

Peripheral artery disease in patients with diabetes: Epidemiology, mechanisms, and outcomes

Thejasvi Thiruvoipati, Caitlin E Kielhorn, Ehrin J Armstrong

Thejasvi Thiruvoipati, Caitlin E Kielhorn, Ehrin J Armstrong, Section of Cardiology, Denver VA Medical Center and University of Colorado School of Medicine, Denver, CO 80220, United States

Author contributions: All the authors contributed to this work.

Conflict-of-interest statement: The authors declare that there is no conflict of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Ehrin J Armstrong, MD, MSc, Section of Cardiology, Denver VA Medical Center and University of Colorado School of Medicine, Denver, CO 80220, United States. ehrin.armstrong@ucdenver.edu
Telephone: +1-415-3122480

Received: August 29, 2014

Peer-review started: August 30, 2014

First decision: October 28, 2014

Revised: November 20, 2014

Accepted: March 30, 2015

Article in press: April 2, 2015

Published online: July 10, 2015

Abstract

Peripheral artery disease (PAD) is the atherosclerosis of lower extremity arteries and is also associated with atherothrombosis of other vascular beds, including the cardiovascular and cerebrovascular systems. The presence of diabetes mellitus greatly increases the

risk of PAD, as well as accelerates its course, making these patients more susceptible to ischemic events and impaired functional status compared to patients without diabetes. To minimize these cardiovascular risks it is critical to understand the pathophysiology of atherosclerosis in diabetic patients. This, in turn, can offer insights into the therapeutic avenues available for these patients. This article provides an overview of the epidemiology of PAD in diabetic patients, followed by an analysis of the mechanisms by which altered metabolism in diabetes promotes atherosclerosis and plaque instability. Outcomes of PAD in diabetic patients are also discussed, with a focus on diabetic ulcers and critical limb ischemia.

Key words: Peripheral artery disease; Epidemiology; Pathophysiology; Outcomes; Diabetes

© **The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Diabetes mellitus (DM) is a major risk factor of peripheral artery disease (PAD), leading to increased morbidity and mortality as well as an accelerated disease course. As such, a more thorough understanding of the multi-factorial mechanisms underlying disease etiology for both DM and PAD is justified. This review provides clinical insight into the current state of research in the pathophysiology of PAD in diabetic patients, as well as highlights the progress of endovascular interventions for PAD, with a focus on techniques that have shown promise for treatment of critical lower limb ischemia.

Thiruvoipati T, Kielhorn CE, Armstrong EJ. Peripheral artery disease in patients with diabetes: Epidemiology, mechanisms, and outcomes. *World J Diabetes* 2015; 6(7): 961-969 Available from: URL: <http://www.wjgnet.com/1948-9358/full/v6/i7/961.htm> DOI: <http://dx.doi.org/10.4239/wjd.v6.i7.961>

INTRODUCTION

Over 170 million people worldwide have diabetes mellitus (DM) and the worldwide burden is projected to increase to 366 million people by 2030^[1,2]. The major causes of DM include impaired insulin secretion or inadequate response to secreted insulin^[3]. DM is a major risk factor for atherosclerotic disease as well as cardiovascular mortality and morbidity^[3,4]. Atherosclerotic disease is not only increased in incidence in diabetic patients, but its course is also accelerated^[4], thereby accounting for as much as 44% of all-cause mortality^[5]. DM-associated atherosclerosis can lead to complications in all major of vascular beds, including the coronary arteries, carotid vessels, and lower extremity arteries^[5,6]. For example, a study by Haffner *et al*^[7], estimated the 7-year incidence of a first-time myocardial infarction (MI) in diabetic patients at 20.2%, compared to 3.5% in nondiabetic patients.

Peripheral artery disease (PAD) is defined as atherosclerotic occlusive disease of lower extremities. PAD is associated with increased risk of lower extremity amputation and is also a marker for atherothrombosis in cardiovascular, cerebrovascular and renovascular beds. Patients with PAD therefore have an increased risk of MI, stroke and death^[8]. Additionally, PAD causes significant long-term disability in diabetic patients^[5,9]. The treatment of patients with PAD can therefore be expensive, owing to need for a variety of diagnostic tests, therapeutic procedures, and hospitalizations^[10].

The purpose of this article is to review the epidemiology and mechanisms that contribute to development of PAD in diabetic patients. The outcomes of PAD in diabetic patients are also compared to nondiabetics, with an emphasis on the prevention of major amputations among patients with DM who have severe PAD.

EPIDEMIOLOGY OF PAD IN PATIENTS WITH DIABETES

PAD affects 12 million people in United States. The most common symptom in PAD is claudication, characterized as a cramping, pain or aching in the calves, thighs or buttocks with exertion and relief with rest^[8]. However, many patients have atypical symptoms that may require formal testing with an ankle brachial index test to diagnose PAD^[11].

The strongest risk factors for PAD are DM and smoking, with an odds-ratio of 2.72 and 1.88, respectively^[12]. With decreased rates of smoking in Western countries, DM is projected to become an increasingly important contributor to the development and progression of PAD. Previous studies have shown that glucose intolerance is associated with a greater than 20% prevalence of an abnormal ankle-brachial index (ABI) relative to 7% in those with normal glucose tolerance^[4]. Moreover, 20%-30% of patients with PAD have DM, although this is likely underestimated by the asymptomatic nature of less severe PAD and the altered

pain perception in diabetic patients due to peripheral neuropathy^[5].

Age, duration of diabetes, and peripheral neuropathy are associated with an increased risk of PAD in patients with pre-existing DM^[8,12]. Using ABI to identify PAD, the prevalence of PAD in people with DM over 40 years of age has been estimated to be 20%^[13]. This prevalence increases to 29% in patients with DM over 50 years of age^[5,14]. The severity and duration of DM are important predictors of both the incidence and the extent of PAD, as observed in United Kingdom Prospective Diabetes Study, where each 1% increase in glycosylated hemoglobin was correlated with a 28% increase in incidence of PAD, and higher rates of death, microvascular complications and major amputation^[15,16]. This correlation is particularly strong in men with hypertension or active tobacco use^[5]. Patients with PAD who have DM also tend to stay longer in hospital, incur greater costs, and account for greater use of hospital resources compared to patients with PAD alone^[10,17].

DM is also associated with more severe below-the-knee PAD (*e.g.*, popliteal, anterior tibial, peroneal and posterior tibial arteries), whereas risk factors such as smoking are associated with more proximal PAD in the aorto-ilio-femoral vessels^[8,16]. The prevalence of concomitant PAD and DM is especially high in those patients who have critical lower limb ischemia, with more than 50% of patients with critical limb ischemia (CLI) also having DM^[18].

