Vascular disease in the lower limb in type 1 diabetes
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This review considers peripheral arterial disease (PAD) in the diabetic ischaemic lower limb including both macrovascular and microvascular aspects. The presentation of PAD is probably not significantly different in type 1 compared with type 2 diabetes. PAD in diabetic patients is diffuse and located distally being most severe in the crural and also the foot arteries. It is associated with arterial calcification and occlusion of the arteries rather than stenosis. Compared with the nondiabetic patient, PAD develops at a younger age, and women are equally affected as men. It is not known whether the presentation of ischaemic lower limb disease in diabetes can be explained by one disease, namely, atherosclerosis, which has particular features peculiar to diabetes such as distal arterial involvement, or by the occurrence of two separate diseases: first, classical atherosclerosis and, second, a diabetic macroangiopathy, a term for nonatherosclerotic arterial disease in diabetes that is characterized by medial arterial calcification. Furthermore, there is controversy with regard to the significance of structural changes in the microcirculation of the diabetic foot. Cardiovasc Endocrinol Metab 8:39–46 Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction
Three great pathologies come together in the diabetic lower limb: neuropathy, ischaemia and infection. Their combined impact results in a swift progression to tissue necrosis, which is the fundamental hallmark of the natural history of the diabetic lower limb.

The diabetic lower limb can be classified into two groups:

1. The neuropathic limb with palpable pulses.
2. The ischaemic limb without pulses and a varying degree of neuropathy.

This review will concentrate on peripheral arterial disease (PAD) in the diabetic ischaemic lower limb [1]. The overall prevalence of PAD in people with diabetes over 40 years of age has been estimated to be 20% [2]. This prevalence increases to 29% in patients with diabetes over 50 years of age [3,4]. However, only a few vascular studies have been carried out specifically in type 1 diabetes (T1DM). In the Pittsburgh Epidemiology of Diabetes Complications Study of childhood-onset T1DM, women who had T1DM for 30 years had a prevalence of PAD of more than 30% compared with only 11% for men when PAD was detected by Ankle–Brachial Index of less than 0.8 at rest or after exercise [5]. The Epidemiology of Diabetes Interventions and Complications (EDIC) study, the long-term follow-up of the Diabetes Control and Complications Trial (DCCT), found that intensively treated participants, with an average duration of T1DM of about 14 years, had a prevalence of PAD of 8.8% among women and 4.6% among men [6]. Calcification of the extremity arteries occurred in 4.6% of the EDIC cohort, more commonly in men, and in individuals older than 30 years of age [7]. The longer the duration of diabetes, the greater is the risk of developing PAD. In the Health Professionals Follow-up Study, the relative risk for PAD compared with men without diabetes was 1.39 [95% confidence interval (CI): 0.82–2.36] for 1–5 years of diabetes, 3.63 (95% CI: 2.23–5.88) for 6–10 years of diabetes, 2.55 (95% CI: 1.50–4.32) for 11–25 years of diabetes and 4.53 (95% CI: 2.39–8.58) for more than 25 years of diabetes [8]. In a meta-analysis of five studies of type 1 diabetic patients, the risk of PAD increased by 18% with each 1% increase in HbA1c [9]. Aggressive glycaemic control to lower the HbA1c did not appear to reduce rates of peripheral arterial occlusion in the DCCT/EDIC study but did reduce the incidence of peripheral arterial calcification [10].

With regard to outcomes after first-time lower-extremity revascularization for patients with chronic limb-threatening ischaemia, patients with T1DM presented at an earlier age and with more severe disease, restenosis or reintervention compared with those without diabetes; also, T1DM was associated with longer preoperative and total hospital length of stay as well as with an increased risk of incomplete wound healing [11]. If the rate of amputation is taken as a marker of PAD, it is high in T1DM, occurring at 0.4–7.2% per year [12]. By 65 years of age, the cumulative probability of lower-extremity amputation in a Swedish administrative database was 11% for women with T1DM and 20.7% for men [13]. In this Swedish population, the rate of lower-extremity amputation among those with T1DM was nearly 86-fold that of the general population.
In T1DM, patients with lower-extremity amputation have a high risk of end-stage renal disease, myocardial infarction and cardiovascular and noncardiovascular mortality [14]. People with T1DM are at a 2–8-fold increased risk of cardiovascular disease and death [15].

