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Medial arterial calcification and diabetes mellitus

Summary Medial arterial calcification (MAC) is a frequent vascular finding in patients with type II diabetes mellitus. Morphologically distinct from focal calcifications of atherosclerosis its radiographically distinct tramline pattern is frequently encountered in the arteries of the lower extremities. MAC is inconsistently related to age, duration and therapy of diabetes. In contrast, a strong association with diabetic polyneuropathy and familial aggregation have been documented. Although initially considered benign MAC is now recognized as a strong predictor of cardiovascular morbidity and mortality in diabetic patients. Investigations into MAC pathogenes and into its role in vascular pathophysiology are underway.

Key words Diabetes mellitus – medial arterial calcification

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Medial arterial calcification (MAC) is a focal calcification in the media distinct from the calcification typically associated with advanced atherosclerotic lesions. Previously it has been regarded as of little significance in diabetes mellitus. However, a study of MAC in the Pima Indians showed it to be significantly associated with patients with type 2 diabetes and an increased prevalence of cardiovascular mortality (1).

This article will summarize the history of MAC in diabetes, its association with other complications of diabetes, and then describe radiological, physiological, and histological studies, with final comments on the pathogenesis and relevance of MAC.

Bowen first described calcification of the arteries in diabetes in 1924 and related its severity to the duration of diabetes (2). In 1928, Morrison noted that the frequency of calcification in his patients depended also on the duration of diabetes (3). In 1950, Lindborn developed techniques to separate intimal and medial calcification (4), and Ferrier, in 1964, in a formal studyof medial calcification, described it as a characteristic finding in long-term diabetes (5).

There are several studies to associate MAC with mortality and other complications of diabetes. Everhart showed that risk factors for arterial calcification were impaired vibration, duration of diabetes, and high plasma glucose (1). Interestingly, the risk factors in nondiabetic patients were age, male gender, and high serum cholesterol. He then went on to show that diabetic patients with MAC had a 1.5-fold mortality rate (95 % confidence interval = 1.0–2.1), a 5.5-fold rate of amputation (95 % confidence interval = 2.1– 14.1), a 2.4-fold rate of proteinuria (95 % confidence interval = 1.3–4.5), a 1.7-fold rate of retinopathy (95 % confidence interval = 0.98–2.8), and a 1.6-fold rate of coronary artery disease (95 % confidence interval

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= 0.48–5.4). Lehto, in a further study of 1059 patients with type 2 diabetes, assessed the predicted value of MAC in relation to seven year cardiovascular mortality, coronary heart disease events, stroke, and lower extremity amputation. MAC was a strong independent predictor of total (risk factor adjusted odds ratio and 95 % confidence interval: 1.6; 1.2, 2.2), cardiovascular (1.6: 1.1, 2.2), and coronary heart disease (1.5; 1.0, 2.2) mortality, and also a significant predictor of future coronary heart disease events (fatal or nonfatal myocardial infarction), stroke, and amputation. This relationship was observed regardless of glycemic control and known duration of diabetes (6).

Breast arterial calcification also has an association with diabetes and cardiovascular mortality. In a study of 12,239 women, 442 of which were diabetic patients, arterial calcification was seen in 9.0 % of all women and 15.4 % of the diabetic women with an excess cardiovascular mortality of 40 % (hazard ratio = 1.4; 95 % confidence interval = 1.1, 1.8) for all women. In diabetic women, the presence of breast arterial calcification was associated with a 90 % (hazard ratio = 1.9; 95 % confidence interval = 1.1, 3.2) increase in cardiovascular mortality (7).

MAC is easily detected on a radiograph by its classical pipe stem or tramline calcification. In a quantitative angiographic study of the large arteries in the legs of 47 insulin-dependent diabetics, representing a uniform cross section of diabetes duration and the young to middle age range, patients with MAC showed no significant decrease of cross sectional area in any arterial region compared to patients without calcification (8). In a Doppler study of the diabetic neuropathic leg, the arteries were rigid and calcified and blood flow was increased (9). Gilbey has shown that in autonomic neuropathy with extensive calcification, blood flow was high in the hallux by venous plethysmography and TcO2 in the resting supine foot (10).

Christensen has studied the physiology of MAC and measured the maximal peak flow, using xenon 133, which was reduced in patients with MAC compared with patients without MAC (11). In patients with MAC, increasing during of diabetes was related to decreasing peak flow. Chantelau measured the affect of MAC on oxygen supply to exercising diabetic feet (12). Transcutaneous oxygen decreased with exercise in feet with peripheral vascular disease regardless of presence or absence of MAC, and transcutaneous oxygen increased with exercise in feet with MAC but without peripheral vascular disease and also in diabetic control subjects.

