



Přehledový článek | Review article

Panvascular risk factor – Diabetes

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ARTICLE INFO

Article history:

Received: 11. 10. 2017

Received in revised form: 12. 1. 2018

Accepted: 15. 1. 2018

Available online: 7. 2. 2018

Klíčová slova:

Diabetes mellitus

Ischemická choroba dolních končetin

Ischemická choroba srdeční

Makrovaskulární

Mikrovaskulární

Panvaskulární

Keywords:

Coronary artery disease

Diabetes mellitus

Macrovascular

Microvascular

Panvascular

Peripheral arterial disease

SOUHRN

Diabetes mellitus je metabolické onemocnění, na jehož podkladě dochází k rozvoji makrovaskulárních a mikrovaskulárních komplikací; proto je diabetes často považován za rizikový faktor panvaskulárního postižení. Diabetes jako významný rizikový faktor rozvoje ischemické choroby srdeční (IHS) je i markerem rozvoje systémové aterosklerózy. Mezi makrovaskulární komplikace patří IHS, cerebrovaskulární onemocnění a ischemická choroba dolních končetin (ICHDK), zatímco mezi mikrovaskulární komplikace patří retinopatie, nefropatie a neuropatie. Vzhledem ke složitosti a multifaktoriální podstatě základního patofyziologického mechanismu diabetické vaskulopatie je třeba aktivně pátrat po potenciálních cílech léčby. Achillovou patou morbidity a mortality v souvislosti s diabetem je diabetická vaskulopatie a přidružené komplikace. Léčba samotného diabetu se tak často stává řešením jeho důsledků pro cévní systém. Hlavním současným úkolem v oblasti léčby diabetu je získat dokonalou představu o tomto onemocnění jako rizikovém faktoru panvaskulárního postižení. Tento přehled se stručně zabývá patofyziologií diabetické vaskulopatie a jejími komplikacemi.

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ABSTRACT

Diabetes mellitus is the metabolic bed rock on which macrovascular and microvascular complications develop, hence diabetes is often regarded as a panvascular risk factor. Diabetes, a major risk factor of coronary artery disease (CAD), is also a marker for systemic atherosclerosis. Macrovascular complications include CAD, cerebrovascular disease and peripheral arterial disease (PAD), while microvascular complications include retinopathy, nephropathy and neuropathy. The underlying pathophysiological mechanism of diabetic vasculopathy is complex and multi-factorial, which requires an active research for potential therapeutic targets. The Achilles heel of diabetes related morbidity and mortality is diabetic vasculopathy and its related complications. Hence the management of diabetes per se is often translated into managing its vascular complications. A comprehensive understanding of diabetes as a panvascular risk factor is important. This review has briefly addressed the pathophysiology of diabetic vasculopathy and its complications.

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DOI: 10.1016/j.crvasa.2018.01.004

Introduction

The global burden of diabetes mellitus (DM) has increased from 30 million in 1985 to 382 million in 2014, and it will continue to rise in coming years [1]. International Diabetes Federation has estimated a burden of 592 million (1 in 10 persons) diabetics worldwide by 2035 [2]. Diabetes is a chronic, progressive metabolic disorder which causes both microvascular and macrovascular complications through a myriad of pathophysiological mechanisms. The most common complication is atherosclerosis of cardiovascular and cerebrovascular beds, which has imparted a significant socioeconomic burden to an individual and health sector. Patients with both type-1 and type-2 DM are at high risk for several cardiovascular disorders as coronary heart disease, cardiomyopathy, congestive heart failure; cerebrovascular and peripheral arterial disease. Often diabetes is accompanied by other vascular risk factors as hypertension, obesity and dyslipidemia, which result in accelerated atherosclerosis and premature death. Hence it is important to understand that diabetes is an important panvascular risk factor with pleomorphic presentation. The objective of the present review is to explain the pathophysiologic mechanism between DM and its various vascular complications.

Pathogenesis of diabetic vasculopathy

Diabetic vasculopathy/angiopathy is basically a functional and structural change in pan-vascular system following long standing diabetes. Diabetic angiopathy is divided into two: microangiopathy involving the arterioles and capillaries of retina (retinopathy), kidney (nephropathy), and nerves (neuropathy); and macroangiopathy affecting arteries of the brain (cerebrovascular disease), heart (ischemic heart disease and congestive heart failure), and the lower extremities (PAD).