Peripheral arterial disease risk factors and microvascular and macrovascular comorbidities in type 1 compared with type 2 diabetes

In a retrospective cross-sectional study of 1087 patients with T1DM and 1060 patients with type 2 diabetes, PAD was diagnosed when the Ankle–Brachial Index was less than 1.0. In general, PAD risk factors and microvascular and macrovascular comorbidity were similar [16]. In both types of diabetes (type 1 vs. type 2) PAD risk [odds ratio (OR)] was increased in the presence of coronary heart disease (OR: 9.3 vs. 3.5), diabetic nephropathy (OR: 3.0 vs. 2.8), neuropathy (OR: 7.9 vs. 1.8), foot ulceration (OR: 8.9 vs. 5.5), increased daily insulin requirement of greater than 0.6 mU/kg body weight (OR: 5.2 vs. 2.9), diabetes duration of 20–29 years (OR: 28.9) and more than 30 years (OR: 51.1) in T1DM, and diabetes duration of 10–19 years (OR: 3.8) and more than 20 years (OR 4.3) in type 2 diabetes. However, only in type 2 diabetes, was PAD risk associated with microalbuminuria (OR: 2.1), macroalbuminuria (OR: 3.3), background retinopathy (OR: 1.9), proliferative retinopathy (OR: 2.8), increased triglycerides (OR: 1.7) and decreased high-density lipoprotein cholesterol (<0.9 mmol/l; OR: 0.49).

The distribution of arterial disease in the diabetic lower limb

The site of arterial disease of the lower extremity can be subdivided to iliac disease, femoropopliteal disease, crural disease, the larger arteries in the foot, namely the lateral and medial plantar and dorsalis pedis, the small arteries of the foot, namely plantar arch, metatarsal and digital and finally the arterioles of the microcirculation. In general, the distribution of arterial disease is distal with a predilection for infrapopliteal disease [17], but it is not different in T1DM compared with type 2 diabetes. Ferrarasi et al. [18] have recently suggested the concept of big artery disease and small artery disease (SAD). Big artery disease can affect the whole vascular tree of the lower limb, from iliac to the big foot arteries (dorsalis pedis and plantar arteries) and is predominantly responsible for a ‘transmission failure’ of blood flow to the foot tissues. SAD affects the plantar arch and the small arteries rising from it and from the big foot arteries (tarsal, metatarsal, digital and calcaneal branches), and is predominantly responsible for a ‘distribution failure’ of blood flow to the foot tissues.

The arterial disease of the diabetic lower extremity has a distal anatomical localization that is associated with arterial calcification and occlusion of the arteries rather than stenosis [19]. Compared with the nondiabetic patient, PAD develops at a younger age, and women are equally affected as men. The vascular changes in diabetic patients are more diffuse and located distally, being most severe in the crural vessels [20]. There is a high prevalence of long occlusions in the tibial arteries that occur more frequently than stenosis [21,22].

Arterial disease in patients with diabetes is both morphologically and pathologically different than in patients without diabetes [20,23,24]. Various clinical and pathological studies have compared arteries in the legs of diabetic patients with those in nondiabetic patients. A combined clinical and pathological study of large and small arteries in diabetic and nondiabetic patients has shown that diabetic patients have the same incidence of occlusion in the femoral–popliteal system but a higher incidence of occlusion below the knee [24]. In a further study, casts were made of the vascular lumen of 20 successive extremities amputated for gangrene [25], half of whom were diabetic patients. The diabetic patients had predominant occlusion of the calf arteries and less occlusion in the foot arteries compared with nondiabetic patients.

