Metabolic disturbances linked to obesity: the role of impaired tissue perfusion

Alterações metabólicas associadas à obesidade: o papel da disfunção da microcirculação tecidual

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ABSTRACT

Associated with elevated risk of cardiovascular events and cancer, obesity is a worldwide problem affecting developed and developing countries. Microcirculatory vessels, represented by arterioles, capillaries and venules (mean internal diameter < 100 μm), are the place where blood/tissue nutrition and exchange effectively take place. Microvascular dysfunction is an early event in obesity probably secondary to endothelial dysfunction and capillaries rarefaction. New research techniques allow the investigation of the microcirculation in different vascular beds in humans. Studies suggest a link between endothelial dysfunction and visceral obesity. Oxidative stress, inflammation and rennin-angiotensin system are among factors considered to be involved on microvascular dysfunction in obesity. Microcirculatory impairment present in obesity suggests that it could be an important causal factor in obesity-related disorders such as insulin resistance and hypertension. Arq Bras Endocrinol Metab. 2009;53(2):238-245.

Keywords
Obesity; endothelial dysfunction; microcirculation; tissue perfusion; metabolic syndrome

RESUMO

Associada ao aumento do risco de eventos cardiovasculares e ao câncer, a obesidade é um problema mundial, que atinge tanto países desenvolvidos quanto em desenvolvimento. A microcirculação é composta por arteríolas, capilares e vênulas (diâmetro interno médio < 100 μm) e é o local onde ocorrem a oferta de nutrientes e as trocas entre o tecido e o sangue. A disfunção microcirculatória é um evento precoce na obesidade e este pode ser secundário à disfunção endotelial ou à redução no número de capilares (rarefação capilar). Novas técnicas em pesquisa permitem a avaliação da microcirculação em diferentes leitos vasculares em humanos. Estudos sugerem uma correlação entre disfunção endotelial e obesidade visceral. Acredita-se que o estresse oxidativo, a inflamação e a atividade aumentada do sistema renina-angiotensina estão entre os fatores envolvidos nessa associação. O comprometimento microcirculatório presente na obesidade sugere que esse pode ser um fator causal importante nas desordens relacionadas com a obesidade, como resistência insulínica e hipertensão. Arq Bras Endocrinol Metab. 2009;53(2):238-245.

Descritores
Obesidade; disfunção endotelial; microcirculação; perfusão tecidual; síndrome metabólica

INTRODUCTION

Obesity is a worldwide problem, reaching epidemic proportions in several industrialized countries (1). Additionally, obesity is rising in many developing countries, resulting in changes in the policy and health maker's focus from undernutrition to obesity and obesity-related diseases (2,3), since it increases risks for *diabetes mellitus*, hypertension, dyslipidemia, coronary artery disease and some types of cancer (4).

The association of known cardiovascular risk factors, including abdominal obesity, impaired glucose tolerance or type 2 diabetes, dyslipidemia, raised blood pressure proinflamatory and prothrombotic factors, is often referred as metabolic syndrome (5) and it has been associated with high risk of cardiovascular events (> 20% for those with diabetes and 10% to 20% for those with two or more risk factors) (6). Metabolic syndrome is linked to endothelial dysfunction (7,8) and insulin resistance, a generalized metabolic disorder in which insulin actions are impaired (7).

Microvascular dysfunction is present in obese subjects and it is secondary to either endothelial dysfunction (9) or structural impairments in the microvasculature (10). Several conditions related to obesity such as hypertension (11), hypercholesterolemia (12) and hyperglycemia (13) are also associated with endothelial dysfunction, although endothelial dysfunction is present in obese subjects even in the absence of these conditions (14), suggesting obesity as a primary cause of microvascular dysfunction. Indeed, microvascular dysfunction is an important factor in metabolic disturbances linked to obesity, since it could influence both vascular resistance and insulin-mediated glucose disposal, contributing to hypertension and insulin resistance in obesity (15).