Differences between type 1 and type 2 diabetic vascular disease

Chronic hyperglycemia and associated risk factors as hypertension, dyslipidemia and smoking are vital in the pathogenesis of diabetic vasculopathy of both type-1 and type-2 diabetes. Microvascular complications are more frequent in type-1 diabetes while macrovascular complications are more frequent in type-2 diabetes. Genetic factors play a crucial role in predicting vascular complications in type-1 compared to type-2 diabetes. Pathophysiological mechanism of vascular complications is almost similar in both types of diabetes.

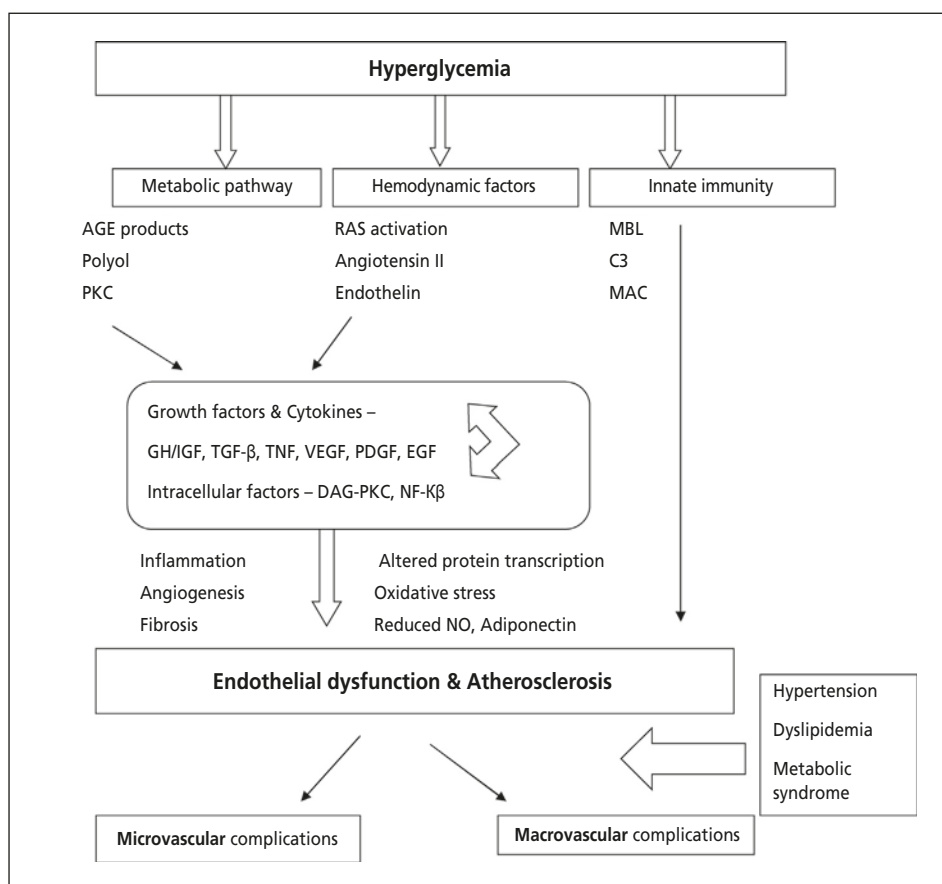


Fig. 1 – Schematic demonstration of multiple pathways of pathogenesis of vascular complications in diabetes (see text for explanation).

AGE – advanced glycation end products; C3 – complement system; DAG-PKC – diacylglycerol protein kinase C; EGF – epidermal growth factor; GH – growth hormone; IGF – insulin like growth factor; MBL – mannose binding lectin; MAC – membrane attack complex; NO – nitric oxide; NF-κβ – nuclear transcription factor κβ; PKC – protein kinase C; PDGF – platelet derived growth factor; RAS – renin angiotensin system; TNF – tumour necrosis factor; TGF-β – transforming growth factor-β; VEGF – vascular endothelial growth factor.

Pathogenesis of vascular complications in DM

In diabetics, various metabolic and hemodynamic factors interact to stimulate and express a variety of cytokines and growth factors at the level of panvascular arterial system (Fig. 1). Overexpression of transforming growth factor- β (TGF- β) is observed in tubules and glomeruli in diabetic kidney. Similarly, angiogenic cytokine – vascular endothelial growth factor (VEGF), VEGF receptors and vascular endothelial growth factor R-2 are overexpressed in retina of both experimental diabetes [3] and diabetic patients [4]. Vasoactive hormones such as angiotensin II and endothelin are potent stimulators of cytokines and growth factors, which in turn play an important role in pathogenesis of atherosclerosis. Various metabolic pathways such as advanced glycation end products (AGEs), activation of protein kinase-C (PKC) isoforms, and sorbitol accumulation through the polyol pathway, are actively involved in diabetes associated panvascular injury.