There is controversy as to whether the arteries below the ankle are spared from the occlusive disease in diabetes. In one study of amputated legs of diabetic patients, the occlusive disease was more severe in arteries above the ankle compared with nondiabetic patients but no difference was shown in the arteries of the ankle and foot [26]. However, when Ferrarasi analysed the obstructive disease distribution in a series of 1624 patients with critical limb ischaemia and Rutherford grades 5 and 6, foot arterial disease was present in more than 70% of patients [27]. Furthermore, when he reviewed 1915 limbs of 1613 patients who underwent angiography, most lesions occurred at distal sites, namely below the knee including the foot arteries [18]. Above the groin, disease occurred in 187 (9.8%) limbs, superficial femoral artery disease in 871 (45.5%) and popliteal–tibioperoneal trunk disease in 886 (46.3%). In patients undergoing a complete evaluation of foot arteries, only 292 (17.8%) had no angiographic evidence of foot arterial disease. SAD was present in 414 (25.1%) limbs. SAD was strongly and independently associated with critical limb ischaemia. Patients with a disease of any of the plantar or dorsalis pedis arteries and SAD had a higher risk of critical limb ischaemia (OR: 13.25, 95% CI: 1.69–104.16). SAD was associated with diabetes and dialysis (both: OR=4.85; dialysis only: OR=3.60; diabetes only: OR=1.70; none: reference OR; P < 0.01).

Further studies have confirmed the distal distribution of PAD in diabetes. Indeed, the anatomic distribution in patients with PAD is different according to the risk factor profile [28]. The aortoiliac and crural segments show specific risk profiles, while the femoropopliteal segment
seems to be a transition zone. Smoking and high plasminogen levels may be related to atherosclerosis of proximal segments and diabetes to that of the distal segments. In a further study investigating the pattern and distribution of PAD in diabetic patients with critical limb ischaemia, diabetic patients collectively had the severe tibio-peroneal occlusive disease [29]. However, diabetic patients who smoked tended to have the disproportionately more occlusive disease in the femoropopliteal segment (P < 0.001). Finally, in a meta-analysis of 15 studies, patients with diabetes were significantly less likely to have disease in the aortic iliak segment (OR: 0.25, 95% CI: 0.15–0.42) and significantly more likely to have disease in the tibial segment (OR: 1.94, 95% CI: 1.27–2.96) [30].

Pathological basis of arterial disease in the lower limb in type 1 diabetes
It is not known whether the presentation of ischaemic lower limb disease in diabetes can be explained by one disease, namely, atherosclerosis, which has particular features peculiar to diabetes such as distal arterial involvement, or by the occurrence of two separate diseases: first, classical atherosclerosis and, second, diabetic macroangiopathy, a term for nonatherosclerotic arterial disease in diabetes [31]. This paper will describe first the features of atherosclerosis in the ischaemic diabetic patient and second those of diabetic macroangiopathy. Finally, the paper will consider the influence of microvascular disease, namely arteriolar and capillary diseases.

Atherosclerosis
Classic atherosclerosis has been described in the proximal arteries of the diabetic limb and presents as iliac, femoral and popliteal diseases. The risk factors for this proximal site disease are hypercholesterolaemia and smoking [32]. Diabetic patients have conventional atherosclerotic lesions in these proximal sites at the same frequency as in nondiabetes [24]. The occlusion is often multisegmental with poor collateral development. The atherosclerotic disease develops 10 years earlier than in patients without diabetes. It progresses faster with a high incidence of multiple occlusions. Associated disease in the coronary and cerebral circulations is more common in diabetes compared with nondiabetes and thus the outlook for survival is less encouraging than for nondiabetic patients.