In patients with PAD, the cardiovascular event rate over a 5-year period, including MI and stroke, is 20%, and the overall mortality rate is 30%^[19]. Among those with CLI, 30% undergo major amputation, and the 6-mo mortality rate is 20%^[20]. Diabetic patients comprise 25%-30% of patients undergoing coronary artery revascularization and up to 60% of patients presenting with acute MI^[21-23]. Cardiovascular and cerebrovascular event rates, both fatal and non-fatal, are increased in patients with PAD and DM relative to nondiabetic patients with PAD^[8].

Similar to the greater likelihood of diffuse and complex coronary artery disease in diabetic patients, patients with DM also tend to have more diffuse PAD, compared to the more focal disease observed in those without DM^[1,5,24]. Although patients with DM tend to present later in the course of disease progression, the incidence of intermittent claudication is also higher than in nondiabetics, as seen in Framingham study^[5,25]. In that cohort, the risk of claudication associated with DM was increased by 3.5 fold in men and 8.6 fold in women^[25]. Concomitant peripheral neuropathy, which diminishes sensory feedback and leads to a lack of symptoms from minimized pain perception, may predispose patients with DM and PAD to present with more advanced disease, such as an ischemic ulcer or gangrene, compared to patients without DM^[8]. The prevalence of major amputation in patients with DM is also higher than in nondiabetics, with rates ranging from 5 to 15 times greater in some studies^[8,16]. In a Medicare population, relative

to nondiabetic patients, the relative risk (RR) for lower extremity amputation was 12.7 in diabetic patients. The RR rose to 23.5 in a cohort aged 65–74 years^[4].

The risk relationship between PAD and DM is noted to be reciprocal: while DM is a risk factor for PAD, higher rates of PAD, up to 30%, have been found in diabetic patients^[26]. The Hoorn study further clarified the discrepancy in prevalence of PAD between diabetic and nondiabetic patients: glucose intolerance was associated with 20.9% prevalence of an ABI less than 0.9, relative to 7% in those with normal glucose tolerance^[27]. Moreover, the prevalence of PAD in diabetic patients is likely underestimated by the asymptomatic nature of the condition, lack of reporting by the patients, and the altered pain perception in diabetic patients due to peripheral neuropathy^[11,26].

MECHANISMS OF PAD IN PATIENTS WITH DIABETES

DM is characterized by hyperglycemia, dyslipidemia, and insulin resistance^[4,28–30]. These pathologic states foster development and progression of PAD through mechanisms similar to that in coronary or carotid artery disease^[31,32]. These mechanisms include derangements in the vessel wall through promotion of vascular inflammation and endothelial cell dysfunction; abnormalities in blood cells, including smooth muscle cells and platelets; and factors affecting hemostasis (Table 1). Such vascular abnormalities that cause atherosclerosis in DM patients are often prevalent prior to the diagnosis of DM, and their severity increases with worsening blood glucose control and duration of DM^[8,33]. Taken together, these mechanisms likely contribute to increased plaque burden, plaque instability, and greater complexity of vascular disease^[3,34–36].

Inflammation

Inflammation is a risk marker for atherothrombosis. Among biomarkers of inflammation, C-reactive protein (CRP) is associated with both the development of PAD and impaired glucose regulation^[37]. CRP may also play a direct pathophysiologic role by promoting production of procoagulant tissue factor, leukocyte adhesion molecules, and chemotactic substances. CRP causes derangement in vascular tone by inhibiting endothelial nitric oxide synthase (eNOS), which produces nitric oxide (NO) *via* phosphoinositol-3-kinase dependent pathway^[3,8,38]. Moreover, CRP impairs fibrinolysis *via* the production of substances such as plasminogen activator inhibitor (PAI)-1, which blocks the breakdown of plasminogen into plasmin, a fibrinolytic^[39]. All of these factors in diabetic patients increase the susceptibility of vascular walls to the development of atherosclerosis^[40].

DM is also associated with increased circulating levels of pro-inflammatory cytokines such as tumor necrosis factor (TNF)- α and interleukin-6^[41,42]. These cytokines bind to endothelial cell surface receptors and activate nuclear

factor (NF)- $\kappa\beta$. This process promotes transcription of endothelial cell adhesion molecules, leading to increased binding of leukocytes and platelets to the endothelial surface, thereby fostering thrombogenesis. Plaque inflammation and instability may also be enhanced due to the increased leukocyte migration, which is associated with an increased risk of rupture and subsequent thrombus formation^[3,40,43].

Endothelial dysfunction

Endothelial cells mediate the interaction between blood cell elements and the vascular wall, thereby affecting blood flow, nutrient delivery, coagulation, and the balance between thrombosis and fibrinolysis^[8,44]. Endothelial cells also release substances that are critical for blood vessel function and structure, including NO, reactive oxygen species, and endothelin^[4,44]. Insulin is critical for the induction of phosphoinositol-3 kinase signaling, leading to production of NO and subsequent smooth muscle cell relaxation^[38,45]. NO also inhibits platelet activation and limits vascular smooth muscle cell (VSMC) migration and proliferation^[46–48]. By mediating the interaction between leukocytes and the vascular wall, NO also plays an important role in vasodilation and inflammation^[8,44].

Hyperglycemia, insulin resistance, and free fatty acid (FFA) production all reduce NO bioavailability in diabetic patients. Hyperglycemia impairs eNOS function, promoting oxidative stress by producing reactive oxygen species in endothelial and VSMCs^[38,49]. In turn, these factors inhibit endothelial vasodilation^[4,38,44]. Insulin resistance induces excess production of FFAs, which activate protein kinase C (PKC), inhibit phosphatidylinositol (PI)-3 kinase (an important agonist of eNOS), and produce reactive oxygen species^[24,28,50,51]. These mediators inhibit NO production and decrease its bioavailability, thereby causing endothelial dysfunction and leading to greater susceptibility of the vascular bed to atherosclerosis^[8,24,38,44,49–51].

DM is also associated with the enhanced production of advanced glycation end products (AGEs), which are formed by binding of reducing sugars to free amino groups *via* the Maillard reaction^[3,52–54]. The interaction of AGEs with their receptors can upregulate the synthesis of pro-inflammatory transcription factors such as NF- $\kappa\beta$ and activator protein 1^[54]. In addition to decreased endothelial function and impaired NO formation, these factors also lead to increased leukocyte chemotaxis, adhesion, transmigration, and transformation into foam cells. The latter process is the first step in the formation of atheromatous plaque^[8].

