Vascular disease in the lower limb in type 1 diabetes

Michael Edmonds

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.

King's College Hospital, Denmark Hill, London, UK

Correspondence to Michael Edmonds, MD, FRCP, King's College Hospital, Denmark Hill, London SE5 8DX, UK
E-mail: michaeleedmonds@gmail.com

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 Ferraresi 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 tibioperoneal occlusive disease [29]. However, diabetic patients who smoked tend 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 aorticiliac 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 Lundbaeck [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 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

41 patients with autonomic neuropathy, which was absent in controls without autonomic neuropathy ($P < 0.001$). Medial arterial calcification has also been described in familial amyloid neuropathy and after lumbar sympathectomy. Medial calcification was noted in both feet in 93% of patients who had undergone bilateral lumbar sympathectomy [62]. After unilateral sympathectomy, the incidence of calcified arteries was higher in the affected limb compared with that of the contralateral limb, 89 vs. 18% ($P < 0.01$). Twenty patients with no previous evidence of calcification underwent unilateral sympathectomy and 13 of these patients later developed calcification. Seven patients had bilateral sympathectomy and calcification was subsequently seen in seven out of seven.

Unilateral sympathectomy in animals leads to excess deposition of cholesterol on the operated side [63] and the development of cholesterol sclerosis in the rabbit's aorta was accelerated by the removal of the coeliac ganglion [64]. Furthermore, in animal models, denervation of smooth muscle leads to striking pathological changes, including atrophy of muscle fibres with foci of degeneration [65]. Thus, calcification may be related to underlying autonomic denervation, which may be important in its pathogenesis [66]. Arterial calcification is initiated within the senescent atrophic smooth muscle [67]. Also, long-term administration of calcitonin impeded the formation of calcareous deposits in an experimental model of atherosclerosis in rabbits and reduced the extent of the atherosclerotic process [68].

Medial arterial calcification is now known to be an active process involving the deposition of hydroxyapatite crystals along concentric elastin fibres, directly abutting vascular smooth muscle cells. Differentiation of vascular smooth muscle cells into osteoblast-like cells underlies the development of vascular calcification [69]. Normally, an equilibrium exists between promoters and inhibitors of calcification [70]. Immunohistochemistry and in-situ hybridization techniques have shown that calcified vessels from diabetic patients show diminished expression of matrix Gla protein and osteonectin, key inhibitors of vascular calcification. Conversely, there is increased expression of osteopontin, alkaline phosphatase, bone sialoprotein, bone Gla protein and collagen II – indicators of osteogenesis/chondrogenesis [69].

Familial aggregation of medial arterial calcification has been noted in the Pima Indians raising the possibility of the importance of genetic factors. To assess whether such familial aggregation was independent of diabetes, members of 1256 Pima Indian nuclear families with 3339 offspring were examined radiologically for medial calcification of the feet [71]. Parental calcification confirmed an increased risk of medial calcification in offspring independent of parental age and disease and independent of offspring age and diabetes.

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 medical 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]. Occlusion 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. Futhermore, the contribution of microvascular disease to the diabetic foot remains controversial.

