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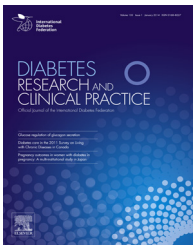

Invited Review

Microvascular dysfunction as a link between obesity, insulin resistance and hypertension

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ABSTRACT

Impaired microvascular dilatation from any cause and impaired insulin-mediated capillary recruitment in particular result in suboptimal delivery of glucose and insulin to skeletal muscle, and subsequently impairment of glucose disposal (insulin resistance). In addition, microvascular dysfunction, through functional and/or structural arteriolar and capillary drop-out, and arteriolar constriction, increases peripheral resistance and thus blood pressure. Microvascular dysfunction may thus constitute a pathway that links insulin resistance and hypertension. Overweight and obesity may be an important cause of microvascular dysfunction. Mechanisms linking overweight and obesity to microvascular dysfunction include changes in the secretion of adipokines leading to increased levels of free fatty acids and inflammatory mediators, and decreased levels of adiponectin all of which may impair endothelial insulin signaling. Microvascular dysfunction may thus constitute a new treatment target in the prevention of type 2 diabetes mellitus and hypertension.

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Contents

1. Introduction

Diabetes is a pandemic disease characterized by a number of metabolic abnormalities as a result from defects in insulin secretion and/or insulin action. About 366 million people worldwide have diabetes and this is expected to rise to ~552 million people in the next 20 years (www.idf.org). More than 90% of these patients have type 2 diabetes (www.who.int). Insulin resistance (i.e. impaired insulin-mediated glucose

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disposal) plays an important role in the development of type 2 diabetes (T2DM). Emerging data suggest that microvascular dysfunction is an important contributor to the pathogenesis of insulin resistance, and may thus constitute a new treatment target in the prevention of T2DM.

Classically, microvascular dysfunction is regarded as a consequence of T2DM, expressing itself in diabetes-related microvascular complications such as retinopathy, nephropathy, and neuropathy. More recently, studies have demonstrated that microvascular dysfunction may also act as a precursor of insulin resistance and T2DM [1,2]. Impaired microvascular dilatation from any cause and impaired insulin-mediated capillary recruitment in particular result in suboptimal delivery of glucose and insulin to skeletal muscle, and subsequently impairment of glucose disposal. In addition, microvascular dysfunction, through functional and/or structural arteriolar and capillary drop-out (so-called rarefaction), and arteriolar constriction, increases peripheral resistance. Microvascular dysfunction is thus thought to play a role in the development of high blood pressure, which often accompanies insulin resistance. Taken together, microvascular dysfunction has been identified both as an antecedent of insulin resistance [3] and to contribute to the development of high blood pressure [4].

2. Definition and measurement of microvascular function

The microcirculation represents the smallest structural and functional units of the cardiovascular system and is composed of a network of blood vessels less than 150 μm in diameter including arterioles, capillaries, and venules. The microcirculation is an important part of the cardiovascular system because it regulates organ perfusion, vascular tone, and transendothelial transport of blood solutes [5,6]. Arterioles consist of endothelial cells surrounded by a layer of smooth muscle cells and play an important role in the local distribution of blood to and within tissues, and also in the regulation of peripheral resistance. More than 90% of all blood vessels of the human body consist of capillaries. Capillaries in turn consist of a single layer of endothelial cells, without a muscle layer. Exchange of nutrients, water and gases takes place at this capillary level. Venules also consist of endothelial cells surrounded by a smooth muscle layer, and they regulate capillary pressure in addition to outflow. Impairment in at least one of the above functions constitutes microvascular dysfunction.

Several methods are available to measure microvascular (dys) function noninvasively. First, assessment of microvascular function in specific microvascular beds is frequently used, such as in (1) skin (by capillaroscopy and laser-Doppler fluxmetry) [4,7–10]; (2) muscle (by plethysmography and contrast-enhanced ultrasonography) [11,12]; (3) bulbar conjunctival bed (by intravital microscopy) [13,14]; and (4) retina (by photography) [15–18]. Besides baseline measurements, stimulus-induced responses can be used to determine microvascular (endothelium- or non-endothelium-dependent) reactivity. Among such stimuli are local ischemia, heating, or local or systemic administration of endothelium-(in)dependent vasoactive agents (e.g. acetylcholine and sodium nitroprusside) [4,10,19]. Second, microvascular function, in particular endothelial function, can be assessed with the use of plasma biomarkers because the large surface area and production capacity of the microcirculation (i.e. 98% of the total vascular surface area [20]) makes it likely that higher circulating concentrations of endothelial biomarkers reflect predominantly microvascular (rather than macrovascular) endothelial function. Measurements of plasma levels of endothelium-derived regulatory proteins such as soluble E-selectin (sE-selectin), soluble intercellular adhesion molecule 1 (sICAM-1), soluble vascular adhesion molecule 1 (sVCAM-1), and von Willebrand factor (vWF) [21] are often used. Increased levels of these markers are thought to reflect endothelial permeability to leucocytes (i.e. sE-selectin, sICAM-1, and sVCAM-1) [22–25], and prothrombotic and procoagulant activity (i.e. vWF) [23–25]. In addition, slight increases in urinary albumin excretion, so-called microalbuminuria, are thought to reflect a generalized increase in endothelial permeability [23], and is frequently used as a marker of general endothelial dysfunction [23–28]. Several studies have confirmed the concept that microalbuminuria is associated with a greater transcapillary escape rate of albumin, i.e. with greater microvascular permeability, and also showed that microalbuminuria, as a marker of endothelial function, is associated with risk of cardiovascular disease [23]. In addition, such associations cannot be explained by conventional risk factors.

3. Role of microvascular dysfunction in insulin resistance

Insulin promotes its own delivery and that of glucose to skeletal muscles by inducing microvascular vasodilation and capillary recruitment. It has been shown that this microvascular action of insulin accounts for ~40% of insulin-stimulated muscle glucose uptake [29,30]. Thus, microvascular dysfunction may lead to suboptimal delivery of plasma insulin and glucose to skeletal muscle cells. In the 1990s, Baron and colleagues first reported insulin's ability to vasodilate resistance vessels and consequently increase total skeletal muscle blood flow [3], which is paralleled by an increase in insulin-mediated glucose uptake [31,32]. Most studies on the vascular action of insulin observed only insulin-mediated increases in total limb blood flow after using supra-physiological doses of insulin or after several hours of delay when physiological concentrations were used [11,33]. Hence, the physiological importance of insulin's ability to increase *total* blood flow remains controversial [34]. Nevertheless, insulin has subsequently been shown to *redirect* blood flow in skeletal muscle from non-nutritive to nutritive capillary networks (capillary recruitment), without increasing total muscle blood flow. These effects are followed by an increase in insulin-mediated glucose uptake [35]. Such capillary recruitment requires physiological concentrations of insulin and has a time course that accords well with the time course for insulin-mediated glucose uptake in skeletal muscle [36]. Moreover, this process has been shown to be endothelium-dependent, requiring activation of the PI3-kinase pathway in the endothelial cell [37] resulting in endothelial nitric oxide synthase (eNOS) activation and production of nitric oxide

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