VSMC

VSMC migration from the medial layer into the intimal layer is associated with deposition of complex extracellular matrix, thereby stabilizing the atheroma. This decreases the risk of plaque rupture associated with thrombosis^[4,48,55,56]. In diabetic patients, plaques have fewer VSMC, increasing the chance of rupture and

Table 1 Mechanisms of peripheral arterial disease in diabetes mellitus patients

Disease characteristics		Mechanisms of pathology	Disease characteristics	
DM	Hyperglycemia Dyslipidemia	→ Vascular inflammation CRP: promotes leukocyte adhesion, coagulation, and chemotaxis; inhibits eNOS; impairs fibrinolysis	→	Atherosclerosis (Increased plaque burden)
	Insulin resistance	TNF- α and IL-6: activate NF- κ B, leading to thrombogenesis; promote leukocyte migration and adhesion, increasing plaque instability/rupture		Atherothrombosis (Increased plaque instability/rupture)
	↑ FFA production	Endothelial cell dysfunction Decreased NO production: inhibits vasodilation Increased reactive oxygen species: inhibits vasodilation Increased AGE production: is proinflammatory; induces leukocyte chemotaxis, adhesion, and transformation into foam cells Vascular smooth muscle cell derangement Tissue factor production: proatherogenic; procoagulation FGF and TGF- α : Extracellular matrix production Impaired synthesis of collagen: destabilizes plaque Apoptosis of VSMC: increases risk of plaque rupture and thrombosis Increased production of endothelin-1, angiotensin II, and prostanoids: leads to vasoconstriction Platelet dysfunction Enhanced uptake of glucose: increases oxidative stress; decreased NO production Upregulation of P-selectin, GP I b, and GP II b/ III a receptors: promotes platelet adhesion and aggregation Calcium dysregulation: increases platelet aggregation Hypercoagulability Increased tissue factor and FVII production: enhances coagulability Decreased antithrombin and protein C synthesis: enhances coagulability Rheology Elevated blood viscosity Increased fibrinogen production Impaired arteriogenesis Inhibited sensing of shear stress Decreased monocyte and growth factor signaling		Restenosis (Increased complexity)

Note that there is significant interplay between the different mechanisms: for example, impaired NO production can affect inflammation, endothelial cell function and arteriogenesis, while increased reactive oxygen species causes platelet and endothelial cell dysfunction. FFA: Free fatty acids; CRP: C-reactive protein; eNOS: Endothelial nitric oxide synthetase; TNF- α : Tumor necrosis factor- α ; IL-6: Interleukin-6; NF- κ B: Nuclear factor- κ B; NO: Nitric oxide; AGE: Advanced glycation end products; FGF: Fibroblast growth factor; TGF- α : Transforming growth factor- α ; VSMC: Vascular smooth muscle cell; GP I b: Glycoprotein I b; GP II b/ III a: Glycoprotein II b/ III a; FVII: Factor 7; DM: Diabetes mellitus; PAD: Peripheral artery disease.

thrombosis^[57]. Moreover, the lipid modifications noted in diabetic patients, such as glycated oxidized low-density lipoprotein, can promote apoptosis of VSMC^[4,46]. The metabolic syndrome that defines DM results in enhanced production of reactive oxygen species, inhibition of PI-3 kinase and upregulation of PKC, AGE receptors and NF- κ B, which in turn further promotes an atherogenic phenotype in VSMCs^[4,58]. These factors further contribute to the increased apoptosis of VSMC and upregulation of proatherogenic tissue factor in diabetic patients, while impairing synthesis of collagen, an important plaque-stabilizing compound^[8,59]. DM is also associated with increased matrix metalloproteinases, which further break down collagen, leading to plaque instability^[60]. Therefore, DM not only promotes atherosclerosis but also destabilizes plaques, triggering thrombus formation and impacting clinical outcomes^[8].

DM has also been found to promote upregulation and enhanced activity of endothelin-1, a protein that activates the endothelin-A receptor on VSMCs, leading to enhanced vascular tone^[61]. Such dysregulated hyperactivation

of endothelin-A receptor can cause pathological vasoconstriction^[62]. Endothelin-1 is also responsible for increasing salt and water retention, inducing the renin-angiotensin system, and causing vascular smooth muscle hypertrophy. Other vasoactive substances, such as vasoconstrictor prostanoids and angiotensin II, are also increased in production, further inducing vasoconstriction^[63].

Platelet function

Platelets mediate the interaction between vascular function and thrombosis. Hence, platelet dysfunction can accelerate atherosclerosis, as well as impact the destabilization of plaque and promote atherothrombosis^[8,64]. Platelets take up glucose independent of insulin, which in turn activates protein kinase-C and decreases NO production^[39]. Oxidative stress is also increased when platelets take up glucose, thus promoting platelet aggregation. Platelet adhesion is enhanced in diabetic patients due to upregulated expression of P-selectin on platelet surfaces^[3].

Diabetic patients also have upregulated expression of platelet receptors, such as glycoprotein I b (which binds to von Willebrand Factor) and II b/III a receptors (integral to platelet-fibrin interaction); these receptors mediate platelet adhesion and aggregation, thus inducing thrombosis^[39]. Intra-platelet calcium regulation, important for regulation of platelet shape change and aggregation, as well as for thromboxane production, is also deranged in diabetic patients, further contributing to atherosclerosis in this patient population^[4,39,65,66].

Coagulation

DM and hyperglycemic states promote hypercoagulability *via* upregulation of tissue factor by endothelial cells and VSMCs^[67,68]. These conditions also increase coagulation factor VIIA production and decrease anticoagulants, such as antithrombin and protein C production^[67,68]. DM also impairs fibrinolytic function and induces PAI-1 production^[69]. Taken together, these factors increase the risk of atherosclerotic plaque rupture and subsequent thrombus formation^[8,68,70].

Rheology

Elevated blood viscosity and fibrinogen production also occur in patients with DM. This is manifested *via* abnormal ABI in patients with PAD as well as development and complications of PAD^[8,71].

Restenosis after angioplasty

Acutely elevated glucose levels may induce inflammation, smooth muscle proliferation, abnormal matrix production, and inactivation of endothelium-derived relaxing factor^[72]. Additionally, hyperglycemia may impact expression of fibroblast growth factor and transforming growth factor- α , which in turn promotes proliferation of smooth muscle cells and extracellular matrix production. Increased TNF- α and CRP, as well as oxidative stress and endothelial dysfunction, may also play roles in explaining the restenosis rates in patients with higher blood glucose values at time of angioplasty^[73]. Acute hyperglycemia also induces production of monocyte chemoattractant-protein-1, which has been linked with a higher risk of restenosis^[73]. Restenosis among patients with DM can therefore be explained by the abnormal inflammatory state, oxidative stress, endothelial and platelet function in patients with acute hyperglycemia^[1].