In addition, hemodynamic pathways along with systemic hypertension also get activated in diabetes. Interaction of hemodynamic and metabolic pathways leads to activation of second messengers such as PKC, transcription factors – nuclear transcription factor- κ B (NF- κ B) and overexpression of cytokines and their receptors, which induces atherosclerotic process in vascular beds. The pathological process includes vascular proliferation, angiogenesis, and extracellular matrix (ECM) accumulation; which leads to various functional and structural abnormalities such as endothelial dysfunction, poor vascular compliance and increased atherosclerosis [3,5].

Certain genetic polymorphisms also predict various vascular complications such as HLA-DQB10201/0302 alleles [6], polymorphisms of the aldose reductase gene [7], sorbitol dehydrogenase gene [8], and promoter of erythropoietin gene [9].

Advanced glycation end products (AGEs) are modified proteins or lipids that become non-enzymatically glycosylated and oxidized after reacting with aldose sugars. It gets accumulated in body with advancing age and in hyperglycaemic environments; and contributes to the pathophysiology of vascular complications of diabetes. It has been implicated in both micro- and macro-vascular complications of diabetes. AGEs modify the extra-cellular matrix; modify the action of hormones, cytokines, and free radicals via cell membrane receptors. This results in denaturation, browning, and cross-linking of intra-cellular targeted proteins [10]. In extra-cellular matrix, AGEs form a variety of molecules such as collagen, laminin, elastin, lipids and vitronectin. This alters the composition of the matrix and increases arterial stiffness. It also activates transforming growth factor (TGF) receptor, which increases extra-cellular matrix production. Binding of AGEs to receptor for advanced glycation end-products (RAGE) on endothelial cell surface activates a signaling cascade by stimulating nicotinamide adenine dinucleotide NAD(P)H oxidase, which increases reactive oxygen species (ROS), p21 RAS, and mitogen-activated protein kinases (MAPKs). A key target of RAGE signaling is nuclear transcription factor- β (NF- β), which increases transcription of different proteins like endothelin-1, intercellular adhesion molecule-1 (ICAM-1), E-selectin, and tissue factor. AGE and ligands for RAGE, such as HMGB1 and s100 calgranulin trigger

inflammatory pathways. AGEs also decrease nitric oxide (NO) availability by decreasing nitric oxide synthase (NOS) activity. It also activates monocytes and expression of macrophage scavenger receptor (MSR) class A and CD36 receptors, which leads to increased oxidized low density lipoprotein (OxLDL) uptake and foam cell formation [11].

In addition, complement system activation also plays certain role in pathogenesis of diabetic vasculopathy and its micro- and macro-vascular complications [3]. Mannose binding lectin (MBL) pathway triggers complement activation in diabetic patients [12]. Individuals with type-1 DM with nephropathy and cardiovascular disease have significantly higher circulating levels of MBL than diabetics without these complications [13].

Diabetic vasculopathy

Diabetes and cerebrovascular disease

The prevalence of cerebrovascular disease is on the rise with estimated 795,000 strokes occurring each year in the United States [14]. The incidence of stroke was 125–361 per 100,000 men and 61–194 per 100,000 women in World Health Organization (WHO) MONICA study [15]. Diabetes alone increases the risk of stroke both in men and women across all races and ethnicities. Moreover the other risk factors for stroke as hypertension, smoking, dyslipidemia, obesity, coronary artery disease, carotid artery disease and atrial fibrillation frequently coexist and perpetuate the pathogenesis of stroke. Diabetes is associated with 2–3-fold increase in risk of thromboembolic stroke [16] and the odds ratio is 2.1–2.7 in various ethnic populations [17]. The relative risk of stroke is higher in diabetics than non-diabetics, as Framingham heart study found it as 1.4 in men and 1.72 in women [18]. In another study, DM is directly attributed to 14% of the strokes in African Americans and 10% in Caribbean Hispanics, which was relatively higher in comparison to white population [19]. Diabetic women have higher risk of stroke compared to diabetic men. The relative risk of ischemic stroke was increased to 2–6.5-fold in diabetic women and 1.5–2-fold in diabetic men [20]. In Atherosclerosis Risk in Communities (ARIC) study, the adjusted relative risk of ischemic stroke increased with increasing tertile of hemoglobin A_{1c} (HbA_{1c}) in both non-diabetes ($p = 0.02$) and diabetes ($p < 0.0001$) [21]. The evidence between insulin resistance and stroke has the conflicting data. The ARIC study had demonstrated that there is mild increase in relative risk of stroke by 1.19 with each increase in 50 pmol/L of fasting insulin levels [22].

