Diabetes Mellitus and Peripheral Vascular Disease

The increasing incidence of diabetes worldwide creates a problem of health care, both for the disease per se and for its chronic complications. Complications at the lower limb (LLC) are, among those related to diabetes, the most prevalent and relevant, both from clinical and social points of view: diabetes is now the major cause of nontraumatic amputation of the lower extremities (LEA), and the trend is positive because of the increasing prevalence of diabetes and the longer life expectancy of patients. Fifty to 60% of all non-traumatic amputations are performed in diabetic patients, and 75 to 85% of these amputations are caused by chronic foot ulcers. (Scatena et al, 2012), (Jörneskog, 2012)

Critical limb ischemia (CLI) plays a crucial role in determining the fate of the patients with LLC, since it exposes them to a risk of amputation, which is almost 60 times higher than that of nonischemic patients. (Scatena et al, 2012)

The foot ulcers in diabetic patients can be divided into neuropathic, ischemic and neuroischemic ulcers, of which the ischemic and neuroischemic together are the most common. In 90% of the patients undergoing amputation ischemia is the main cause. The healing of neuropathic foot ulcers is most often successful if local pressure to the area

can be avoided. However, a real challenge is to improve healing of ischemic or neuroischemic foot ulcers due to the low distal perfusion pressure, which is superimposed to the already existing disturbances in microvascular function. Patients with ischemic or neuroischemic foot ulcers should be considered for vascular surgery or angioplasty in order to optimise the peripheral circulation and ulcer healing, and to avoid amputation. Due to the neuroischemic pattern of the disease, dysfunction in microcirculation and challenges in diagnostics, the threshold for revascularization should be lower in diabetic patients with foot ulcer. (Jörneskog, 2012)

Epidemiology:

Peripheral arterial occlusive disease is 2–4 times more common in patients with diabetes than in patients without diabetes. (Beckman et al , 2002)

Peripheral arterial occlusive disease develops at a younger age in diabetic patients. (Jörneskog, 2012)

Many studies have shown an association between diabetes mellitus and the development of PAD. In patients with diabetes, for every 1% increase in hemoglobin A1c there is a corresponding 26% increased risk of PAD. (Norgren al, 2007), (Adler et al,2002)

A consensus statement from the American Diabetes Association recommends PAD screening with an ABI every 5 years in patients with diabetes. (Norgren et al, 2007)

Comorbidities:

Diabetics with CLI have a limited life expectancy and often die from a non-limb-related cause. It is known that in diabetic patients, coexisting cardiovascular morbidity and mortality, as well as renal impairment, pose an even greater risk to mortality than CLI. (Taneja et al, 2010)

Pathogenesis:

Over the last decade, mounting evidence has suggested that insulin resistance plays a key role in a clustering of cardiometabolic risk factors which include hyperglycemia, dyslipidemia, hypertension and obesity. Insulin resistance is a risk factor for PAD even in subjects without diabetes, raising the risk approximately 40% to 50%. (Norgren et al, 2007)

DM affects CLI in many ways. Premature and advanced atherosclerosis, together with peripheral neuropathy, impaired cellular immunity and impaired wound healing make CLI a complex problem among diabetic patients. (Taneja et al, 2010)

The abnormal metabolic state that accompanies diabetes directly contributes to the development of atherosclerosis; proatherogenic changes include increases in vascular inflammation and alterations in multiple cell types. (Marso & Hiatt, 2006)

Stiff arteries (i.e. mediasclerosis or Mönckeberg´s sclerosis), is more common in patients with diabetes, neuropathy and/or kidney failure. Mediasclerosis is characterized by calcification of the smooth muscle cells in the arteries sometimes causing incompressible arteries and falsely

elevated blood pressure (pseudohypertention) especially at the ankle level. (Jörneskog, 2012)

Vascular Dysfunction:

Type 1 and 2 DM are two distinct conditions, but, in respect to vascular function, they share several mechanisms. The most important shared factors seem to be hyperglycaemia, oxidative stress, formation of AGEs (advanced glycosylation end-products) and PKC (protein kinase C) production. (Ruiter et al , 2010)

In addition, in Type 2 DM, the constant state of low-grade inflammation of the endothelium affects vascular function, and may play an important part in the aetiology of the disease. Furthermore, Type 2 DM is associated with several imbalances, including dyslipidaemia and hypertension, which also affect vascular structure and function. (Ruiter et al , 2010)

The diabetic artery displays a change in phenotype and function of the endothelium and smooth muscle, and an altered structure and composition of the extracellular matrix compared with the non-diabetic artery. As a result, the diabetic artery in general has a decreased wall/lumen ratio and a stiffer vessel wall compared with the non-diabetic artery. (Ruiter et al , 2010)