Arteriogenesis

Outward remodeling of pre-existing arteries in response to obstruction of blood flow to restore blood flow distal to the occlusion is termed arteriogenesis^[74]. Endothelial shear stress, detected by the vessel wall through integrins, adhesion molecules, tyrosine kinases, and ion channels, is hypothesized to be the main trigger for arteriogenesis^[45,75,76]. DM limits the adaptive arteriogenesis response and collateral blood flow development by attenuating the remodeling process^[77,78]. Specifically, diabetes attenuates the sensing of shear

stress and increases the response to vasodilatory stimuli, which reduces the recruitment and dilation of collateral arteries. Additionally, DM impairs various other factors critical to remodeling, such as the downstream signaling of monocytes, growth factor signaling, and endothelial NO synthetase, thus inhibiting arteriogenesis and contributing to the severity of occlusive disease in these patients^[74].

OUTCOMES OF PATIENTS WITH PAD AND DM

The outcomes of patients with coexistent diabetes and PAD depend on the interplay between factors such as patient comorbidities, presence of infection, neuropathy, and immunologic factors^[79]. Poor glycemic control has been associated with a higher prevalence of PAD and risk of adverse outcomes, including need for lower extremity bypass surgery, amputation or death^[80]. Poor glycemic control is also associated with worse outcomes following vascular surgery or endovascular intervention^[80].

It is therefore important to identify therapies that can affect the multifactorial pathophysiologic mechanisms of DM in order to provide effective long-term treatments^[3]. Lifestyle interventions, such as weight loss, physical activity, and reduced cholesterol and fat intake, all help reduce the risk of progression from glucose intolerance to diabetes, as well as improve cardiovascular risk factors^[81]. Tobacco cessation is also critical and has been associated with improved outcomes after surgical and endovascular interventions. Such secondary risk factor reduction can help reduce the prevalence and severity of PAD in diabetic patients and also minimize adverse events post revascularization^[3].

Revascularization in patients with PAD and diabetes

Revascularization, either *via* a surgical or endovascular approach, is an important therapeutic option for treatment of symptomatic PAD in diabetic patients^[5]. Due to the greater prevalence of below-the knee disease in patients with DM, some studies have shown that endovascular interventions are associated with worse outcomes in diabetics, especially as distal runoff diminishes^[4]. Endovascular interventions were initially therefore considered more appropriate in patients with focal disease above the knee. Diabetic patients were also noted to have greater durability with surgical approach to revascularization, especially in the setting of tibial disease managed *via* bypass with autologous saphenous vein^[5]. However, recent studies have suggested that diabetic patients with adequate distal runoff appear to have patency rates comparable to that of nondiabetics^[4].

This association of glucose control and vessel patency has been investigated in a single-center retrospective study of outcomes after infrapopliteal balloon angioplasty among diabetic patients. Patients were divided based on median pre-procedure fasting blood glucose (FBG) values into two groups. At one-year follow-up, primary patency,

defined as freedom from restenosis or reintervention based on duplex ultrasound, was 16% for those with FBG values above the median and 46% for patients with below the median FBG values. Amputation rates also trended higher among patients with high pre-procedure FBG compared to low FBG. One-year major adverse limb event rates were significantly higher for patients with FBG values above the median, even after adjusting for insulin use and lesion-specific characteristics. No association between FBG values and overall mortality, amputation-free survival or rates of major adverse cardiovascular events was noted^[80]. When the FBG levels were divided into quartiles, a fivefold increase was noted in primary patency in the lowest quartile of FBG relative to those in the highest quartile of FBG. These results remained significant even after adjusting for baseline insulin use. These outcomes failed to show an association between HbA1C and restenosis, therefore implying that glycemic control at the time of intervention may be a better predictor of primary patency than overall glycemic control^[80]. Furthermore, these results suggest that the acute metabolic milieu at the time of intervention plays an important role in restenosis.

Treatment of critical limb ischemia

In patients with CLI, revascularization is usually required for successful limb preservation^[5]. The prevalence of DM in patients with CLI is extremely high, with some studies suggesting a prevalence of up to 76%^[18]. Disease severity at the time of presentation and progression of CLI in diabetics has also been noted to be worse^[82]. Current recommendations suggest arterial reconstruction in patients with CLI who have a predicted 1-year amputation-free survival of at least 75%^[18].

While patients with CLI may require multiple procedures and close follow-up, the choice of initial revascularization does not appear to influence success in diabetic patients with CLI^[18]. Whether chosen initially or subsequently, surgical and endovascular approaches both are associated with similar outcomes in terms of survival without major amputation or repeated target extremity revascularization (TER)^[18]. However, that study did confirm that repeat TER is more frequently required in diabetic patients. Despite the increased need for repeat revascularization, repeated procedures were associated with overall success rates comparable to that in nondiabetic patients^[18]. Immediate revascularization was also associated with improved outcomes relative to delayed revascularization in patients with CLI, regardless of diabetic status^[13]. Additional studies have also shown that an aggressive multidisciplinary approach in diabetic patients who present with CLI had similar limb salvage, 30-d mortality, cumulative survival, amputation-free survival, and major amputation rates, relative to nondiabetic patients^[83]. Revascularization rates do appear to be better in this patient population when both endovascular and bypass grafting procedures are available relative to one of the two approaches only^[84].

While most patients with CLI can be revascularized,

the presence of irreversible gangrene, the absence of a target vessel, and the lack of availability of an autologous vein can limit successful limb preservation. In these patients, amputation may be the best option^[5]. In general, however, medical management and use of multidisciplinary approach that includes revascularization can lead to reduced amputation rates in patients with DM^[79].

Diabetic foot ulcer is another complication in these patients that is associated with an increased risk of call-cause mortality^[79]. In those patients with PAD whose course is complicated by diabetic foot ulcer, similar outcomes in terms of limb salvage rates were seen with endovascular and open surgical approaches^[85]. It is important to note, however, that concomitant PAD in patients with diabetic foot ulcers is linked to greater failure rates of wound healing and need for amputation. This association is complex, and different studies have shown that successful revascularization and ulcer healing are not always correlated^[79].

CONCLUSION

DM is associated with greater severity and more diffuse PAD relative to nondiabetics. It also correlates to greater risk of mortality and impaired quality of life. The mechanisms by which diabetes induces atherosclerosis are multifactorial and include inflammatory processes, derangements of various cell types within the vascular wall, promotion of coagulation, and inhibition of fibrinolysis. These factors both increase the susceptibility of the vasculature to atherosclerosis, as well as the instability that makes plaque prone to rupture and thrombosis. Thus, it is important for different specialists, from cardiology and internal medicine to vascular surgery, to collaborate and use a multidisciplinary approach to improve the clinical outcomes in this patient population.