In the histological study of Ferrier in 1967, 10 diabetic and 10 nondiabetic limbs were investigated (13). In the metatarsal arteries, occlusion was present in 60 % of diabetics and 21 % of nondiabetics and in digital arteries, occlusion was noted in 19 % of diabetics and 10 % of nondiabetics. There was a higher incidence of advanced MAC in the metatarsal arteries of diabetics associated with significant metatarsal artery obstruction. In a recent study, we demonstrated that MAC is much more frequent in the tibial arteries of diabetic limbs with peripheral vascular disease compared to nondiabetic limbs (13).

Initially, MAC was thought to be related to age and duration of diabetes but Edmonds showed that MAC was a specific complication strongly associated with neuropathy (15). In two large series of cases with Charcot neuroarthropathy, MAC was found in 90 % (16), and 78 % (17), respectively. In a further study of 54 neuropaths with foot ulceration compared with 40 neuropaths without ulceration, 43 non-neuropathic controls and 50 control subjects, MAC was significantly greater in neuropaths with foot ulceration. MAC correlated with vibration, $r = 0.35$, duration of diabetes, $r = 0.32$, and serum creatinine, $r = 0.41$, all $p < 0.01$ (18). Furthermore, Forst reported a strong association between MAC and diminished heart rate variation and diminished sweat response (19), and Gentile showed linear calcification in 37 out of 41 patients with autonomic neuropathy, which was absent in controls without autonomic neuropathy $p < 0.001$ (20). MAC has been described in familial amyloid neuropathy and after lumbar sympathectomy. MAC was noted in both feet in 93 % of patients who had undergone bilateral lumbar sympathectomy; after unilateral sympathectomy, incidence of calcified arteries was higher than that of the contralateral limb, 89 % vs. 18 % $p < 0.01$. Twenty patients with no evidence of previous calcification underwent unilateral sympathectomy, and 13 of these subsequently developed calcification. Seven underwent bilateral sympathectomy and calcification was subsequently seen in 7 out of 7 (21).

Thus, calcification may be related to an underlying autonomic denervation, which may be important in its pathogenesis. Unilateral sympathectomy in animals leads to excess deposition of cholesterol on the operated side (22) and the occurrence of cholesterol sclerosis in the rabbit's aorta was accelerated by removal of the coeliac ganglion (23). Furthermore, in animal models, denervation of smooth muscle leads to striking pathological changes, including atrophy of muscle fibers with foci of degeneration (24). Arterial calcification is initiated within senescent atrophic smooth muscle (25). Furthermore, long-term administration of calcitonin inhibited the formation of calcareous deposits in an experimental model of atherosclerosis in rabbits and reduced the extent of the atherosclerotic process (26).

MAC is a notable feature of the diabetic leg but the relationship between medical calcification and the development of clinically important peripheral vascular disease is unknown. Diabetic patients are particularly prone to atherosclerosis which leads to ulceration, and in some cases, gangrene with limb loss. There is a predilection for macrovascular occlusive disease to involve the distal tibial/peroneal arteries. Chantelau reported an association of below knee atherosclerosis to MAC (27). In 42 diabetic patients, subjected to arteriography for

peripheral vascular disease, forefoot radiographs were obained for assessment of MAC. The distribution of the number of partial and total arterial stenoses per leg was assessed according to the coexistence of MAC. A total of 242 partial and complete stenoses was found in 35 MAC positive legs and 28 MAC negative legs. MAC positive legs had more than twice as many stenoses located in the lower (2.6 (2.3–2.8) stenoses below knee) in the lower leg as compared to 1.3 (1.0–1.07) stenoses in the upper leg, $p < 0.05$. MAC negative legs showed stenoses equally distributed above and below the knee.

Familial aggregation of MAC has been noted in the Pima Indians and this was studied to determine the importance of potential genetic factors and to assess whether such familial aggregation was independent of diabetes. Members of 1256 Pima Indian nuclear families with 3339 offspring were examined radiologically for MAC of the feet. Multiple logistic regression analyses were used to compare the presence of the disorder in a parent with the presence of MAC in an offspring and to determine whether familial aggregation of MAC was independent of parental diabetes. Parental MAC confirmed an increased risk of MAC in offspring independent of parental age and disease, and independent of offspring age and diabetes. These findings suggest that the factors responsible for the familial clustering of MAC may be different from those for diabetes (28).

The significance of MAC in diabetes is not fully known. It may lead to stiffening of arterial tone, the increase of systolic blood pressure in conduit arteries of legs, and acceleration of the occlusive atherosclerosis process. Recently, an impairment of endothelium-dependent relaxation has been described in association with MAC using aortic strips from rats with arteriosclerosis (29). Endothelium-dependent relaxation to acetylcholine was impaired in proportion to the degree of calcification. The cause of the excess mortality associated with MAC remains speculative. Loss of arterial elasticity may lead to abnormal flow characteristics with further injury to the endothelium and increased atherosclerosis.

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