The development of diabetes-related atherosclerosis follows the same pathological course as atherosclerosis in nondiabetic patients [33]. Some authorities state that the arterial lesions in diabetes in the lower limb can be explained by atherosclerosis and that there is no histological or histochemical evidence to define a specific type of diabetic macroangiopathy [34]. The lesions of atherosclerosis do include varying amounts and types of lipids, connective tissues, inflammatory cells and a variety of extracellular components including matrix proteins and enzymes and calcium deposits [35]. However, atherosclerosis in diabetes is characterized by excessive intimal calcification in association with macrophages, lipids and proliferation of vascular smooth muscle cells resulting from proinflammatory cytokine production by activated macrophages. Calcification of advanced atherosclerotic plaques takes place adjacent to lipid and cholesterol depositions and these plaques have necrotic cores. This results in complex plaque formation that are susceptible to rupture and superimposed thrombosis. Heavily calcified plaques do not increase plaque vulnerability, which is more associated with a large lipid pool, thin fibrous cap, microcalcifications and excessive local inflammation [36].

Intimal calcification results from modified lipid accumulation, proinflammatory cytokines and apoptosis within the plaque that provoke osteogenic cell differentiation [37]. Osteogenic differentiation with bone deposition is rarely observed in intimal calcification, although it is more often seen in medial arterial calcification [38].

Clinical presentation of atherosclerosis
Classic atherosclerosis occurs as a segmental occlusion in the aortoiliac region when it presents as intermittent claudication of the buttocks or in the femoropopliteal region when it is associated with claudication of the calf [39]. In a more advanced stage of atherosclerosis, multiple segmental occlusions may be present. Multiple aortoiliac occlusions result in disabling claudication. Often multiple occlusions occur in aortoiliac together with superficial femoral arteries and lead not only to claudication but also to rest pain and necrosis.

However, atherosclerosis can be nonsegmental specifically in the femoropopliteal region with occlusion of the superficial femoral artery when blood flow to the leg then comes from the deep femoral artery. Intermittent claudication, rest pain and gangrene can occur. Also, atherosclerosis may be diffuse. It is seen in the elderly patient above 70 years or the diabetic patient in the fifth and sixth decades. There is generalized narrowing of all arteries of the lower limb with occlusions in the advanced stage. Symptoms are claudication and in advanced disease, rest pain and foot necrosis.

The term ‘diabetic atherosclerosis’ is also used. This ‘condition’ develops at an early stage, often in the second or third decade. There is specific involvement of the popliteal, leg and foot arteries with progression to include the superficial femoral artery. This probably represents diabetic macroangiopathy.

Diabetic macroangiopathy
The term diabetic macroangiopathy was first used by Lundbaek [40]. The main element of diabetic macroangiopathy is a medial arterial disease of the muscular arteries that may be accompanied by intimal pathology.
This condition has a predilection for disease below the knee. The medial arterial disease is conventionally medial calcification although accumulation of laminin, fibronectin, type IV collagen with hyaluronic acid has been reported [41]. Diffuse fibrosis of the medial wall has also been described [42].

**Medial arterial calcification**

Medial arterial calcification is easily detected on a radiograph by its classical pipe stem or tramline calcification [43]. Bowen et al. [44] was the first to describe the calcification of the arteries in diabetes and related its severity to the duration of diabetes. Morrison and Bogan [44] then also observed that the frequency of calcification depended on the duration of diabetes [45]. In a formal study of medial calcification, Ferrier and Ferner [46] described it as a characteristic finding in long-term diabetes. Amputation studies have shown that diabetic patients are likely to have more medial calcification in the arteries than nondiabetic patients [26].

**Prognostic significance of medial arterial calcification**

There are several studies that link medial calcification with mortality and other complications of diabetes. Everhart et al. reported that diabetic patients with medial calcification had a 1.5-fold mortality rate (95% CI: 1.0–2.1) and a 5.5-fold rate of amputation (95% CI: 2.1–14.1) [47]. A further study of 1059 patients but with T1DM assessed the predicted value of medial calcification in relation to 7-year cardiovascular mortality, coronary heart disease events, stroke and lower-extremity amputation [48]. Medial calcification was a strong independent predictor of total (risk factor adjusted OR: 1.6, 95% CI: 1.2–2.2), cardiovascular (risk factor adjusted OR: 1.6, 95% CI: 1.1–2.2), and coronary heart disease (risk factor adjusted OR: 1.5, 95% CI: 1.0–2.2) mortality, and also a significant predictor of future coronary heart disease events (fatal or nonfatal myocardial infarction), stroke and amputation. The relationship was noted regardless of glycaemic control and known duration of diabetes.