MICROCIRCULATION

Considering that the function of the cardiovascular system is to supply an appropriated milieu for tissues and organs, the microcirculation is the portion of the cardiovascular system in which blood/tissue nutrition and exchange effectively occur. Microvessels (mean internal diameter < 100 μm) are represented by arterioles, capillaries and venules – the largest portion of vessels in the body subjected to multiple, fine-tuning regulations. This regulation is achieved by local nervous and humoral control with the main objective of supplying specific metabolic requirements for each tissue. Furthermore, it is in the microcirculation where the main resistance to blood flow takes place, since large and medium-sized arteries and veins offer little resistance to flow (16). Thus, microcirculatory functions can be summarized as delivery of oxygen and nutrients, removal of metabolic waste products from tissues, maintenance of tissue environment for cell survival and maintenance of peripheral resistance (17).

The mechanisms that regulate local blood flow are myogenic activity, in which arterioles respond to acutely increased pressure with vasoconstriction and local chemical and humoral factors, like interstitial PO_2, PCO_2 and pH, as well as local concentration of K^+, lactic acid, ATP, ADP and adenosine. However, when high pressure in the microcirculation is maintained, vascular remodeling may occur and components of the vessel wall are rearranged in a process known as eutrophic inward remodeling. Increased production of reactive oxygen species (ROS), inflammation, extracellular matrix alterations and increased levels of apoptosis are some factors involved in remodeling (18,19). Angiotensin II is also thought to be an important factor involved in this process (20).

Microvascular rarefaction is defined as reduction on microvessel density in a given volume of tissue and it can be classified as a) functional – when the number of perfused number of microvessels is maintained, or b) structural – and when the actual number of microvessels is reduced (19). Research on spontaneously hypertensive rats showed that functional rarefaction may progress to structural one (21). Oxydative stress, endothelial dysfunction and apoptosis are important mechanisms implicated on microvascular rarefaction (22,23).

In physiological conditions, autoregulatory mechanisms maintain tissue perfusion according to its metabolic needs, while in situations that vascular reactivity is impaired, as it occurs in obesity, microvascular dysfunction, mainly secondary to microvascular remodeling and rarefaction, reduces tissue perfusion and prevents blood-tissue exchange, producing tissue hypoxia in situations of high metabolic demand (24).

The microcirculation can be studied in humans by direct intravital videocapillaroscopy (Figure 1A) on skin, nailfold, lip or bulbar conjunctiva, or by laser Doppler measurements. Sidestream Dark Field (SDF) imaging is a new noninvasive method for assessment of human microcirculation and it was incorporated into a hand device called MicroScan (Figure 1B). In animal studies, these techniques can be used in different microvascular beds such as skeletal muscle, hamster cheek pouch or mesentery. Several microvessels are not perfused under resting conditions but can be activated during reactive hyperemia, as a result of recruitment – one of the microcirculatory parameters often studied by videocapillaroscopy or skin flow in humans.
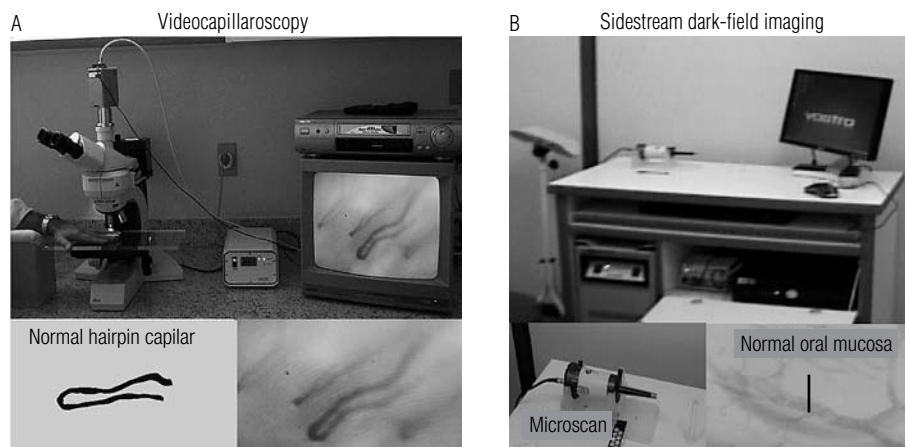
Figure 1. Microcirculatory evaluation in humans; (A) nailfold videocapillaroscopy showing a normal capillary bed; (B) MicroScan (it uses a Sidestream Dark Field imaging technique) showing a normal oral mucosa – objective 5X; 325X magnification on screen).