Although diabetics have a higher risk of adverse outcomes when compared to nondiabetics, the rates are improving thanks to recent advances in pharmacology and procedural techniques. Nonetheless, further work remains necessary. For instance, while trials such as TRITON-TIMI 38 and PLATO show better clinical outcomes with prasugrel or ticagrelor compared to clopidogrel after percutaneous coronary intervention, it is unclear if similar benefit is seen in DM patients with PAD^[3]. Further studies should also include the impact of biochemical factors found in central obesity, which are known to promote atherothrombosis^[86]. Better understanding of the mechanisms responsible for restenosis among diabetic patients will also ultimately improve the outcomes of surgical and endovascular procedures in these patients.

REFERENCES

- 1 **Armstrong EJ**, Waltenberger J, Rogers JH. Percutaneous coronary intervention in patients with diabetes: current concepts and future directions. *J Diabetes Sci Technol* 2014; **8**: 581-589 [PMID: 24876623 DOI: 10.1177/1932296813517058]
- 2 **Wild S**, Roglic G, Green A, Sicree R, King H. Global prevalence

- of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004; **27**: 1047-1053 [PMID: 15111519 DOI: 10.2337/diacare.27.5.1047]
- 3 **Armstrong EJ**, Rutledge JC, Rogers JH. Coronary artery revascularization in patients with diabetes mellitus. *Circulation* 2013; **128**: 1675-1685 [PMID: 24100481]
 - 4 **Beckman JA**, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. *JAMA* 2002; **287**: 2570-2581 [PMID: 12020339 DOI: 10.1001/jama.287.19.2570]
 - 5 **Marso SP**, Hiatt WR. Peripheral arterial disease in patients with diabetes. *J Am Coll Cardiol* 2006; **47**: 921-929 [PMID: 16516072 DOI: 10.1016/j.jacc.2005.09.065]
 - 6 **Forbang NI**, McDermott MM, Liao Y, Ix JH, Allison MA, Liu K, Tian L, Evans N, Criqui MH. Associations of diabetes mellitus and other cardiovascular disease risk factors with decline in the ankle-brachial index. *Vasc Med* 2014; **19**: 465-472 [PMID: 25358555]
 - 7 **Haffner SM**, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998; **339**: 229-234 [PMID: 9673301 DOI: 10.1056/NEJM199807233390404]
 - 8 **American Diabetes Association**. Peripheral arterial disease in people with diabetes. *Diabetes Care* 2003; **26**: 3333-3341 [PMID: 14633825 DOI: 10.2337/diacare.26.12.3333]
 - 9 **Vogt MT**, Cauley JA, Kuller LH, Nevitt MC. Functional status and mobility among elderly women with lower extremity arterial disease: the Study of Osteoporotic Fractures. *J Am Geriatr Soc* 1994; **42**: 923-929 [PMID: 8064098]
 - 10 **Hirsch AT**, Hartman L, Town RJ, Virnig BA. National health care costs of peripheral arterial disease in the Medicare population. *Vasc Med* 2008; **13**: 209-215 [PMID: 18687757 DOI: 10.1177/1358863X08089277]
 - 11 **Criqui MH**, Fronck A, Klauber MR, Barrett-Connor E, Gabriel S. The sensitivity, specificity, and predictive value of traditional clinical evaluation of peripheral arterial disease: results from noninvasive testing in a defined population. *Circulation* 1985; **71**: 516-522 [PMID: 3156007 DOI: 10.1161/01.CIR.71.3.516]
 - 12 **Fowkes FG**, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, Norman PE, Sampson UK, Williams LJ, Mensah GA, Criqui MH. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet* 2013; **382**: 1329-1340 [PMID: 23915883 DOI: 10.1016/S0140-6736(13)61249-0]
 - 13 **Elhadd TA**, Robb R, Jung RT, Stonebridge PA, Belch JFF. 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 [DOI: 10.1002/pdi.1960160605]
 - 14 **Hirsch AT**, Criqui MH, Treat-Jacobson D, Regensteiner JG, Creager MA, Olin JW, Krook SH, Hunninghake DB, Comerota AJ, Walsh ME, McDermott MM, Hiatt WR. Peripheral arterial disease detection, awareness, and treatment in primary care. *JAMA* 2001; **286**: 1317-1324 [PMID: 11560536 DOI: 10.1001/jama.286.11.1317]
 - 15 **Selvin E**, Marinopoulos S, Berkenblit G, Rami T, Brancati FL, Powe NR, Golden SH. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med* 2004; **141**: 421-431 [PMID: 15381515 DOI: 10.7326/0003-4819-141-6-200409210-00007]
 - 16 **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 [PMID: 11473082 DOI: 10.2337/diacare.24.8.1433]
 - 17 **Malone M**, Lau NS, White J, Novak A, Xuan W, Iliopoulos J, Crozier J, Dickson HG. The effect of diabetes mellitus on costs and length of stay in patients with peripheral arterial disease undergoing vascular surgery. *Eur J Vasc Endovasc Surg* 2014; **48**: 447-451 [PMID: 25116276 DOI: 10.1016/j.ejvs.2014.07.001]
 - 18 **Dick F**, Diehm N, Galimanis A, Husmann M, Schmidli J, Baumgartner I. Surgical or endovascular revascularization in patients with critical limb ischemia: influence of diabetes mellitus on clinical outcome. *J Vasc Surg* 2007; **45**: 751-761 [PMID: 17306950 DOI: 10.1016/j.jvs.2006.12.022]
 - 19 **Weitz JI**, Byrne J, Clagett GP, Farkouh ME, Porter JM, Sackett DL, Strandness DE Jr, Taylor LM. Diagnosis and treatment of chronic arterial insufficiency of the lower extremities: a critical review. *Circulation* 1996; **94**: 3026-3049 [PMID: 8941154 DOI: 10.1161/01.CIR.94.11.3026]
 - 20 **Dormandy JA**, Rutherford RB. Management of peripheral arterial disease (PAD). TASC Working Group. TransAtlantic Inter-Society Consensus (TASC). *J Vasc Surg* 2000; **31**: S1-S296 [PMID: 10666287]
 - 21 **Aronson D**, Edelman ER. Revascularization for coronary artery disease in diabetes mellitus: angioplasty, stents and coronary artery bypass grafting. *Rev Endocr Metab Disord* 2010; **11**: 75-86 [PMID: 20221852 DOI: 10.1007/s11154-010-9135-3]
 - 22 **Lankisch M**, Füth R, Gülker H, Lapp H, Bufe A, Haastert B, Martin S, Rathmann W. Screening for undiagnosed diabetes in patients with acute myocardial infarction. *Clin Res Cardiol* 2008; **97**: 753-759 [PMID: 18491170 DOI: 10.1007/s00392-008-0674-5]
 - 23 **Shore S**, Borgerding JA, Gyls-Colwell I, McDermott K, Ho PM, Tillquist MN, Lowy E, McGuire DK, Stolker JM, Arnold SV, Kosiborod M, Maddox TM. Association between hyperglycemia at admission during hospitalization for acute myocardial infarction and subsequent diabetes: insights from the veterans administration cardiac care follow-up clinical study. *Diabetes Care* 2014; **37**: 409-418 [PMID: 24089537 DOI: 10.2337/dc13-1125]
 - 24 **Creager MA**, Lüscher TF, Cosentino F, Beckman JA. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: Part I. *Circulation* 2003; **108**: 1527-1532 [PMID: 14504252 DOI: 10.1161/01.CIR.0000091257.27563.32]
 - 25 **Kannel WB**, McGee DL. Update on some epidemiologic features of intermittent claudication: the Framingham Study. *J Am Geriatr Soc* 1985; **33**: 13-18 [PMID: 3965550]
 - 26 **Setacci C**, de Donato G, Setacci F, Chisci E. Diabetic patients: epidemiology and global impact. *J Cardiovasc Surg (Torino)* 2009; **50**: 263-273 [PMID: 19543188]
 - 27 **Beks PJ**, Mackaay AJ, de Neeling JN, de Vries H, Bouter LM, Heine RJ. Peripheral arterial disease in relation to glycaemic level in an elderly Caucasian population: the Hoom study. *Diabetologia* 1995; **38**: 86-96 [PMID: 7744233 DOI: 10.1007/BF02369357]
 - 28 **Chahil TJ**, Ginsberg HN. Diabetic dyslipidemia. *Endocrinol Metab Clin North Am* 2006; **35**: 491-510, vii-viii [PMID: 16959582 DOI: 10.1016/j.ecl.2006.06.002]
 - 29 **Grundy SM**. Hypertriglyceridemia, insulin resistance, and the metabolic syndrome. *Am J Cardiol* 1999; **83**: 25F-29F [PMID: 10357572 DOI: 10.1016/S0002-9149(99)00211-8]
 - 30 **Rizzo M**, Pernice V, Frasher A, Berneis K. Atherogenic lipoprotein phenotype and LDL size and subclasses in patients with peripheral arterial disease. *Atherosclerosis* 2008; **197**: 237-241 [PMID: 17485096 DOI: 10.1016/j.atherosclerosis.2007.03.034]
 - 31 **MacGregor AS**, Price JF, Hau CM, Lee AJ, Carson MN, Fowkes FG. Role of systolic blood pressure and plasma triglycerides in diabetic peripheral arterial disease. The Edinburgh Artery Study. *Diabetes Care* 1999; **22**: 453-458 [PMID: 10097928 DOI: 10.2337/diacare.22.3.453]
 - 32 **Paneni F**, Beckman JA, Creager MA, Cosentino F. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part I. *Eur Heart J* 2013; **34**: 2436-2443 [PMID: 23641007 DOI: 10.1093/eurheartj/eh149]
 - 33 **Price JF**, Lee AJ, Fowkes FG. Hyperinsulinaemia: a risk factor for peripheral arterial disease in the non-diabetic general population. *J Cardiovasc Risk* 1996; **3**: 501-505 [PMID: 9100085]
 - 34 **Johnstone MT**, Creager SJ, Scales KM, Cusco JA, Lee BK, Creager MA. Impaired endothelium-dependent vasodilation in patients with insulin-dependent diabetes mellitus. *Circulation* 1993; **88**: 2510-2516 [PMID: 8080489 DOI: 10.1161/01.CIR.88.6.2510]
 - 35 **Steinberg HO**, Tarshoby M, Monestel R, Hook G, Cronin J, Johnson A, Bayazeed B, Baron AD. Elevated circulating free fatty acid levels impair endothelium-dependent vasodilation. *J Clin*