Acknowledgements

References
1   Thiruvoipati T, Kielhorn CE, Armstrong EJ. Peripheral artery disease in patients with diabetes: Epidemiology, mechanisms, and outcomes. *World J Diabetes* 2015; **6**:961–969.
2   Elhadd TA, Robb R, Jung RT, Stonebridge PA, Belch JJF. Pilot study of prevalence of asymptomatic peripheral arterial occlusive disease in patients with diabetes attending a hospital clinic. *Practical Diabetes Int* 1999; **16**:163–166.
3   Hirsch AT, Criqui MH, Treat-Jacobson D, Regensteiner JG, Creager MA, Olin JW, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. *JAMA* 2001; **286**:1317–1324.
4   Marso SP, Hiatt WR. Peripheral arterial disease in patients with diabetes. *J Am Coll Cardiol* 2006; **47**:921–929.
5   Orchard TJ, Dorman JS, Maser RE, Becke DJ, Drash AL, Ellis D, et al. Prevalence of complications in IDDM by sex and duration. Pittsburgh Epidemiology of Diabetes Complications Study II. *Diabetes* 1990; **39**:1116–1124.
6   Nathan DM, Lachin J, Cleary P, Orchard T, Brillon DJ, Backlund JY, et al. Intensive diabetes therapy and carotid intima-media thickness in type 1 diabetes mellitus. *N Engl JMed* 2003; **348**:2294–2303.
7   Maser RE, Wolfson SK Jr, Ellis D, Stein EA, Drash AL, Becker DJ, et al. Cardiovascular disease and arterial calcification in insulin-dependent diabetes mellitus: interrelations and risk factor profiles. Pittsburgh Epidemiology of Diabetes Complications Study-V. *Arterioscler Thromb* 1991; **11**:958–965.
8   Al-Delaimy WK, Merchant AT, Rimm EB, Willett WC, Stampfer MJ, Hu FB. Effectof type 2 diabetes and its duration on therisk of peripheral arterial disease amongmen. *Am J Med* 2004; **116**:236–240.
9   Adler AI, Erqou S, Lima TA, Robinson AH. Association between glycated haemoglobin and the risk of lower extremity amputation in patients with diabetes mellitus-review and meta-analysis. *Diabetologia* 2010; **53**:840–849.
10 Carter RE, Lackland DT, Cleary PA, Yim E, Lopes-Virella MF, Gilbert GE, et al. Intensive treatment of diabetes is associated with a reduced rate of peripheral arterial calcification in the diabetes control and complications trial. *Diabetes Care* 2007; **30**:2646–2648.
11 Darling JD, Bodewes TCF, Deery SE, Guzman RJ, Wyers MC, Hamdan AD, et al. Outcomes after first-time lower extremity revascularization for chronic limb-threatening ischemia between patients with and without diabetes. *J Vasc Surg* 2018; **67**:1159–1169.
12 Moss SE, Klein R, Klein BE. The 14-year incidence of lower-extremity amputations in a diabetic population. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. *Diabetes Care* 1999; **22**:951–959.
13 Jonasson JM, Ye W, Sparén P, Apelqvist J, Nyrén O, Brismar K. Risks of nontraumatic lower-extremity amputations in patients with type 1 diabetes: a population-based cohort study in Sweden. *Diabetes Care* 2008; **31**:1536–1540.
14 Mohammedi K, Potier L, Belhatem N, Matallah N, Hadjadj S, Roussel R, et al. Lower-extremity amputation as a marker for renal and cardiovascular events and mortality in patients with long standing type 1 diabetes. *Cardiovasc Diabetol* 2016; **15**:5.
15 Katsarou A, Gudbjörnsdottir S, Rawshani A, Dabelea D, Bonifacio E, Anderson BJ, et al. Type 1 diabetes mellitus. *Nat Rev Dis Primers* 2017; **3**:17016.
16 Zander E, Heinke P, Reindel J, Kohnert KD, Kairies U, Braun J, et al. Peripheral arterial disease in diabetes mellitus type 1 and type 2: are there different risk factors? *Vasa* 2002; **31**:249–254.
17 Nativel M, Potier L, Alexandre L, Baillet-Blanco L, Ducasse E, Velho G, et al. Lower extremity arterial disease in patients with diabetes: a contemporary narrative review. *Cardiovasc Diabetol* 2018; **17**:138.
18 Ferraresi R, Mauri G, Losurdo F, Troisi N, Brancaccio D, Caravaggi C, et al. BAD transmission and SAD distribution: a new scenario for critical limb ischemia. *J Cardiovasc Surg (Torino)* 2018; **59**:655–664.
19 Faglia E, Favales F, Quarantiello A, Calia P, Clelia P, Brambilla G, et al. Angiographic evaluation of peripheral arterial occlusive disease and its role as a prognostic determinant for major amputation in diabetic subjects with foot ulcers. *Diabetes Care* 1998; **21**:625–630.
20 Jude EB, Oyibo SO, Chalmers N, Boulton AJ. Peripheral arterial disease in diabetic and nondiabetic patients: a comparison of severity and outcome. *Diabetes Care* 2001; **24**:1433–1437.
21 Graziani L, Silvestro A, Bertone V, Manara E, Andreini R, Sigala A, et al. Vascular involvement in diabetic subjects with ischemic foot ulcer: a new morphologic categorization of disease severity. *Eur J Vasc Endovasc Surg* 2007; **33**:453–460.
22 Faglia E. Characteristics of peripheral arterial disease and its relevance to the diabetic population. *Int J Low Extrem Wounds* 2011; **10**:152–166.

