Available online at www.sciencedirect.com
ScienceDirect
journal homepage: http://www.elsevier.com/locate/crvasa

Review article – *Special issue: Panvascular medicine*

Panvascular risk factor – Diabetes

Ramalingam Vadivelu, Rajesh Vijayvergiya *

Department of Cardiology, Advanced Cardiac Centre, Post Graduate Institute of Medical Education & Research, Chandigarh 160012, India

ARTICLE INFO

Article history:
Received 11 October 2017
Received in revised form
12 January 2018
Accepted 15 January 2018
Available online xxx

Keywords:
Coronary artery disease
Diabetes mellitus
Microvascular
Macrovascular
Panvascular
Peripheral arterial disease

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 maker 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.

Contents

* *Corresponding author at*: Department of Cardiology, Advanced Cardiac Centre, Post Graduate Institute of Medical Education & Research, Sector 12, Chandigarh 160012, India.
E-mail address: rajeshvijay999@hotmail.com (R. Vijayvergiya).
https://doi.org/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 like coronary heart disease, cardiomyopathy, congestive heart failure; cerebrovascular and peripheral arterial disease. Often diabetes is accompanied by other vascular risk factors like 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 changes 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 like 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 I compared to type-2 diabetes. Pathophysiological mechanism of vascular complications is almost similar in both types of diabetes.

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 over expressed 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-κβ (NF-κβ) and over-expression 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 increase 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 glycated 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

Please cite this article in press as: R. Vadivelu, R. Vijayvergiya, Panvascular risk factor – Diabetes, Cor et Vasa (2018), https://doi.org/10.1016/j.crvasa.2018.01.004