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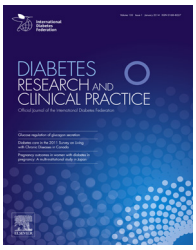

Invited Review

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.

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

(NO). Consequently, insulin-induced increase in NO production stimulates capillary recruitment [38,39] and transendothelial transport of insulin [40]. On the other hand, insulin also has vasoconstrictor effects in endothelial cells involving the MAP kinase pathway and resulting in the production of endothelin-1 (ET-1) [37]. Under physiological conditions, when insulin binds to the insulin or insulin-like growth factor receptor on endothelial cells [41], the net result usually favors NO production [38] and thus vasodilatation and capillary recruitment. Prospective studies support the hypothesis that microvascular dysfunction precedes and even predicts the development of T2DM, as these studies show that microvascular dysfunction is associated with incident impaired fasting glucose (IFG) and incident T2DM [1,42]. Recently, Muris et al. pooled thirteen prospective population-based studies in a meta-analysis, and concluded that the risks for incident T2DM was 25% higher per 1 SD greater microvascular dysfunction (as measured with plasma markers of endothelial function (sE-selectin, sICAM-1, sVCAM-1, and vWF), retinal microvessels, peripheral vascular reactivity, and microalbuminuria) in a follow-up period ranging from 2.6 to 12 years [1]. In the same meta-analysis, retinal microvasculature was also associated with risk for incident impaired fasting glucose (IFG). One SD greater retinal venular diameters were associated with a 15% higher incidence of IFG, and one SD lower arteriolar-to-venular ratio (AVR) was associated with 14% higher incidence of IFG. In addition, in animals with diet-induced insulin resistance it was demonstrated that microvascular endothelial dysfunction develops well before impaired insulin activation of PI3K in skeletal muscle [43]. All these data strongly suggest that microvascular dysfunction is a cause of insulin resistance, by affecting insulin-mediated glucose uptake in skeletal muscle through impaired capillary recruitment.

Overweight and obesity may be an important cause of microvascular dysfunction. Studies in obese subjects described diminished skin capillary recruitment [44]. And impaired capillary recruitment has been shown to be inversely associated with visceral adiposity and truncal subcutaneous adipose tissue [45]. 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 [46], all of which may impair endothelial insulin signaling [47,48]. Apart from visceral adipose tissue, perivascular adipose tissue (PVAT) may play a role in microvascular dysfunction [48,49]. Under normal circumstances, adiponectin release from PVAT enhances insulin's vasodilator effects in a paracrine fashion, whereas in the *db/db* mice, an increased PVAT and reduced adiponectin release was demonstrated, which was associated with decreased insulin-mediated vasodilation [50]. In conclusion, both systemic and local adipose tissue derived agents seem to contribute to the development of microvascular dysfunction through impairing insulin signaling pathways.

4. Microvascular dysfunction and blood pressure

Impaired microvascular function and structure is generally accepted as a consequence of high BP, but there is also evidence that microvascular changes, i.e. capillary rarefaction, may antedate the clinical onset of high BP [4]. All components of the microcirculation contribute to some extent to peripheral resistance. Small arteries and arterioles amount to 40–45% of total peripheral resistance, capillaries up to 23–30%, and the venules up to 3–4% [51]. Decreased capillary density may contribute to increased peripheral resistance, subsequently resulting in an increase in BP [52]. In a mathematical model based on the hamster cheek pouch microcirculation, functionally removing microvessels resulted in an elevation in vascular resistance [53]. Cross-sectional studies indeed demonstrated that skin capillary density was 10–20% lower in subjects with untreated hypertension as compared to normotensive controls [4,54]. In a longitudinal study of untreated hypertensive subjects, a low muscle capillary density at baseline was associated with an increase in mean arterial pressure during 20 years follow-up [55]. Also, the fact that decreased capillary density has been found in borderline hypertensive subjects [56] and even in normotensive offspring of hypertensive parents [57] also supports the concept that microvascular dysfunction may precede the development of hypertension. On the one hand, capillary rarefaction may be a structural phenomenon as in subjects with low birth weight. In prepubertal children (born at term), it was shown that lower birth weight was associated with decreased capillary recruitment [58]. On the other hand, capillary rarefaction may be a functional phenomenon [4] potentially related to impaired insulin-mediated microvascular actions. Besides the effects of capillary rarefaction, reduced arteriolar diameter (due to increased vasoconstriction and/or a thickened arteriolar wall) also contributes to the development of high blood pressure. Several longitudinal human studies have demonstrated that retinal arteriolar narrowing in normotensive subjects is independently associated with the development of high BP during a 3–6.6 years follow-up [59–62]. Part of this retinal arteriolar narrowing may be functional as flicker-light induced retinal arteriolar vasodilation, a response partly dependent on NO [63], was reduced in subjects with untreated hypertension as compared with normotensive subjects, suggesting that functional defects are also present in untreated hypertension [64]. In addition, the fact that anti-hypertensive treatment in previously untreated hypertensive subjects improves skin microvascular function adds to the concept that these (early) changes are functional [65]. Also, a prospective study in subjects with obesity showed that pre-surgical impaired microvascular function, as measured with laser-Doppler fluxmetry, was fully normalized 1 year after a gastric bypass surgery, and was also associated with a decrease in BP [66]. Taken together, these data suggest that microvascular dysfunction, represented as rarefaction and/or arteriolar constriction, contributes to the development of high BP.