ENDOTHELIAL DYSFUNCTION

The endothelium maintains the vascular homeostasis regulating the vascular tonus by balancing the production of vasodilators, such as nitric oxide (NO), vasoconstrictors, like endothelin, direct action on blood fluidity and coagulation through production of factors that modulate platelet activity, clotting cascade and fibrinolysis (25). NO also regulates leukocyte-endothelium interaction (26).

Endothelial dysfunction, defined as loss of normal homeostatic function of the endothelium, partly secondary to a reduction of NO bioavailability, results in a defect on endothelium-blood interaction, abnormal vasomotor activity, development of a procoagulant endothelial surface, intimal growth and inflammation (27). Traditional cardiovascular risk factors such as hypertension (28), *diabetes mellitus* (29), hypercholesterolemia (12) and, recently, obesity (30) are associated with endothelial dysfunction. Endothelial dysfunction is an early marker of cardiovascular risk preceding any visible structural atheromatous plaques (31,32).

Endothelial function can be determined by either invasive or non-invasive methods in global, such as arm, limb or skin, or specific, like coronary, local techniques. Stimuli that increase production and release of endothelial NO, such as increased shear stress due to increased blood flow, or use of receptor-agonists, like acetylcholine, bradykinin or substance P (Figure 2), have been used to access endothelial-dependent vasodilation.

Several techniques have been proposed and used to access endothelial function – each one of them with advantages and disadvantages. Thus, NO appears to be more related to flow-mediated dilation in large and small arteries than in arterioles (33) and associated to re-

active hyperemia in skeletal muscle but not in skin (34). Moreover, reactive hyperemia after an ischemia of short duration is mainly secondary to NO release, while ischemia of long duration has additional factors playing a role, like prostaglandins and autonomic nervous system. Thus, depending on the technique or the tissue used, studies of endothelial function may give different results. Vasodilators, such as nitrates or sodium nitroprusside, directly induce vascular smooth muscle cell relaxation, independent of endothelium, and its use allow the evaluation of endothelium-independent vasodilation (35).
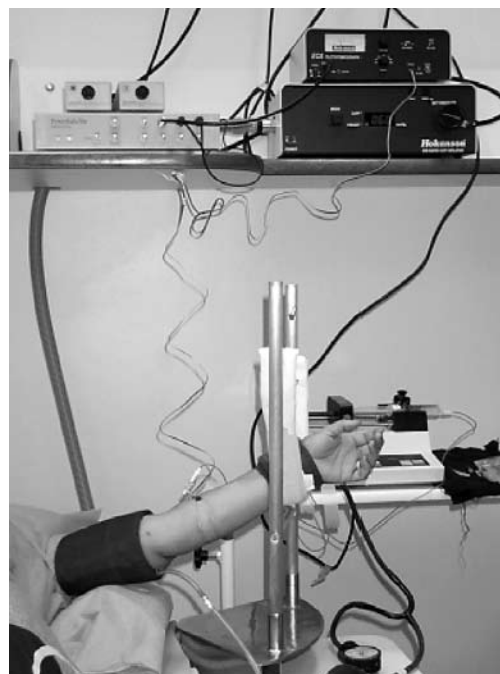

Figure 2. Venous occlusion plethysmography. Forearm blood flow is measured after infusion of increasing doses of acetylcholine (endothelium-dependent vasodilator) or sodium nitroprusside (endothelium-independent vasodilator) into the brachial artery. A mercury-in-silastic strain gauge detects forearm volume changes after venous occlusion (40 mmHg) on the upper blood pressure cuff.

Vascular dysfunction does not depend only on structural and functional changes in feeding arteries but also and largely on the microcirculation. Thus, while endothelial dysfunction in conductance vessels (36,37) is a known predictor of cardiovascular risk, endothelial dysfunction on the microcirculation is emerging as an independent predictor of cardiovascular risk as well (38,39).

ENDOTHELIAL DYSFUNCTION AND OBESITY

Endothelial dysfunction is an early process in the evolution of atherosclerosis in obesity and it could be seen even in obese children aged 9 to 12 years, when obesity could be associated to impaired endothelium-dependent vasodilation, reduced arterial complacence and carotid artery intimal-medial thickening (40,41). Obesity also accelerates the atherosclerosis process observed in young persons (42,43).

Microvascular dysfunction is present in overweight and obese subjects, even in absence of hyperglycemia or hypertension (10,14). Obese subjects have blunted endothelial-dependent vasodilation in either skin or resistance vessels (44,45) and microcirculatory dysfunction could also be observed on these subjects, using nailfold videocapillaroscopy (46). Furthermore, obesity is associated with a decreased response to insulin-induced endothelium-dependent vasodilation (47).