Skin Microvascular Dysfunction (chronic capillary ischemia):

Diabetes mellitus is associated with severe vascular complications involving both micro- and macrocirculation. Poor glycemic control is an important contributing factor for the development of the microangiopathy seen in skin, nerves, retina and kidney. (Jörneskog, 2012)

Skin microcirculation is regulated by several mechanisms of which the sympathetic nerve system, endothelial- (nitric oxide, prostanoids, hyperpolarising factor) and non-endothelial dependent (smooth muscle cells, basement membrane, extracellular matrix) factors are most well known.

Neurogenic factors play a prominent role in the regulation of skin microcirculation due to the presence of thermoregulating arteriovenous shunt vessels which are innervated by the sympathetic nerves. In the diabetic foot, the skin capillary blood circulation is reduced and disturbances in microvascular function have been shown early after onset of type 1 diabetes. It is more pronounced when other complications are present, and in patients with poor glycemic control. The disturbances in foot skin capillary circulation were found despite a normal or even increased total blood supply to the region in diabetic patients without PAD. Similar disturbances have been found in patients with type 2 diabetes and neuropathy. The reason for this markedly reduced capillary blood flow is primarily due to an arterio-venous shunting, bypassing the nutritional skin capillaries. This impaired capillary circulation is even more pronounced in diabetic patients with PAD. The capillary circulation in diabetic patients with CLI is already very low during resting conditions, and cannot be improved in situations where an increased nutritional circulation is needed, such as in the healing process of ischemic foot ulcers. These microvascular disturbances are of great importance for the reduced skin oxygenation, poor tissue survival and impaired foot ulcer healing. (Jörneskog, 2012)

Although the pathophysiological mechanisms behind “the chronic capillary ischemia” in the diabetic foot are not fully known, some possible explanations are described. Thermoregulating arteriovenous (AV) shunts are common in skin microcirculation and these channels are mainly innervated by the sympathetic nervous system. Autonomic neuropathy, which is common in patients with diabetes, causes sympathetic denervation and loss of vessel autoregulation. The denervated AV-shunts loose their normal contraction and stay open leading to blood bypassing the capillaries. This

also transforms the arteriolar blood pressure into the subcapillary venules resulting in a decreased AV pressure difference leading to a reduced capillary circulation. Thus, in diabetic patients, especially those with neuropathy, the total skin microcirculation is normal, or even overperfused, while the capillary circulation is markedly reduced. (Jörneskog, 2012)