Once hypertension has become manifest, high BP may also contribute to (further) deterioration of microvascular dysfunction. Increases in BP results in remodeling of the resistance arterioles because of changes in circumferential wall stress [51,67]. Vascular remodeling refers to alterations in structure of resistance vessels and can be classified as hypertrophic, hypotrophic, or eutrophic remodeling. In the eutrophic situation, changes of the vessel wall will occur without

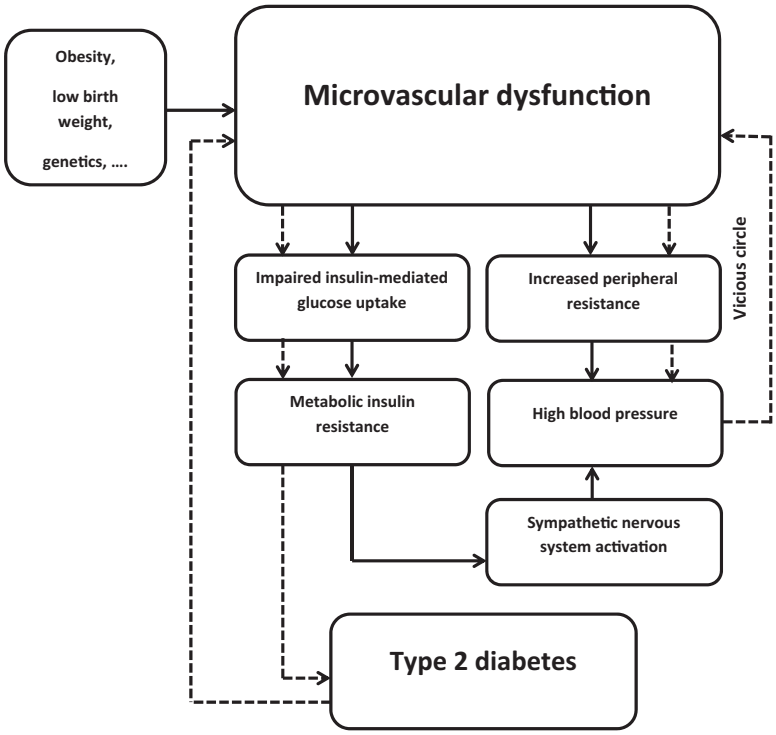

Fig. 1 – Hypothesis: contribution of microvascular dysfunction to insulin resistance, type 2 diabetes and hypertension.

changes in the amount or characteristics of wall material. On the other hand, the amount of wall material can increase (hypertrophic remodeling) or decrease (hypotrophic remodeling) [68]. Changes in vessel wall composition can lead to an increase or decrease in vessel wall diameter (inward or outward remodeling). In individuals with hypertension, structural changes of the microvessels result in reduced lumen diameter and increased media-to-lumen ratio. These vascular changes can be classified as inward eutrophic remodeling [69], and can result in higher peripheral resistance [67,70]. Thus, high BP and microvascular dysfunction form a vicious circle in which both mechanisms reinforce each other.

5. Conclusion

Taken together, all these data suggest that microvascular dysfunction is a linking factor between insulin resistance and high BP (Fig. 1). We hypothesize that microvascular dysfunction contributes to type 2 diabetes through insulin resistance, and that microvascular dysfunction in addition contributes to the development of hypertension. Therefore, microvascular dysfunction may be a target in the prevention and treatment of insulin resistance, (pre)diabetes, and high BP. Obesity is associated with impaired microvascular function, but more studies are required to unravel the exact pathophysiological pathways that link obesity to microvascular dysfunction.

6. Conflicts of interest

The authors declare that they have no conflict of interest.

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