23 Halperin JL. Arterial obstructive diseasesof the extremities. In: Loscalzo CM, Dzau VJ, editors. *Vascular medicine*. Boston, MA: Little Brown; 1992.

24 Strandness DE Jr, Priest RE. Combined clinical and pathologic study of diabetic and nondiabetic peripheral arterial disease. *Diabetes* 1964; **13**:366–372.

25 Conrad MC. Large and small artery occlusion in diabetics and nondiabetics with severe vascular disease. *Circulation* 1967; **36**:83–91.

26 Mozes G, Keresztury G, Kadar A, Magyar J, Sipos B, Dzsinich S, *et al*. Atherosclerosis in amputated legs of patients with and without diabetes mellitus. *Int Angiol* 1998; **17**:282–286.

27 Ferraresi R, Palena L, Mauri G, Manzi M. Interventional treatment of the below the ankle peripheral artery disease. In: Lanzer P, editor. *Panvascular medicine*, 2nd ed. Heidelberg: Springer-Verlag; 2014. pp. 3205–3226.

28 Haltmayer M, Mueller T, Horvath W, Luft C, Poelz W, Haidinger D. Impact of atherosclerotic risk factors on the anatomical distribution of peripheral arterial disease. *Int Angiol* 2001; **20**:200–207.

29 Motsumi MJ, Naidoo NG. Pattern and distribution of peripheral arterial disease in diabetic patients with critical limb ischemia (Rutherford clinical category 4–6). *S Afr J Surg* 2017; **55**:48–54.

30 Lowry D, Saeed M, Narendran P, Tiwari A. A review of distribution of atherosclerosis in the lower limb arteries of patients with diabetes mellitus and peripheral vascular disease. *Vasc Endovascular Surg* 2018; **52**:535–542.

31 Edmonds ME, Shanahan C, Petrova NL. The diabetic foot syndrome. In: Piaggesi A, Apelqvist J, editors. *Frontiers in diabetes*. Basel: Karger; 2018. **26**:60–69.

32 Janka HU, Standl E, Mehnert H. Peripheral vascular disease in diabetes mellitus and its relation to cardiovascular risk factors: screening with the Doppler ultrasonic technique. *Diabetes Care* 1980; **3**:207–213.

33 Siracuse JJ, Chaikof EL. The pathogenesis of diabetic atherosclerosis. In: Shrikhande GV, McKinsey JF, editors. *Diabetes and peripheral vascular disease: diagnosis and management Contemporary diabetes*. New York: Springer; 2012. pp. 13–26.

34 Birrer M. Macroangiopathy in diabetes mellitus. *Vasa* 2001; **30**:168–174.

35 Stary HC, Blankenhorn DH, Chandler AB, Glagov S, Insull W Jr, Richardson M, *et al*. A definition of the intima of human arteries and of its atherosclerosis-prone regions: a report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. *Arterioscler Thromb* 1992; **12**:120–134.

36 Huang H, Virmani R, Younis H, Burke AP, Kamm RD, Lee RT. The impact of calcification on the biomechanical stability of atherosclerotic plaques. *Circulation* 2001; **103**:1051–1056.

37 Rocha-Singh KJ, Zeller T, Jaff MR. Peripheral arterial calcification: prevalence, mechanism, detection, and clinical implications. *Catheter Cardiovasc Interv* 2014; **83**:212–220.

38 Amann K. Media calcification and intima calcification are distinct entities in chronic kidney disease. *Clin J Am Soc Nephrol* 2008; **3**:1599–1605.

39 De Wolfe VG, Bevan IG. Arteriosclerosis obliterans in the lower extremities: correlation of clinical and angiographic findings. In: Gifford RD, editor. *Cardio-vascular clinics*. Philadelphia, PA: F.A. Davies Company; 1971; **3**:62–72.

40 Lundbaek K. Diabetic angiopathy. A new concept of pathogenesis (author's transl) [Article in German]. *MMW Munch Med Wochenschr* 1977; **119**:647–654.

41 Andresen JL, Rasmussen LM, Ledet T. Diabetic macroangiopathy and atherosclerosis. *Diabetes* 1996; **45** (**Suppl 3**):91–94.

42 Capron L. Pharmacologic approaches to the treatment of atherosclerotic arterial obstruction. *J Cardiovasc Pharmacol* 1995; **25** (**Suppl 2**):40–43.