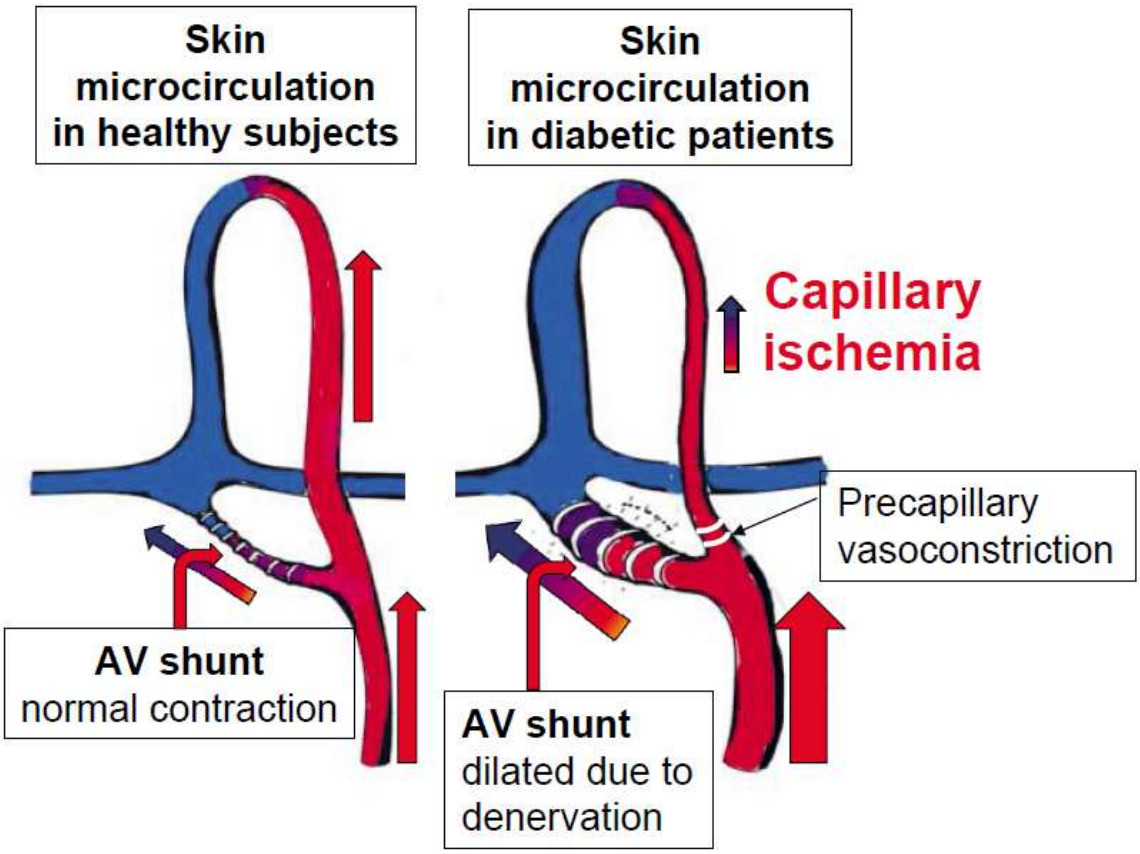

Figure 3: Possible explanations behind "chronic capillary ischemia" in the diabetic foot. (Jörneskog, 2012)

In line with the hypothesis of AV shunting as a mechanism behind chronic capillary ischemia, diabetic patients with peripheral neuropathy have warm and red feet indicating a good total skin blood flow, in spite of the fact that the skin capillary flow is markedly reduced in the same region. (Jörneskog, 2012)

Another contributing factor to the chronic capillary ischemia might be an altered balance between endogenous vasodilators (nitric oxide, hyperpolarizing factor, prostanoids) and vasoconstrictors (angiotensin II, endothelin-1) at the precapillary level leading to reduced capillary circulation. (Kalani et al, 2008)

A third factor contributing to the maldistribution of blood between nutritive and deeper non-nutritive blood circulation, is altered hemorheology, such as elevated levels of plasma fibrinogen. Fibrinogen is an acute phase reactant and an independent predictor of cardiovascular disease. Concentration of plasma fibrinogen is often increased in patients with diabetes and even more so in the presence of PAD. Fibrinogen increases blood viscosity and elevated levels have been associated with impaired forefoot tcPO2 in diabetic patients with CLI. (Jörneskog, 2012)

Inflammation:

Inflammation is an established risk factor for the development of atherosclerosis. Elevated levels of C-reactive protein (CRP) are strongly associated with the development of PAD. Furthermore, CRP levels are abnormally elevated in patients with impaired glucose tolerance. In addition to being a marker of atherosclerosis, elevated levels of CRP may also be a risk factor for PAD. C-reactive protein has procoagulant effects related to its ability to enhance expression of tissue factor. C-reactive protein also inhibits endothelial cell nitric oxide (NO) synthase, resulting in abnormal regulation

of vascular tone, and increases production of plasminogen activator inhibitor-1, which inhibits the formation of fibrinolytic plasmin from plasminogen. (Marso & Hiatt, 2006)

Endothelial Cell Dysfunction:

Most patients with diabetes and PAD demonstrate generalized endothelial cell dysfunction. In healthy vessels, endothelial cells synthesize NO, a potent vasodilator that inhibits platelet activation and vascular smooth muscle cell migration. Diabetes impairs NO-mediated vasodilatation. A number of mechanisms contribute to the decreased bioavailability of endothelium-derived NO in diabetes, including hyperglycemia, excess free fatty acids, and insulin resistance. The effects of endothelial cell dysfunction increase arterial susceptibility to atherosclerosis. In addition to reducing NO concentrations, diabetes increases the production of vasoconstrictors, such as endothelin-1, which increase vascular tone and vascular smooth muscle cell growth and migration. Diabetes also stimulates other atherogenic pathways in vascular smooth muscle cells. For example, hyperglycemia activates protein kinase C and nuclear factor kappa-B, increasing the production of reactive oxygen species that promote the formation of atherosclerotic lesions. Vascular smooth muscle cells cultured from patients with diabetes demonstrate enhanced migration, an important step in the progression to advanced plaque formation. These cells strengthen the atheroma, making it less likely to rupture and cause thrombosis. (Marso & Hiatt, 2006)

Diabetes and Thrombotic Phenomena:

Platelet aggregation is enhanced in diabetes. Elevated glucose levels activate protein kinase C, decrease production of platelet-derived NO, and increase oxidative stress. In diabetes, platelets also have increased expression of glycoprotein Ib and IIb/IIIa receptors, enhancing their

thrombotic potential. In addition to potentiating platelet aggregation, diabetes augments blood coagulability by increasing the expression of tissue factor and decreasing levels of anticoagulants, such as antithrombin III. Consequently, it is more likely that atherosclerotic plaque rupture will result in thrombus formation. (Marso & Hiatt, 2006)

Diabetes and Arteriogenesis:

A natural adaptive response to obstructed blood flow in a conducting artery is outward remodeling of pre-existing anastomoses. In this process, termed arteriogenesis, blood flow to the tissue distal to an occlusion can largely be restored. The sprouting of capillaries in response to tissue ischaemia, a process called angiogenesis, also occurs, but is not sufficient to restore flow to the distal part of the lower extremities. (Ruiter et al, 2010)

The functional outward remodelling of pre-existing anastomoses starts after blood flow obstruction in an artery. In experimental models, the process takes 4 weeks, after which a number of pre-existing collateral arterioles are remodelled into conducting arteries. When an arterial occlusion becomes manifest, blood takes the path of lowest resistance, through the pre-existing collateral anastomoses, increasing local blood flow in these vessels up to 200-fold. After remodelling, the collateral artery is barely distinguishable from a normal artery, except for slightly higher collagen content between the SMC (smooth muscle cell) layers. Collateral vessels grow from 30 to 50 μm in diameter to almost a 20-fold increase, and typically present a tortuous geometry. Notably, this dramatic remodeling does not restore conductance to the initial level. Without intervention, the conductance of the collateral circulation reaches up to 50%of the unobstructed artery. (Ruiter et al, 2010)

EFFECTS OF DIABETES ON ARTERIOGENESIS

In arteriogenesis, the presence of DM limits the amount of collateral development and the adaptive response to blood flow obstruction. Type 2 DM attenuates recruitment and functional outward remodelling of pre-existing collateral arterioles, demonstrated clinically in the coronary circulation and experimentally in the lower extremities. The impairment of arteriogenesis by Type 1 DM appears to be less severe. (Ruiter et al, 2010)

Disease Distribution and Lesion Characterestics:

Diabetes mellitus is a common cause of small vessel vasculopathy, hence accounting for the many forms of clinical presentation. The described pattern of atherosclerotic disease is often more diffuse in diabetics, with more severe involvement of the distal vessels. (Taneja et al, 2010)

Patients with diabetes more commonly present with involvement of the deep femoral and tibial arteries compared with patients who are not diabetic; however, patients with diabetes present with heterogeneous patterns and may have arterial occlusive disease in any vascular territory. (Ihnat & Mills, 2010)

The morphological characteristics of the occlusive peripheral arteriopathy in diabetic patients, which is mainly located in the distal vessels are a diffuse disease, heavy calcifications and high prevalence of occlusions respect to stenosis. (Faglia et al, 2012), (Van der Feen et al , 2002)

In the study of Shabestari et al, it was described that vasculopathy, namely stenosis, tortuosity, mural irregularity and calcification of the arterial walls,

is more frequent in patients with diabetes than those without. However, these were often non-occlusive lesions, particularly calcification along the arterial walls. They found that patients with diabetes had arterial occlusions less frequently than non-diabetic patients. (Tan et al, 2010), (Shabestari et al, 2006)

The vascular changes in diabetic patients are more diffuse and distally located, commonly at an infrapopliteal level. (Taneja et al, 2010), (Graziani et al, 2007) (Beckman et al, 2002)

A typical feature of PAD in DM is the predilection for the infrapopliteal arteries. A second characteristic is altered mechanical properties of the arterial wall. Specifically, the latter exhibits decreased distensibility and increased stiffness even in vessels not yet affected by the severe atherosclerotic disease. Third, medial arterial calcification of medium- and small-sized arteries is frequent. This is associated with both increased resistance to the radial force during angioplasty and high peripheral flow resistance, predisposing to poor primary patency rates of the endovascular interventions. As a result of absent arterial distensibility, increased peripheral outflow resistance due to atherosclerotic stenosis and medial arterial calcification, restenosis at the site of endovascular intervention, and increased rates of elastic recoil after angioplasty are quite common. (Georgakarakos et al, 2012)

Disease Presentation:

PAD in patients with diabetes is more aggressive compared to nondiabetics, with early large vessel involvement coupled with distal symmetrical neuropathy. (Norgren et al, 2007)

