Life Sciences 92 (2013) 1037–1045

Contents lists available at SciVerse ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Minireview

Neovascularization in diabetes and its complications. Unraveling the angiogenic paradox

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ARTICLE INFO

Article history:
Received 12 February 2013
Accepted 1 April 2013

Keywords:
Arteriogenesis
Endothelial cells
Growth factors
Hyperglycemia
Signal transduction

ABSTRACT

Diabetes mellitus (DM) is a chronic metabolic disease characterized by the presence of hyperglycemia, which can lead to many complications over time. These complications, such as nephropathy, retinopathy, neuropathy, impaired wound healing and accelerated atherosclerosis, are implicated with a large number of cellular and subcellular changes on vessels. In agreement, evidence indicates that in retinopathy, nephropathy and atherosclerotic plaque, there is excessive angiogenesis, whereas in wound healing and myocardial perfusion, blood vessel growth is impaired. Despite the awareness of this angiogenic paradox, many questions remain unanswered. This review aims at highlighting the different microvascular and macrovascular complications that are often concurrent in diabetic patients. A revision of the recent findings published in the literature regarding the angiogenic paradox will be performed. Apparently, endothelial dysfunction, as well as molecules such as vascular endothelial growth factor (VEGF) and hypoxia-inducible factor (HIF) play a major role in diabetic vascular complications. Specific tissues with impaired angiogenesis exhibit microenvironment features, such as increased PAI-1/uPA ratio and decreased blood flow, whereas TGFbeta increases extracellular matrix deposition, preventing the vascularization process. In addition, the monocytes/macrophages are important in endothelium activation for arteriogenesis and its arteriogenic response is reduced, leading to impaired collateral artery growth. Moreover, molecular mechanisms involved will be addressed, including abnormalities in growth factor, cytokines and metabolic derangements.

Contents

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0024-3205/$ – see front matter
http://dx.doi.org/10.1016/j.lfs.2013.04.001

Introduction

Diabetes Mellitus (DM) is a chronic metabolic disease associated with vascular complications as well as the failure of several organ systems. The number of affected individuals encompasses 171 million worldwide in the year 2000 and it is expected to rise to 366 million by the year 2030 (Wild et al., 2004; Kota et al., 2012). It is an "epidemic" condition, nowadays without a cure (Liday, 2011) and the cause of enormous human and economic losses (Wild et al., 2004).

Diabetes and vascular disease

Diabetic vascular disease results from endothelial and smooth muscle cell dysfunction caused by inflammatory changes in the blood vessel wall. This dysfunction results in the imbalance between vasoconstrictors and vasodilators, characterized by a change in the availability of nitric oxide (NO), increased expression of adhesion molecules, cytokines and chemokines as well as changes in platelet and anti-coagulant functions (Kolluru et al., 2012).

Vascular smooth muscle cell dysfunction also contributes to this process. Autonomous nervous system impairment leads to loss of physiological feedback mechanisms involved in the regulation of blood flow, inflammatory response, vasoconstriction, oxygen diffusion and leukocyte migration. These feedback mechanisms are, in turn, essential for wound healing (Gibbons and Shaw, 2012; Ahmad et al., 2005).

DM is also associated with a pro-thrombotic state, characterized by changes in platelet function and coagulation (Vazzana et al., 2012).

Micro vs. macrovascular disease

DM is associated with micro- and macrovascular abnormalities: microvascular disease affects small resistance arteries, arterioles and capillaries. These abnormalities manifested as retinopathy, nephropathy and neuropathy, clinically resulting in blindness, kidney failure and nerve damage; macrovascular disease affects medium and large caliper vessels, often leading to atherosclerosis and thromboembolism. Clinically, this translates into coronary, carotid, cerebrovascular disease as well as disease of the peripheral vessels, which is more prevalent in the arteries of the distal segment of the lower limbs. Interestingly, diabetic patients who smoke are more frequently affected in the proximal segment (Ahmad et al., 2005; Vazzana et al., 2012; Madonna and De Caterina, 2011).