Carotid intima-media thickness (IMT) is a surrogate marker of early atherosclerosis. It is strongly associated with primary and recurrent stroke. There is an increased risk of stroke in diabetic patients with increasing carotid IMT [23]. Each 0.1 mm increase in IMT is associated with 18% increase risk of recurrent stroke [24]. In a study of 438 Japanese diabetic patients, carotid IMT was significantly associated with stroke after adjusting for age, body mass index, and smoking [25]. Similarly, in a Czech cohort, carotid IMT was increased in diabetics with stroke [26]. The Insulin Resistance Atherosclerosis Study (IRAS) demonstrated an increase in common carotid artery IMT

only in long-standing diabetics, but not in newly diagnosed diabetics [27].

Transient ischemic attack (TIA) is less common in diabetics compared to non-diabetics. Diabetics are more likely to present with complete infarct rather than TIA [28]. These individuals when present with TIA are more likely to progress into full-blown infarct within 2 days of presentation, as predicted by the ABCD2 score (age >60 years, blood pressure >140/90 mmHg, clinical features of motor or speech involvement, duration >60 min, and diabetes) [29]. Diabetes also increases the risk of cardiac embolization. Diabetes alone would increase the risk of stroke from 1.9 to 2.8 in atrial fibrillation [30]. It is commonly associated with CAD, hypertension and obesity, which are important risk factors for atrial fibrillation and cardio-embolic stroke. An association of diabetes with hemorrhagic stroke is controversial. In majority of the studies there is no significant correlation; however one of the study had shown increase risk of hemorrhagic stroke in diabetics [31].

Diabetes increases the risk of death following stroke. A prospective Finnish study involving 8077 men and 8572 women with an average follow-up period of 16.4 years showed that DM was the strongest predictor of death from stroke among both the sexes. The relative risk of mortality following ischemic stroke for men and women was 6.0 and 8.2, respectively. These relative risks were higher than those for systolic blood pressure, smoking or total serum cholesterol. In this cohort, the fractions of stroke death directly attributed to diabetes were 16% in men and 33.3% in women [32]. In a systematic review and meta-analysis of 64 cohorts, the pooled maximum-adjusted relative risk for stroke associated with diabetes was 2.28 and 1.83 in women and men, respectively [33]. Overall evidence suggests that diabetic women are at increased risk for both ischemic stroke and stroke related mortality, in comparison to diabetic men.

Management of stroke in diabetics is similar to that of non-diabetics. Thrombolysis in diabetic patients with acute stroke is not as successful as in non-diabetic patients. In a series of 27 diabetic patients treated with intravenous tissue plasminogen activator (t-PA), none achieved recanalization of the occluded artery as measured by transcranial Doppler ultrasound [34]. Brown et al., in their analysis of 312 ischemic stroke treated with recombinant tPA, found that patients with diabetes and high pre-treatment blood sugar had a trend towards incomplete neurological improvement following thrombolysis [35]. Arnold et al., in their study of intra-arterial thrombolysis with Urokinase in 100 acute ischemic stroke patients had also shown that diabetes had poor functional outcome at 3-month follow-up [36]. Mechanical thrombectomy in acute thrombotic stroke has shown an improved neurological outcome, however data in diabetic subpopulation is really lacking [37].

Diabetes and coronary artery disease

Diabetes is associated with 2–4-fold increase in the CAD risk. They have a higher mortality compared to non-diabetics with CAD [37–39]. The most common cause of death in diabetics is again CAD. Certain risk factors as hypertension, dyslipidemia, smoking and obesity are co-

mon in diabetes, which attribute to accelerated atherosclerosis. Metabolic and hematological risk factors as micro-albuminuria, macro-albuminuria, elevated serum creatinine, abnormal platelet function, increased inflammation, oxidative stress, hyper-coagulation and endothelial dysfunction – all contribute to atherosclerosis. Insulin resistance and its association with elevated levels of plasminogen activator inhibitor (PAI) and fibrinogen also promote athero-thrombosis [40]. Adiponectin has anti-atherosclerotic property by increasing NO production, reducing the expression of adhesion molecules and inhibiting low density lipoprotein (LDL) oxidation [41]. Diabetic patients usually have low adiponectin levels, which results in endothelial dysfunction and accelerated atherosclerosis [42]. An increased level of inflammatory cytokine interleukin-1 (IL-1) also contributes in plaque destabilization resulting into acute coronary syndrome [43]. Diabetic individuals without previous myocardial infarction (MI) have a similar risk of future ischemic events, as of a non-diabetic individual with prior MI [44]. Therefore, DM is considered as CAD equivalent and requires aggressive control of cardiovascular risk factors as recommended for secondary prevention of cardiovascular disease. Cardiovascular event rate is higher in diabetics with angiography proven CAD compared to those without or with insignificant CAD [44–47]. Saely et al. reported that the risk of future cardiovascular events in 8 years was 53.5% and 22% in diabetics with CAD and without CAD, respectively [46].