43 Edmonds M. Medial arterial calcification and diabetes mellitus. *Z Kardiol* 2000; **89** (**Suppl 2**):101–104.

44 Bowen BD, Koenig EC, Viele A. A study of the lower extremities in diabetes as compared with non-diabetic states from the standpoint of x-ray findings with particular reference to the relationship of arteriosclerosis and diabetes. *Bulletin Buffalo Gen Hosp* 1924; **2**:35–41.

45 Morrison LB, Bogan IK. Calcification of the vessels in diabetes. *JAMA* 1929; **92**:1424–1426.

46 Ferrier TM, Ferner TM. Radiologically demonstrable arterial calcification in diabetes mellitus. *Australas Ann Med* 1964; **13**:222–228.

47 Everhart JE, Pettitt DJ, Knowler WC, Rose FA, Bennett PH. Medial arterial calcification and its association with mortality and complications of diabetes. *Diabetologia* 1988; **31**:16–23.

48 Lehto S, Niskanen L, Suhonen M, Ronnemaa T, Laakso M. Medial artery calcification. A neglected harbinger of cardiovascular complications in non-insulin-dependent diabetes mellitus. *Arterioscler Thromb Vasc Biol* 1996; **16**:978–983.

49 Ferrier TM. Comparative study of arterial disease in amputated lower limbs from diabetics and non-diabetics (with special reference to feet arteries). *Med J Aust* 1967; **1**:5–11.

50 Meema HE, Oreopoulos DG, Rapoport A. Serum magnesium level and arterial calcification in end-stage renal disease. *Kidney Int* 1987; **32**:388–394.

51 Edmonds ME, Roberts VC, Watkins PJ. Blood flow in the diabetic neuropathic foot. *Diabetologia* 1982; **22**:9–15.

52 Neubauer B, Gundersen HJG. Calcifications, narrowing and rugosities of the leg arteries in diabetic patients. *Acta Radiol Diagn (Stockh)* 1983; **24**:401–413.

53 Gilbey SG, Walters H, Edmonds ME, Archer AG, Watkins PJ, Parsons V, Grenfell A. Vascular calcification, autonomic neuropathy, and peripheral blood flow in patients with diabetic nephropathy. *Diabet Med* 1989; **6**:37–42.

54 Christensen NJ. Muslce blood flow, measured by zenon 133 and vascular calcification in diabetic. *Acta Med Scan* 1968; **183**:449–454.

55 Chantelau E, Ma XY, Herrnberger S, Dohmen C, Trappe P, Baba T. Effect of medial arterial calcification on O2 supply to exercising diabetic feet. *Diabetes* 1990; **39**:938–941.

56 Neubauer B, Christensen NJ, Christensen T, Gundersen HJ, Jørgensen J. Diabetic macroangiopathy. Medial calcifications, narrowing, rugosities, stiffness, norepinephrine depletion and reduced blood flow capacity in the leg arteries. *Acta Med Scand Suppl* 1984; **687**:37–45.

57 Sinha S, Munichoodappa CS, Kozak GP. Neuro-arthropathy (Charcot joints) in diabetes mellitus (clinical study of 101 cases). *Medicine (Baltimore)* 1972; **51**:191–210.

58 Clouse ME, Gramm HF, Legg M, Flood T. Diabetic osteoarthropathy. Clinical and roentgenographic observations in 90 cases. *Am J Roentgenol Radium Ther Nucl Med* 1974; **121**:22–34.

59 Young MJ, Adams JE, Anderson GF, Boulton AJM, Cavanagh PR. Medial arterial calcification in the feet of diabetic patients and matched non-diabetic control subjects. *Diabetologia* 1993; **36**:615–621.

60 Forst T, Pfutzner A, Kann P, Lobmann RR, Schafer H, Beyer J. Association between diabetic-autonomic-C-fibre-neuropathy and medial wall calcification and the significance in the outcome of trophic foot lesions. *Exp Clin Endocrinol Diabetes* 1995; **103**:94–98.

61 Gentile S, Bizzarro A, Marmo R, de Bellis A, Orlando C. Medial arterial calcification and diabetic neuropathy. *Acta Diabetol Lat* 1990; **27**:243–253.

62 Goebel FD, Fuessl HS. Mönckeberg's sclerosis after sympathetic denervation in diabetic and non-diabetic subjects. *Diabetologia* 1983; **24**:347–350.