- Invest* 1997; **100**: 1230-1239 [PMID: 9276741 DOI: 10.1172/JC1119636]
- 36 **Li Y**, Woo V, Bose R. Platelet hyperactivity and abnormal Ca(2+) homeostasis in diabetes mellitus. *Am J Physiol Heart Circ Physiol* 2001; **280**: H1480-H1489 [PMID: 11247757]
- 37 **Ridker PM**, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Plasma concentration of C-reactive protein and risk of developing peripheral vascular disease. *Circulation* 1998; **97**: 425-428 [PMID: 9490235 DOI: 10.1161/01.CIR.97.5.425]
- 38 **Kawashima S**, Yokoyama M. Dysfunction of endothelial nitric oxide synthase and atherosclerosis. *Arterioscler Thromb Vasc Biol* 2004; **24**: 998-1005 [PMID: 15001455 DOI: 10.1161/01.ATV.0000125114.88079.96]
- 39 **Vinik AI**, Erbas T, Park TS, Nolan R, Pittenger GL. Platelet dysfunction in type 2 diabetes. *Diabetes Care* 2001; **24**: 1476-1485 [PMID: 11473089 DOI: 10.2337/diacare.24.8.1476]
- 40 **Schaper NC**, Nabuurs-Franssen MH, Huijberts MS. Peripheral vascular disease and type 2 diabetes mellitus. *Diabetes Metab Res Rev* 2000; **16** Suppl 1: S11-S15 [PMID: 11054881]
- 41 **Pradhan AD**, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA* 2001; **286**: 327-334 [PMID: 11466099 DOI: 10.1001/jama.286.3.327]
- 42 **Pickup JC**, Chusney GD, Thomas SM, Burt D. Plasma interleukin-6, tumour necrosis factor alpha and blood cytokine production in type 2 diabetes. *Life Sci* 2000; **67**: 291-300 [PMID: 10983873 DOI: 10.1016/S0024-3205(00)00622-6]
- 43 **Ross R**. Atherosclerosis is an inflammatory disease. *Am Heart J* 1999; **138**: S419-S420 [PMID: 10539839 DOI: 10.1016/S0002-8703(99)70266-8]
- 44 **De Vriese AS**, Verbeuren TJ, Van de Voorde J, Lameire NH, Vanhouette PM. Endothelial dysfunction in diabetes. *Br J Pharmacol* 2000; **130**: 963-974 [PMID: 10882379 DOI: 10.1038/sj.bjp.0703393]
- 45 **Troidl K**, Schaper W. Arteriogenesis versus angiogenesis in peripheral artery disease. *Diabetes Metab Res Rev* 2012; **28** Suppl 1: 27-29 [PMID: 22271719 DOI: 10.1002/dmrr.2232]
- 46 **Suzuki LA**, Poot M, Gerrity RG, Bornfeldt KE. Diabetes accelerates smooth muscle accumulation in lesions of atherosclerosis: lack of direct growth-promoting effects of high glucose levels. *Diabetes* 2001; **50**: 851-860 [PMID: 11289052 DOI: 10.2337/diabetes.50.4.851]
- 47 **Radomski MW**, Palmer RM, Moncada S. The role of nitric oxide and cGMP in platelet adhesion to vascular endothelium. *Biochem Biophys Res Commun* 1987; **148**: 1482-1489 [PMID: 2825688 DOI: 10.1016/S0006-291X(87)80299-1]
- 48 **Sarkar R**, Meinberg EG, Stanley JC, Gordon D, Webb RC. Nitric oxide reversibly inhibits the migration of cultured vascular smooth muscle cells. *Circ Res* 1996; **78**: 225-230 [PMID: 8575065 DOI: 10.1161/01.RES.78.2.225]
- 49 **Giacco F**, Brownlee M. Oxidative stress and diabetic complications. *Circ Res* 2010; **107**: 1058-1070 [PMID: 21030723 DOI: 10.1161/CIRCRESAHA.110.223545]
- 50 **Laakso M**, Sarlund H, Salonen R, Suhonen M, Pyörälä K, Salonen JT, Karhapää P. Asymptomatic atherosclerosis and insulin resistance. *Arterioscler Thromb* 1991; **11**: 1068-1076 [PMID: 2065028 DOI: 10.1161/01.ATV.11.4.1068]
- 51 **Steinberg HO**, Baron AD. Vascular function, insulin resistance and fatty acids. *Diabetologia* 2002; **45**: 623-634 [PMID: 12107742 DOI: 10.1007/s00125-002-0800-2]
- 52 **Bierhaus A**, Hofmann MA, Ziegler R, Nawroth PP. AGEs and their interaction with AGE-receptors in vascular disease and diabetes mellitus. I. The AGE concept. *Cardiovasc Res* 1998; **37**: 586-600 [PMID: 9659442 DOI: 10.1016/S0008-6363(97)00233-2]
- 53 **Miyazawa T**, Nakagawa K, Shimasaki S, Nagai R. Lipid glycation and protein glycation in diabetes and atherosclerosis. *Amino Acids* 2012; **42**: 1163-1170 [PMID: 20957396 DOI: 10.1007/s00726-010-0772-3]
- 54 **Bierhaus A**, Nawroth PP. Multiple levels of regulation determine the role of the receptor for AGE (RAGE) as common soil in inflammation, immune responses and diabetes mellitus and its complications. *Diabetologia* 2009; **52**: 2251-2263 [PMID: 19636529 DOI: 10.1007/s00125-009-1458-9]