Intensive glycemic control did not reduce the cardiovascular events in both type-1 diabetes (Diabetes Control and Complications Trial) [48] and type-2 diabetes (UK Prospective Diabetes Study Group) [49] during the trial years, but later on it got reduced by 10–17 years of follow-up. This effect has been termed as legacy effect or metabolic memory. Intensive glycemic control having HbA_{1c} below 7% does not improve adverse cardiovascular outcomes, hence current guidelines do not recommend more aggressive glycemic control in diabetics with established CAD. The Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) [50] and Action to Control Cardiovascular Risk in Diabetes (ACCORD) [51] trials had shown that near-normal glycemic control does not reduce cardiovascular events within the time frame of 3.5–5 years. ACCORD trial revealed that near-normal glucose control is associated with significant increase risk of cardiovascular death and all cause mortality.

Diabetic patients are more likely to develop diffuse and multi-vessel CAD. Coronary revascularization including both percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) is less efficacious in diabetics compared to non-diabetics. Though initial success and efficacy rates of PCI are similar in diabetic and non-diabetic population, diabetic have higher rate of in-stent restenosis, lower long-term stent patency and survival rates [51–54]. The use of drug-eluting stents (DES) and glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors have improved the outcomes in diabetics [55]. In diabetes with multi-vessel CAD, CABG is still superior to PCI in term of long term morbidity and mortality [55–58].

Diabetes is associated with increased risk of heart failure [59–61]. Long-standing hyperglycemia even in the absence of risk factors as CAD, valvular heart disease or hypertension, may result in diabetic cardiomyopathy. The possible mechanisms of diabetic cardiomyopathy include altered expression of contractile proteins, change in myocardial energy production, β -adrenergic receptor stimulation, a desynchronized excitation–contraction coupling, myocyte depletion and increased inflammatory cytokines activity [62]. Poor glycemic control is one of the predictor of future heart failure. There is 30% higher risk of heart failure with each 1% increase in HbA_{1c} in type-1 DM. The incidence of heart failure in diabetics is 12.6/100 person years, while prevalence is 9.5–22.3% of patients [62–64].

Diabetes and peripheral artery disease (PAD)

Different manifestations of peripheral arterial diseases in diabetics include peripheral arterial disease of lower extremities (PAD), carotid artery disease, aortic aneurysm, renovascular hypertension, abdominal angina, and ischemia of the upper extremities. Atherosclerosis is associated with more proximal PAD localized to aorto-ilio-femoral segment, whereas diabetic vasculopathy involves below-the-knee arterial segment as popliteal, anterior tibial, peroneal and posterior tibial arteries [65].

Diabetes is the leading cause of lower extremity amputation following trauma in United States. By using ankle brachial index (ABI), Lange et al. found a PAD prevalence of 26.3% in diabetics compared to 15.3% in non-diabetics [66]. Other studies had also shown 20–30% prevalence rate of PAD in diabetics [65–68]. Use of ABI for assessing PAD should be used in caution in diabetic patients because of high prevalence of arterial medial sclerosis and calcification and the most common site for such calcification is in the ankle arteries. Using cut off value of ABI <0.9 for diagnosing PAD lowers the sensitivity in diabetics because of arterial medial calcification; hence an alternative method of toe pressure measurement is more precise in diagnosing diabetic PAD [69]. Both American Diabetes Association and the American Heart Association have recommended toe-brachial index (TBI) to evaluate atherosclerotic PAD in diabetic individuals with incompressible ankle arteries or when the ABI is high (>1.30) [65].

