (24.2%; 156 men and 100 women), and 125 diabetic patients had fatal or nonfatal stroke. The incidence of first lower extremity amputation was 5.6% (58 of 1044 patients).

Diabetic patients with MAC were found to have a significantly higher total mortality (38.0% vs. 22.3%, $P<0.001$), CVD mortality (26.9% vs. 14.5%, $P<0.001$), CHD mortality (20.3% vs. 11.1%, $P<0.001$), and stroke mortality (4.6% vs. 2.3%, $P<0.05$) than patients without MAC. NIDDM patients with MAC also had a higher incidence of all CHD events (30.1% vs. 20.0%, $P<0.001$), all stroke events (14.6% vs. 9.8%, $P<0.05$), and amputations of lower extremity (9.2% vs. 3.1%, $P<0.001$) than those without MAC. Even after adjustment for many cardiovascular risk factors (age, gender, area of residence, intimal artery calcification, plasma glucose level, duration of diabetes, hypertension, body mass index, smoking, serum total and HDL-cholesterol levels, serum triglycerides (log), and previous myocardial infarction and stroke), MAC remained an independent

predictor of death from all causes, cardiovascular disease, and CHD. Furthermore, MAC was a nearly significant predictor of death from stroke in patients with NIDDM. This large population-based study demonstrates that MAC is a powerful and hitherto largely unrecognized marker for future total and cardiovascular mortality in patients with NIDDM. This study was the first to show that MAC is a also a powerful predictor of nonfatal events of all arterial branches.

Together with other data, this study underlines the under recognized importance of MAC in diabetic patients as a prognostic factor.

Conclusions and future perspectives

Medial arterial calcification is a pathologic process that is readily diagnosed with largely available methods such as plain radiological films. It has shown a consistent and strong epidemiological association with prevalent conditions such as diabetes mellitus, chronic kidney disease and osteoporosis, and, moreover, it appears to have a prognostic role as far as total and cardiovascular mortality is concerned. In the present there are no treatments for MAC, nor it is known whether any therapeutic approach involving MAC would modify cardiovascular risk. Further prospective trials are needed in order to better clarify the link between MAC and other pathological processes that occur in diabetes, and also the link with other chronic complications which drive morbidity and mortality in diabetic patients.

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