- 55 **Libby P**. Current concepts of the pathogenesis of the acute coronary syndromes. *Circulation* 2001; **104**: 365-372 [PMID: 11457759 DOI: 10.1161/01.CIR.104.3.365]
- 56 **Davies MJ**, Richardson PD, Woolf N, Katz DR, Mann J. Risk of thrombosis in human atherosclerotic plaques: role of extracellular lipid, macrophage, and smooth muscle cell content. *Br Heart J* 1993; **69**: 377-381 [PMID: 8518056 DOI: 10.1136/hrt.69.5.377]
- 57 **Fukumoto H**, Naito Z, Asano G, Aramaki T. Immunohistochemical and morphometric evaluations of coronary atherosclerotic plaques associated with myocardial infarction and diabetes mellitus. *J Atheroscler Thromb* 1998; **5**: 29-35 [PMID: 10077455 DOI: 10.5551/jat1994.5.29]
- 58 **Quehenberger P**, Bierhaus A, Fasching P, Muellner C, Klevesath M, Hong M, Stier G, Sattler M, Schleicher E, Speiser W, Nawroth PP. Endothelin 1 transcription is controlled by nuclear factor-kappaB in AGE-stimulated cultured endothelial cells. *Diabetes* 2000; **49**: 1561-1570 [PMID: 10969841 DOI: 10.2337/diabetes.49.9.1561]
- 59 **Geng YJ**, Libby P. Progression of atheroma: a struggle between death and procreation. *Arterioscler Thromb Vasc Biol* 2002; **22**: 1370-1380 [PMID: 12231554 DOI: 10.1161/01.ATV.0000031341.84618.A4]
- 60 **Uemura S**, Matsushita H, Li W, Glassford AJ, Asagami T, Lee KH, Harrison DG, Tsao PS. Diabetes mellitus enhances vascular matrix metalloproteinase activity: role of oxidative stress. *Circ Res* 2001; **88**: 1291-1298 [PMID: 11420306 DOI: 10.1161/hh1201.092042]
- 61 **Cardillo C**, Campia U, Bryant MB, Panza JA. Increased activity of endogenous endothelin in patients with type II diabetes mellitus. *Circulation* 2002; **106**: 1783-1787 [PMID: 12356630 DOI: 10.1161/01.CIR.0000032260.01569.64]
- 62 **Nugent AG**, McGurk C, Hayes JR, Johnston GD. Impaired vasoconstriction to endothelin I in patients with NIDDM. *Diabetes* 1996; **45**: 105-107 [PMID: 8522053 DOI: 10.2337/diab.45.1.105]
- 63 **Hopfner RL**, Gopalakrishnan V. Endothelin: emerging role in diabetic vascular complications. *Diabetologia* 1999; **42**: 1383-1394 [PMID: 10651255 DOI: 10.1007/s001250051308]
- 64 **Tschoepe D**, Roesen P, Kaufmann L, Schauseil S, Kehrel B, Ostermann H, Gries FA. Evidence for abnormal platelet glycoprotein expression in diabetes mellitus. *Eur J Clin Invest* 1990; **20**: 166-170 [PMID: 2112481 DOI: 10.1111/j.1365-2362.1990.tb02264.x]
- 65 **Trovati M**, Anfossi G, Cavalot F, Massucco P, Mularoni E, Emanuelli G. Insulin directly reduces platelet sensitivity to aggregating agents. Studies in vitro and in vivo. *Diabetes* 1988; **37**: 780-786 [PMID: 2838353 DOI: 10.2337/diab.37.6.780]
- 66 **Davi G**, Catalano I, Averna M, Notarbartolo A, Strano A, Ciabattini G, Patrono C. Thromboxane biosynthesis and platelet function in type II diabetes mellitus. *N Engl J Med* 1990; **322**: 1769-1774 [PMID: 2345567 DOI: 10.1056/NEJM199006213222503]
- 67 **Kario K**, Matsuo T, Kobayashi H, Matsuo M, Sakata T, Miyata T. Activation of tissue factor-induced coagulation and endothelial cell dysfunction in non-insulin-dependent diabetic patients with microalbuminuria. *Arterioscler Thromb Vasc Biol* 1995; **15**: 1114-1120 [PMID: 7627704 DOI: 10.1161/01.ATV.15.8.1114]
- 68 **Carr ME**. Diabetes mellitus: a hypercoagulable state. *J Diabetes Complications* 2001; **15**: 44-54 [PMID: 11259926 DOI: 10.1016/S1056-8727(00)00132-X]
- 69 **Carmassi F**, Morale M, Puccetti R, De Negri F, Monzani F, Navalesi R, Mariani G. Coagulation and fibrinolytic system impairment in insulin dependent diabetes mellitus. *Thromb Res* 1992; **67**: 643-654 [PMID: 1440530 DOI: 10.1016/0049-3848(92)90068-L]
- 70 **Wilcox JN**, Smith KM, Schwartz SM, Gordon D. Localization of tissue factor in the normal vessel wall and in the atherosclerotic plaque. *Proc Natl Acad Sci USA* 1989; **86**: 2839-2843 [PMID: 2704749 DOI: 10.1073/pnas.86.8.2839]
- 71 **Cooke JP**. The pathophysiology of peripheral arterial disease: rational targets for drug intervention. *Vasc Med* 1997; **2**: 227-230 [PMID: 9546972]
- 72 **Nakamura N**, Ueno Y, Tsuchiyama Y, Koike Y, Gohda M, Satani O. Isolated post-challenge hyperglycemia in patients with normal