Claudication is twice more common in diabetes than non-diabetic individuals. The cause of PAD is multifactorial as it involves macrovascular, microvascular complications of diabetes, vascular inflammation, thrombosis, peripheral (sensory, motor) and autonomic neuropathy, poor wound healing, increased susceptibility to infections and abnormal foot biomechanics. A repeated trauma of foot is common following sensory diabetic neuropathy. Defective proprioception and motor neuropathy leads to abnormal weight bearing, callus and ulcer formation. Other changes in the foot like hammer toe, charcot joint, claw toe deformity and prominent metatarsal heads are also frequent following repeated injury. Moreover infection in diabetic foot is more often poly-microbial involving gram positive, negative and anaerobic pathogens. Gas gangrene and sepsis is more frequent in diabetics than non-diabetics patients. Approximately 15% of the diabetic population develops a foot ulcer and among them 14–24% eventually undergo amputation. The 5-year

risk of amputation is around 1–2%. About 25% of people with claudication experience a worsening of symptoms over time [70]. In patients with PAD, the 5-years mortality is 15–25% and incidence of non-fatal myocardial infarction or stroke is even much higher. The mortality risk in patients with PAD is almost double in the presence of diabetes [68–70]. An individual with diabetes has eight times higher risk of amputation at trans-metatarsal level, as compared to non-diabetics [71]. Diabetics have distal atherosclerotic lesions with poor runoff, hence surgical or percutaneous revascularization is technically challenging usually have iliac or femoral arterial disease, while diabetics have diffuse femoro-popliteal disease and most often there is involvement of crural or pedal arteries which is not amenable to revascularization. Even after revascularization, there is higher recurrence rate of PAD and a poor long term patency of bypass grafts.

Hyperglycemia, long duration of diabetes, arterial hypertension, dyslipidemia and inflammatory markers have been considered as independent risk factors for carotid atherosclerosis in diabetes. Carotid atherosclerosis is associated with higher risk of major adverse cardiovascular events [73]. Diabetes and carotid artery stenosis (CAS) severity correlates with the increased likelihood of stroke. The prevalence of CAD in diabetic patients with carotid atherosclerosis is higher when compared to those without. In a study, the prevalence of CAD increased from 17.8% in those with 0% stenosis of extracranial carotid artery to 45.8% in those with >75% stenosis. The odds ratio for CAD increased from 1.50 for those with <25% stenosis to 3.90 for those with >75% carotid artery stenosis [74]. Noh et al. demonstrated that patients with long standing diabetes and significant CAS demonstrated additive and high risk for major adverse cardiovascular events (HR, 2.07; 95% CI 1.17–3.66; $p = 0.012$) [75]. Prevalence of a significant CAS requiring revascularization in asymptomatic diabetic population is around 1.7% [75]. In general population, diabetes is an independent risk factor for high grade CAS [76]. Extra-cranial and intra-cranial CAS and diabetic microvascular disease are the main determinants of stroke in diabetics. Carotid IMT is usually higher in diabetic in comparison to non-diabetics. Fasting blood glucose, HbA_{1c}, diabetes duration, plasma cholesterol and non HDL-cholesterol have been found to correlate with carotid IMT in diabetics [77]. Non HDL-cholesterol is found to be an independent predictor for ischemic stroke and total cardiovascular risk in diabetic population [18,19,29,30]. In another study, carotid IMT was greater in diabetic women compared to those with normal glucose tolerance [78]. The mean value of carotid IMT was between 0.91 and 0.89 mm in diabetic population [79,80]. Patients with diabetic nephropathy revealed greater carotid IMT than those without nephropathy. A renal involvement accelerates carotid atherosclerosis in diabetic population [81,82].

Diabetes and hypertension

Arterial hypertension is present in up to 40% and 70% of type-1 and type-2 diabetics, respectively [83]. Hypertension accelerates development and progression of both macro-vascular and micro-vascular complications. Arterial hypertension also causes endothelial dysfunction

and vascular remodeling [84]. Studies have shown that strict blood pressure control is associated with reduction in both microvascular and macrovascular complications. UK Prospective Diabetes Study Group (UKPDS) trial had shown that tighter BP control was associated with 34% risk reduction in macrovascular complications (myocardial infarction, sudden death, PAD and stroke) and 37% risk reduction in microvascular complications (retinopathy requiring photocoagulation, vitreous hemorrhage and renal failure) compared to standard blood pressure control group [85]. In contrast ACCORD blood pressure trial had shown no significant difference in outcomes between tighter v/s standard blood pressure control arm. Rather intensive control group had increase adverse outcomes such as hypotension, hyperkalemia, bradycardia, syncope, angioedema and renal failure [86].