63 Harrison CV. The effect of sympathectomy on the development of experimental arterial disease. *J Pathol* 1938; **616**:353–360.

64 Danisch F. Die sympathischen Ganglien in ihrer Bedeutung für die Cholesterinsklerose des Kaninchens. *Beitr Path Anat* 1928; **79**:333–398.

65 Kerper HA, Collier WD. Pathological changes in arteries following partial denervation. *Proc Soc Exp Biol Med* 1926; **24**:493–494.

66 Petrova NL, Shanahan CM. Neuropathy and the vascular-bone axis in diabetes: lessons from Charcot osteoarthropathy. *Osteoporos Int* 2014; **25**:1197–1207.

67 Morgan AJ. Mineralised deposits in the thoracic aorta of aged rats: ultrastructural and electron probe x-ray microanalysis study. *Ext Geront* 1980; **15**:563–573.

68 Robert AM, Miskulin M, Godeau G, Tixier JM, Milhaud G. Action of calcitonin on the atherosclerotic modifications of brain microvessels induced in rabbits by cholesterol feeding. *Exp Mol Pathol* 1982; **37**:67–73.

69 Shanahan CM, Cary NR, Salisbury JR, Proudfoot D, Weissberg PL, Edmonds ME. Medial localization of mineralization-regulating proteins in association with Mönckeberg's sclerosis: evidence for smooth muscle cell-mediated vascular calcification. *Circulation* 1999; **100**:2168–2176.

70 Ho CY, Shanahan CM. Medial arterial calcification: an overlooked player in peripheral arterial disease. *Arterioscler Thromb Vasc Biol* 2016; **36**:1475–1482.

71 Narayan KM, Pettitt DJ, Hanson RL, Bennett PH, Fernandes RJ, De Courten M, *et al*. Familial aggregation of medial arterial calcification in Pima Indians with and without diabetes. *Diabetes Care* 1996; **19**:968–971.

72 London GM, Guérin AP. Influence of arterial pulse and reflected waves on blood pressure and cardiac function. *Am Heart J* 1999; **138**:220–224.

73 Kitagawa S, Yamaguchi Y, Kuitomo M, Amaizame N, Fujiwara M. Impairment of endothelium-dependent relaxation in aorta from rats with arteriosclerosis induced by excess vitamin D and a high-cholesterol diet. *Jpn J Pharmacol* 1992; **59**:339–347.

74 Chantelau E, Lee KM, Jungblut R. Association of below-knee atherosclerosis to medial arterial calcification in diabetes mellitus. *Diabetes Res Clin Pract* 1995; **29**:169–172.

75 Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. *N Engl J Med* 1987; **316**:1371–1375.

76 Fishbein GA, Fishbein MC. Arteriosclerosis: rethinking the current classification. *Arch Pathol Lab Med* 2009; **133**:1309–1316.

77 O'Neill WC, Han KH, Schneider TM, Hennigar RA. Prevalence of nonatheromatous lesions in peripheral arterial disease. *Arterioscler Thromb Vasc Biol* 2015; **35**:439–447.

78 Soor GS, Vukin I, Leong SW, Oreopoulos G, Butany J. Peripheral vascular disease: who gets it and why? A histomorphological analysis of 261 arterial segments from 58 cases. *Pathology* 2008; **40**:385–391.

79 Goldenberg S, Alex M, Joshi RA, Blumenthal HT. Non atheromatous peripheral vascular disease of the lower extremity in diabetes mellitus. *Diabetes* 1959; **8**:261–273.

80 Logerfo FW, Coffman JD. Current concepts. Vascular and microvascular disease of the foot in diabetes. Implications for foot care. *N Engl J Med* 1984; **311**:1615–1619.

81 Fiordaliso F, Clerici G, Maggioni S, Caminiti M, Bisighini C, Novelli D, et al. Prospective study on microangiopathy in type 2 diabetic foot ulcer. *Diabetologia* 2016; **59**:1542–1548.

82 Korzon-Burakowska A, Edmonds M. Role of the microcirculation in diabetic foot ulceration. *Int J Low Extrem Wounds* 2006; **5**:144–148.

83 Jörneskog G, Brismar K, Fagrell B. Skin capillary circulation severely impaired in toes of patients with IDDM, with and without late diabetic complications. *Diabetologia* 1995; **38**:474–480.