- fasting glucose concentration exaggerates neointimal hyperplasia after coronary stent implantation. *Circ J* 2003; **67**: 61-67 [PMID: 12520154 DOI: 10.1253/circj.67.61]
- 73 **Marfella R**, Sasso FC, Siniscalchi M, Paolisso P, Rizzo MR, Ferraro F, Stabile E, Sorropago G, Calabrò P, Carbonara O, Cinquegrana G, Piscione F, Ruocco A, D'Andrea D, Rapacciuolo A, Petronella P, Bresciani A, Rubino P, Mauro C, Paolisso G. Peri-procedural tight glycemic control during early percutaneous coronary intervention is associated with a lower rate of in-stent restenosis in patients with acute ST-elevation myocardial infarction. *J Clin Endocrinol Metab* 2012; **97**: 2862-2871 [PMID: 22639289 DOI: 10.1210/jc.2012-1364]
- 74 **Ruiter MS**, van Golde JM, Schaper NC, Stehouwer CD, Huijberts MS. Diabetes impairs arteriogenesis in the peripheral circulation: review of molecular mechanisms. *Clin Sci (Lond)* 2010; **119**: 225-238 [PMID: 20545627 DOI: 10.1042/CS20100082]
- 75 **Pipp F**, Boehm S, Cai WJ, Adili F, Ziegler B, Karanovic G, Ritter R, Balzer J, Scheler C, Schaper W, Schmitz-Rixen T. Elevated fluid shear stress enhances postocclusive collateral artery growth and gene expression in the pig hind limb. *Arterioscler Thromb Vasc Biol* 2004; **24**: 1664-1668 [PMID: 15242864 DOI: 10.1161/01.ATV.0000138028.14390.e4]
- 76 **Li YS**, Haga JH, Chien S. Molecular basis of the effects of shear stress on vascular endothelial cells. *J Biomech* 2005; **38**: 1949-1971 [PMID: 16084198 DOI: 10.1016/j.jbiomech.2004.09.030]
- 77 **van Golde JM**, Ruiter MS, Schaper NC, Vöö S, Waltenberger J, Backes WH, Post MJ, Huijberts MS. Impaired collateral recruitment and outward remodeling in experimental diabetes. *Diabetes* 2008; **57**: 2818-2823 [PMID: 18633114 DOI: 10.2337/db08-0229]
- 78 **De Vivo S**, Palmer-Kazen U, Kalin B, Wahlberg E. Risk factors for poor collateral development in claudication. *Vasc Endovascular Surg* 2005; **39**: 519-524 [PMID: 16382273 DOI: 10.1177/153857440503900609]
- 79 **Forsythe RO**, Jones KG, Hinchliffe RJ. Distal bypasses in patients with diabetes and infrapopliteal disease: technical considerations to achieve success. *Int J Low Extrem Wounds* 2014; **13**: 347-362 [PMID: 25123371]
- 80 **Singh S**, Armstrong EJ, Sherif W, Alvandi B, Westin GG, Singh GD, Amsterdam EA, Laird JR. Association of elevated fasting glucose with lower patency and increased major adverse limb events among patients with diabetes undergoing infrapopliteal balloon angioplasty. *Vasc Med* 2014; **19**: 307-314 [PMID: 24939930 DOI: 10.1177/1358863X14538330]
- 81 **Reynolds K**, He J. Epidemiology of the metabolic syndrome. *Am J Med Sci* 2005; **330**: 273-279 [PMID: 16355011 DOI: 10.1097/0000441-200512000-00004]
- 82 **Kullo IJ**, Bailey KR, Kardia SL, Mosley TH, Boerwinkle E, Turner ST. Ethnic differences in peripheral arterial disease in the NHLBI Genetic Epidemiology Network of Arteriopathy (GENOA) study. *Vasc Med* 2003; **8**: 237-242 [PMID: 15125483 DOI: 10.1191/1358863x03vm511oa]
- 83 **Awad S**, Karkos CD, Serrachino-Ingloft F, Cooper NJ, Butterfield JS, Ashleigh R, Nasim A. The impact of diabetes on current revascularisation practice and clinical outcome in patients with critical lower limb ischaemia. *Eur J Vasc Endovasc Surg* 2006; **32**: 51-59 [PMID: 16488631 DOI: 10.1016/j.ejvs.2005.12.019]
- 84 **Faglia E**, Clerici G, Losa S, Tavano D, Caminiti M, Miramonti M, Somalvico F, Airoidi F. Limb revascularization feasibility in diabetic patients with critical limb ischemia: results from a cohort of 344 consecutive unselected diabetic patients evaluated in 2009. *Diabetes Res Clin Pract* 2012; **95**: 364-371 [PMID: 22104261 DOI: 10.1016/j.diabres.2011.10.033]
- 85 **Hinchliffe RJ**, Andros G, Apelqvist J, Bakker K, Friederichs S, Lammer J, Lepantalo M, Mills JL, Reekers J, Shearman CP, Valk G, Zierler RE, Schaper NC. A systematic review of the effectiveness of revascularization of the ulcerated foot in patients with diabetes and peripheral arterial disease. *Diabetes Metab Res Rev* 2012; **28** Suppl 1: 179-217 [PMID: 22271740 DOI: 10.1002/dmrr.2249]
- 86 **Reisin E**, Alpert MA. The metabolic syndrome: an overview. *Am J Med Sci* 2005; **330**: 263 [PMID: 16355008 DOI: 10.1097/00000441-200512000-00001]

P- Reviewer: Masaki T, Okumura K, Wiwanitkit V

S- Editor: Tian YL **L- Editor:** A **E- Editor:** Liu SQ





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>