Notably, the pain associated with critical limb ischemia is often less dramatic in diabetic patients due to a concomitant peripheral neuropathy. There are also other factors which may disguise the clinical suspicion of ischemic ulcers in diabetic patients, e.g falsely high ankle blood pressure due to mediasclerosis and reduced inflammatory responses to tissue injury. Consequently, medical investigation and treatment may be delayed both due to patient's delay and doctor's delay. (Jörneskog, 2012)

Treatment Outcomes, Fate of Contralateral Limb:

The coronary literature clearly demonstrates a significantly increased mortality rate and need for repeat interventions in patients with diabetes who undergo angioplasty compared to surgical bypass. The increased mortality rate and increased rate of secondary interventions imply that patients with diabetes have higher restenosis rates after endovascular interventions (Ihnat & Mills, 2010)

The need for a major amputation is five- to ten-times higher in diabetics than non-diabetics. This is contributed to by sensory neuropathy and decreased resistance to infection. (Norgren et al, 2007)

Technical success rates for infrainguinal endovascular interventions are worse in the tibial arteries compared to the femoropopliteal arteries.

Similarly, heavy lesion calcification portends technical failure. Because patients with diabetes are more susceptible to developing more heavily calcified atherosclerotic arteries and tibial artery occlusive disease, it is expected that patients with diabetes would have lower technical success rates compared with patients without diabetes. (Ihnat & Mills, 2010)

In a retrospective review of infrainguinal endovascular interventions primarily in the femoropopliteal segment, Lazaris et al found a decreased technical success rate in patients with diabetes, 81% compared to 93% (P = .05) in patients without diabetes. More dramatically, they found a significantly increased rate of complications in patients with diabetes, 16.7% vs 3.9% (P = .03). (Lazaris et al, 2004), (Ihnat & Mills, 2010)

Large series of infrainguinal surgical bypasses generally demonstrate no difference in the technical success or patency rates of patients with diabetes compared to patients without diabetes. In contrast, DeRubertis et al evaluated 1000 consecutive percutaneous interventions in the femoropopliteal and tibial arteries and found a diminished primary patency rate in patients with diabetes (hazard ratio [HR], 1.7). In fact, diabetes was one of the most important risk factors affecting primary patency, second only to the indication for the procedure (HR, 2.5). (DeRubertis et al, 2007), (Ihnat & Mills, 2010)

In a prospective, nonrandomized study, Dick et al compared both surgical and endovascular interventions for iliac, femoropopliteal, and tibial artery occlusive disease and found poorer sustained clinical benefit in patients with diabetes. Sustained clinical benefit was defined as improvement in Rutherford category, amputation-free survival, and freedom from target extremity revascularization; however, the difference was primarily due to target extremity revascularization. Both secondary sustained clinical benefit

and limb salvage were equivalent to patients without diabetes. Multiple revascularizations might be required in patients with diabetes to achieve similar limb salvage rates. (Dick et al, 2007), (Ihnat & Mills, 2010)

In a registry of 219 limbs that underwent femoropopliteal angioplasty, Clark et al found diabetes to be significantly associated with reduced primary patency (relative risk [RR], 5.5; this was a stronger association than renal failure (RR, 4.0), but weaker than poor tibial runoff (RR, 8.5). (Clark et al, 2001), (Ihnat & Mills, 2010)

Another retrospective study compared subintimal angioplasty with placement of covered stents in long-segment superficial femoral artery occlusions, and found diabetes to be strongly associated with decreased primary patency (HR, 7.2). (Kougias et al, 2009), (Ihnat & Mills, 2010)

On the other hand, Baril et al evaluated predominantly claudicants with TASC II B and C femoropopliteal lesions, and did not find an association between diabetes and restenosis. (Baril et al, 2008)

Bakken et al separately evaluated patients with claudication and critical limb ischemia who underwent EVT of superficial femoral artery occlusive disease. In the claudication group, insulin-dependent diabetics maintained primary patency rates similar to patients without diabetes, but decreased assisted patency rates and increased restenosis rates at 3 years. Conversely, in patients with CLI, diabetes did not affect patency or restenosis rates, although it did negatively impact limb salvage rates. (Bakken et al,2007)

In the study of Faglia et al, it was found that 50% of diabetic patients with unilateral CLI would develop a CLI in the contralateral limb over a 6-year period. However, there was significantly lower frequency of midfoot and above-the-ankle amputations of contralateral limb compared to that of initial limb. This could be attributed to patient education, along with the use of a

proper orthesis after the hospitalization for the initial limb, which allowed intervening on less serious foot lesions, thus significantly decreasing the number of major amputations and allowing a minor amputation, if needed, at a more distal level. (Faglia et al, 2007)