**Pathology**

When Ferrier [49] compared lower limb arteries in the legs and feet of 10 diabetic patients with 10 nondiabetic patients, he observed an increased incidence of advanced medial calcification in the metatarsal arteries of diabetic patients that was associated with significant metatarsal artery obstruction. Occlusion of the metatarsal arteries was present in 60% of diabetics and 21% of nondiabetics and occlusion in the digital arteries was noted in 19% of diabetics and 10% of nondiabetics. Meema et al. [50] have indicated that there may be two different types of medial calcifications. The first is a benign type, of gradual onset, with thin medial calcification and not reducing the lumen. This condition does not result in ischaemia. The second type is a rapidly progressive form, in which considerable medial calcification may displace the internal elastica toward the lumen, resulting in narrowing of the lumen.

**Physiological effects of calcification**

Medial arterial calcification may have major haemodynamic effects. It is initially associated with increased blood flow. In a Doppler study of the diabetic neuropathic leg, the arteries were rigid and calcified and blood flow was increased [51]. In a quantitative angiographic study of the large arteries in the legs of 47 insulin-dependent diabetics, patients with medial arterial calcification showed no significant decrease of cross-sectional area in any arterial region compared with patients without calcification [52]. Gilbey et al. [53] have shown that in diabetic patients with autonomic neuropathy and extensive calcification, blood flow was high in the hallux as assessed by venous plethysmography and transcutaneous oxygen in the resting supine foot. However, in another study, maximal peak flow, which was measured using xenon 133, was reduced in patients with calcification compared with patients without calcification and increasing duration of diabetes was related to decreasing peak flow [54]. Chantelau et al. [55] measured the effect of medial calcification on oxygen supply to exercising diabetic feet. Transcutaneous oxygen decreased with exercise in feet with PAD regardless of presence or absence of calcification, but transcutaneous oxygen increased with exercise in feet with calcification but without PAD and also in diabetic controls. In a further study, Neubauer et al. [56] reported that diabetic patients have a uniform narrowing of the superficial femoral arteries associated with rugosities, stiffness, medial calcification, norepinephrine depletion and reduced blood flow capacity.

**Pathogenesis**

Medial arterial calcification occurs independently of atherosclerosis and is strongly associated with aging, chronic kidney disease and diabetes mellitus. Initially, medial calcification was thought to be related to the duration of diabetes but it has been shown that calcification is a specific complication strongly associated with neuropathy [43]. In two large series of cases with Charcot neuroarthropathy, medial calcification was found in 90 [57] and 78% [58], respectively. In a further study of 54 neuropathic patients with foot ulceration compared with 40 neuropathic patients without ulceration, 43 non-neuropathic controls and 50 controls, medial arterial calcification was significantly more extensive in the neuropathic patients with foot ulceration [59]. Medial calcification correlated with vibration (r = 0.35, P < 0.01), duration of diabetes (r = 0.32, P < 0.01) and serum creatinine (r = 0.41, P < 0.01). Furthermore, Forst et al. [60] reported a strong association between medial arterial calcification and autonomic neuropathy as indicated by diminished heart rate variation and sweat response. Gentile et al. [61] showed linear calcification in 37 out of
Sequelae of medial arterial calcification

Arterial stiffening: In addition to a pathological, structural component in the form of medial calcification, macroangiopathy has physiological consequences including increased arterial stiffness, resulting in an increase in pulse wave velocity and increase in pulse pressure. The ‘cushioning’ effect of the arteries is dampened leading to a diminished ability of the arteries to smooth out the pulsatile flow occurring with intermittent ventricular ejection [72]. The principal outcome of arterial stiffening is increased systolic pressure, resulting in elevated cardiac afterload and left ventricular hypertrophy. There is a decrease in diastolic pressure and impaired coronary perfusion. An impairment of endothelium-dependent relaxation also occurs in association with medial arterial calcification [73]. Endothelium-dependent relaxation to acetylcholine was impaired in proportion to the degree of calcification.