Diabetes and Monckeberg's media sclerosis (MMS)

Pathological vascular calcification can involve intima or media or both layers of the vessel wall. MMS is the most common variant of calcification of media of arterial wall and is commonly found in type-2 diabetes and chronic kidney disease. It is secondary to abnormal calcium and phosphorous metabolism resulting in hydroxyapatite crystal deposition in media and ectopic calcification. MMS primarily affects small and medium sized arteries. The prevalence of vascular medial calcification in newly diagnosed type-2 diabetic population was around 17% [87,88] and in patients with already established type-2 diabetes on treatment it was approximately 41.5% [88]. Vascular medial calcification results in narrowing of the lumen which predispose to arterial ulcers on the skin predominantly affecting the lower extremities. Stiffening and loss of Windkessel property of the vessel wall contributes to organ hypoperfusion, left ventricular hypertrophy and diastolic dysfunction. MMS is an independent predictor of adverse cardiovascular events and mortality in diabetics [87]. MMS is diagnosed by ABI >1.1, X-ray of pelvis or lower extremities demonstrating classical "rail-road track" sign of calcification and histopathological confirmation. There is no specific treatment, other than treating the underlying disease as diabetes or chronic kidney disease.

Microvascular complications

Arterioles, capillaries, and venules constitute microvascular bed. Micro-vessels differ from large caliber vessels in respect to function, architecture and cellular components. In contrast to large vessels which provide blood to organs, micro-vessels regulate blood pressure and are vital in nutrient supply at cellular level. The micro-circulation adapts the local flow depending upon metabolic requirement, by the regulatory systems of vasomotion, permeability, and myogenic responses. Disturbances in microvascular function may arise even before the overt pathological vascular changes. The most consistent structural change is about the thickening of basement membrane of arterioles and capillaries of glomeruli, retina, skin and muscle. This results into classical diabetic microangiopathy manifested as hypertension and local tissue hypoxia and injury. In later stages, micro-vessels

loss results in drop-out and pruning; manifested as severe microvascular complications [89,90]. Other risk factors for microvascular complications are dyslipidemia and hypertension. Increased levels of LDL and oxidized LDL accelerate the pathogenesis of retinopathy, neuropathy and nephropathy, while low HDL levels are also linked to retinopathy [91–93]. Lipoprotein lipase dysfunction promotes microvascular changes through decrease levels of endogenous peroxisome proliferator-activated receptor (PPAR) agonists. PPAR- agonists inhibit the VEGF pathway and its effects as angiogenesis, cell migration and inflammation [94,95]; regulate retinal extra-cellular survival; limits apoptotic cell death [96] and improve endothelial dysfunction. In the Fenofibrate Intervention and Event Lowering in Diabetes study, the PPAR- α agonist – fenofibrate reduces the laser-based intervention of diabetic retinopathy [97]. In the Diabetes Atherosclerosis Intervention Study trial, the improved lipid profile with fenofibrate therapy was associated with reduced progression of micro-albuminuria [98].

Diabetic nephropathy

Diabetic nephropathy is one of the common causes of end stage renal disease (ESRD). It is a leading cause of morbidity and mortality in diabetics. Its incidence has increased by 150% in last 10 years in US and a similar trend is observed in Europe and Japan [99,100]. The earliest clinical manifestation of diabetic nephropathy is micro-albuminuria. Albuminuria is a marker of cardiovascular disease and adverse cardiovascular outcomes. Factors associated with progressive diabetic nephropathy are poor glycemic control, high blood pressure and baseline albuminuria. However, 50% of diabetics who develops chronic kidney disease (CKD) do not have preceding albuminuria [101]. The pathophysiological mechanisms include basement membrane thickening, mesangial expansion, glomerular hyperfiltration, increased glomerular capillary pressure and fibrosis. The main molecular mediators of nephropathy are various growth factors, angiotensin II and endothelin.

Diabetics with nephropathy invariably have other microvascular complications. Significant retinopathy is almost always present in diabetics with albuminuria. Diabetics have 2–4-fold increase in cardiovascular risk following albuminuria, while the risk exponentially increases with raised creatinine levels. The median survival is only 2.6 years following initiation of renal replacement therapy [102].