Unlike macrovascular disease, which normally affects early in diabetics due to the cluster of cardiovascular risk factors colloquially referred to as "metabolic syndrome", microvascular disease usually is not present in the early stages of diabetes (Madonna and De Caterina, 2011).

Studies show that intensive treatment of hyperglycemia can reduce the progression of microvascular disease, but not macrovascular, for which the only observed effect in a long term follow-up, has been a reduction in the incidence of its known complications (Ahmad et al., 2005; Vazzana et al., 2012; Madonna and De Caterina, 2011). This is explained by the different response of large and small vessel endothelium to insulin and glucose (Wang et al., 2009). Studies also show that hyperglycemia is not a determinant factor for macrovascular disease since whereas an increase in glycosylated hemoglobin (HbA1c) from 5.5 to 9.5% implies a two-fold increase in the incidence of macrovascular disease, the same increase in HbA1C implies a ten-fold increase in microvascular disease. It is thus suspected that the explanation for this phenomenon lies with other factors, namely low-density lipoprotein (LDL) and triglycerides which co-exist with hyperglycemia (Brownlee, 2005).

Interestingly, in regard to angiogenesis, endothelial cells from different origins exhibit different behaviors (Wang et al., 2009).

Pathological characteristics of vascular disease in diabetes mellitus

Angiogenesis plays an ambiguous role when it comes to the pathogenesis of vascular disease in diabetes mellitus. Exacerbated angiogenesis occurs in diabetic retinopathy, nephropathy and diabetic atherosclerosis. This excess leads to the increased risk of cardiovascular events — the growth of *vasa vasorum* inside vascular wall is stimulated, leading to bleeding, plaque instability and consequent rupture. On the other hand, in diabetic foot disease there is a clear deficit in angiogenesis. Accordingly, deficit is responsible for impaired arteriole growth that leads to the deficit of myocardial perfusion often seen in diabetic patients (Kota et al., 2012; Waltenberger, 2007; Khazaei et al., 2011).

There is also a reduced recruitment of endothelial progenitor cells (EPC), as well as a decrease in their function under the conditions of diabetic disease, which implies an angiogenic deficit, adding to the aforementioned risk of cardiovascular complications (Capla et al., 2007; Kim et al., 2012).

Processes of neovascularization in diabetes

There are several processes of neovascularization occurring both in physiological and pathological situations (Simons, 2005a, 2005b). Angiogenesis is frequently assumed as the growth of new blood vessels and remodeling of existing ones with the purpose of restoring their function and structure (Ouma et al., 2012). The term angiogenesis has increasingly been used to describe the specific biological process of sprouting, the formation of a network of newly formed blood vessels from pre-existing ones, through migration and proliferation of endothelial cells (Stavrou, 2008). Angiogenesis is a complex process that involves the interaction between pro and anti-angiogenic mediators, growth factors, cytokines, cells and extracellular matrix (Kota et al., 2012). Conversely, arteriogenesis stands as the maturation and broadening of small pre-existing arteries through remodeling or collateral growth (Kolluru et al., 2012). Arteriogenesis normally occurs outside ischemic areas in response to the accumulation of mononuclear cells in stenosed or occluded locations due to changes in shear stress (Kolluru et al., 2012; Simons, 2005a, 2005b; Persson and Buschmann, 2011). The formation of new vessels from vascular progenitor cells (hemangioblasts), which then differentiate into endothelial cells is termed vasculogenesis (Ouma et al., 2012; Stavrou, 2008), another crucial form of neovascularization both in embryogenesis and in adulthood. All of these vascularization processes are imbalanced in diabetic patients.

VEGF is the most potent pro-angiogenic growth factor and is required during the whole process. It increases not only vessel permeability, but also EC proliferation, migration, matrix degradation and