Does medial arterial calcification predispose to peripheral arterial disease?: The relationship between medial calcification and the development of clinically important PAD is not fully understood. Chantelau et al. [74] reported an association of below knee atherosclerosis to medial arterial calcification. In 42 diabetic patients, subjected to arteriography for peripheral vascular disease, forefoot radiographs were obtained for assessment of medial calcification. The distribution of the number of partial and total arterial stenoses per leg was assessed according to the coexistence of calcification. A total of 242 partial and complete stenoses were found in 35 legs with medial calcification and 28 without calcification. Legs with medial calcification had more than twice as many stenoses located in the lower leg, 2.6 (95% CI: 2.3–2.8) stenoses below the knee as compared with 1.3 (95% CI: 1.0–1.07) stenoses in the upper leg (P < 0.05). Legs with no medial calcification showed stenoses equally distributed above and below the knee.

Medial arterial calcification prevents the compensatory remodelling in response to atherosclerotic lesions and this may accelerate the progression of the disease [75]. Furthermore, extensive medial calcification with a secondary invasion of the intima increases the risk of thromboembolic events.

Intimal disease: Diabetic macroangiopathy may have an intimal component that may take the form of intimal hyperplasia, neointima, hypertrophy and fibroplasia. It includes smooth muscle cells, which may have migrated from the media or adventitia, or have been deposited from circulating progenitor cells.

Although intimal thickening has been described in arteriolosclerosis, it also occurs in larger arteries where it is usually labelled as adaptive intimal thickening or diffuse intimal thickening [76]. Recent histology of peripheral arteries has indicated that intimal hyperplasia can lead to significant stenosis and occasional occlusion or thrombus
and this is noted in the absence of plaque [77]. Studies of amputated specimens have showed intimal thickening that has been labelled as atherosclerotic [78]. Oclusion may occur because of concentric intimal thickening or thrombus. It is possible that the occlusive intimal thickening also includes old organized thrombus [77]. The link between intimal thickening and medial calcification is not fully understood as the degree of intimal thickening does not relate to the extent of medial calcification [77].

**Microvascular disease**

**Structural changes**
There is considerable controversy regarding the significance of structural changes in the small vessels of the diabetic foot. It centres on a study of 152 amputation specimens (92 diabetic patients), which described a specific diabetic vascular lesion, namely, an endothelial proliferation sufficient to almost occlude the lumen of digital arteries and smaller vessels [79]. Subsequent studies using light microscopy, vascular casting, and physiological studies did not confirm the presence of occlusion [80]. However, a recent study admittedly in T2DM, reported that capillary microangiopathy was present in both neuroischaemic and neuropathic diabetic foot skin. There was also a predominance of arteriolar occlusions in the neuroischaemic foot [81].

**Physiological changes**
Functional abnormalities of the microcirculation in the lower limb have been described in the resting blood flow, capillary flow, the microvascular response to tissue injury, vasoconstriction responses, the neurovascular flare response, haemoglobin oxygen saturation and blood rheology [82]. Skin capillary circulation has been reported to be impaired in toes of patients with T1DM [83]. Although total skin microcirculation in the toes of such insulin-dependent diabetic patients was reported as normal, the nutritional capillary circulation was severely impaired.

**Conclusion**
PAD in the lower limb is a major contributor to the diabetic foot. In diabetes, PAD develops at a younger age and women and men are equally affected. There is controversy as to whether the presentation of ischaemic foot disease in diabetes can be explained by one disease namely atherosclerosis with particular features such as distal arterial involvement or by the occurrence of two diseases: a diabetic macroangiopathy, a term for nonatherosclerotic arterial disease, and classical atherosclerosis. Diabetic macroangiopathy is characterized by medial arterial calcification. Furthermore, the contribution of microvascular disease to the diabetic foot remains controversial.

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**References**


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