End-stage renal disease develops in 50% of type-1 diabetics with overt nephropathy in 10 years and in >75% of type-1 diabetics by 20 years in the absence of treatment. A greater proportion of patients with type-2 diabetes have microalbuminuria and overt nephropathy at the time of initial diagnosis. Progression from microalbuminuria to overt nephropathy occurs in 20–40% of Caucasians by 10 years, while 20% of those overt nephropathy cases progressed to end-stage renal disease by 20 years [103]. The risk factors for development of nephropathy include race, genetic susceptibility, high blood pressure and blood sugar, hyperfiltration, smoking, male gender, dyslipidemia, and age [83,104]. Aggressive control of hypertension, optimal

glycemic control and angiotensin converting enzyme inhibitors (ACEI) therapy is shown to be beneficial in diabetic nephropathy. Dialysis dependent diabetic patients had 22% and 15% higher mortality at one and five years, respectively, in comparison to non-diabetic dialysis dependent patients. The average survival of dialysis dependent patients is 4–5 years in US, and death is usually secondary to cardiovascular disease or infection [99]. Five year survival rate is about 5% among dialysis dependent diabetic patients in Germany [105]. Diabetics may manifest with uremic symptoms at a relatively less-advanced nephropathy stage, compared to non-diabetic counterparts.

Diabetics with autonomic dysfunction are more likely to have hypotensive episodes during hemodialysis, because of poor tolerance to volume shifts. PAD is also common in chronic diabetic patients, which may lead to difficult vascular access for hemodialysis. The long-term patency of arterio-venous fistula and grafts is also limited in diabetic population. Renal transplant patients have better survival, improved quality of life and higher degree of rehabilitation compared to dialysis dependent patients. The 18-month relative risk of death following renal transplantation was significantly lower compared to dialysis dependent diabetics waiting for transplantation ($p < 0.001$) [106].

Diabetic retinopathy

Diabetic retinopathy is one of the leading causes of blindness in the western world. One-third of patients with diabetes have retinopathy and one-tenth of patients have severe vision loss [107]. Various stages of diabetic retinopathy include background retinopathy, non-proliferative, pre-proliferative and proliferative retinopathy. The pathophysiological mechanism of non-proliferative retinopathy includes loss of retinal pericytes, increase vascular permeability, alterations in retinal blood flow and abnormal retinal microvasculature leading to retinal ischemia and hypoxemia. The retinal neovascularization response to hypoxia and ischemia forms the pathophysiological hall mark of proliferative retinopathy. The newly formed vessels are abnormal, fragile and more easily ruptures, resulting in vitreous hemorrhage, fibrosis and retinal detachment. It takes around 5 years for progression of severe non-proliferative to proliferative retinopathy. Initial manifestations of retinopathy appear by 10 years, while advanced proliferative retinopathy develops in all by 20 years in type-1 diabetics [108]. About 50% of individuals develop vision threatening retinopathy, out of which two-thirds have proliferative retinopathy and one-third have diabetic maculopathy [109]. Some of the diabetic patient's first presentation can be vision-threatening retinopathy [110]. The incidence of retinopathy is less in type-2 compared to type-1 diabetics. Approximately 10% of diabetics develop proliferative retinopathy and maculopathy, which requires further intervention to prevent blindness [110].

Diabetic neuropathy

One of the microvascular complications of diabetes is neuropathy involving sensory, motor and autonomic nerve fibres with pleomorphic manifestations involving multiple organ systems as gastrointestinal, cardiovascular, genitourinary, central and peripheral nervous systems. Approximately every third diabetic person has some form of neuropathy and the incidence of neuropathy is 2% per year [111]. As with other vascular complications, uncontrolled diabetes, longer duration and associated risk factors as smoking, hypertension and dyslipidemia contributes in development of neuropathy.

Experimental interventions targeting diabetic vasculopathy

Aminoguanidine is a potent inhibitor of the AGEs formation in body [3,112,113]. Its treatment has resulted in reduced microvascular complications in experimental and clinical diabetics [114]. Alagebrium or ALT-711 is proven for metabolizing pre-formed AGEs [115]. Phenylthiazolium bromide, original prototype of ALT-711 has been shown to reverse large vessel stiffness, improves collagen solubility, reduces vascular AGE accumulation, prevent the progression of nephropathy and causes significant reduction in atherosclerotic process in diabetic animal models [3,116]. Its use is associated with reduced pulse pressure and vascular stiffness in patients with systolic hypertension.

Conclusion

Diabetes mellitus is a metabolic disease with underlying inflammatory, prothrombotic and profibrotic pathophysiological mechanisms leading to panvascular manifestations. Despite the identification of various molecular targets involved in pathogenesis of diabetic vasculopathy, none of pharmacological interventions has become effective to retard the progression of macro- and micro-vascular complications. Diabetes often involves more than one vascular bed, resulting in a greater comorbidity and mortality. These pan-vascular complications impose a greater economic and health burden compared to diabetes alone for an individual and society.

Conflict of interest

None declared.

Ethical statement

Authors state that the research was conducted according to ethical standards.

Funding body

None.

References

References are available at ScienceDirect.