Fat distribution has been found to be an important determinant in endothelial dysfunction (48) and body fatness is associated with microvascular dysfunction even in lean subjects (49). Thus, waist/hip ratio, a determinant of abdominal obesity, is a better marker of endothelial dysfunction than body mass index (BMI) by itself (50,51), as presented in Figure 3.

Insulin resistance is associated with endothelial dysfunction. High levels of lipids and glucose could be associated to reduction on NO availability (52,53). These findings suggest that endothelial dysfunction might be treated as cause and consequence of the metabolic disturbance observed in states of insulin resistance (54). In fact, insulin cross the endothelial barrier to reach its receptor on the cell membrane, and impairment on insulin diffusion across the capillary bed may represent a rate-limiting step in peripheral insulin action (54,55).

These observations, associated with the fact that weight loss improves endothelial function (56), establish a strong association between obesity and microvascular dysfunction in different tissues.

MICROVASCULAR DYSFUNCTION AND OBESITY

Studies on obese Zucker rat, in which a defective receptor gene causes obesity, type 2 diabetes and hypertension, showed microvascular remodeling and rarefaction in skeletal muscle, even before any elevation of blood pressure could be observed (57). In humans, Gavin and cols. (58) demonstrated a reduction on capillary density in skeletal muscle of obese subjects when compared to
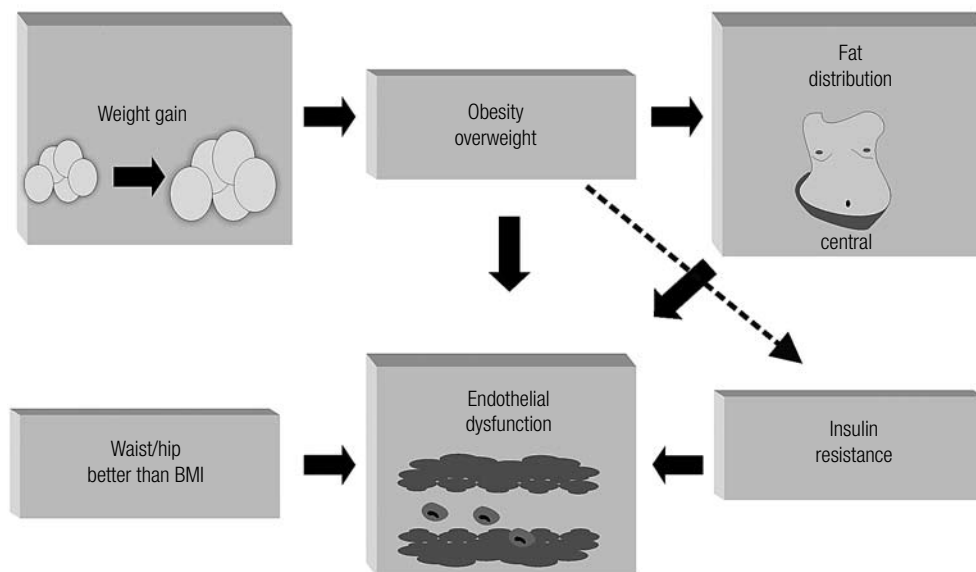

Figure 3. Relationship between endothelial dysfunction and overweight/obesity. Fat distribution plays an important role on endothelial dysfunction and waist/hip ratio might be a better correlated with it than the body mass index.

lean individuals. Obesity was also associated with lower capillary density in the skin (46).

Although of doubtful physiological importance, insulin dilates resistance vessels and increases skeletal muscle blood flow, promoting the delivery of glucose and insulin to this tissue (59,60). Besides these actions on resistance vessels, insulin also has one secondary action, named capillary recruitment that redirects blood flow from non-nutritive to nutritive vessels, increasing functional capillary density in skeletal muscle and, consequently, the delivery of glucose and insulin (59).

Obesity produces a blunted response to vasodilation induced by oral glucose loading (61). This blunted response probably is due to impaired capillary recruitment in response to an increase on plasma insulin level (45,62). Also, there is a reduction in transcapillary delivery of insulin to muscle in obese subjects (63).

Although studies suggest that chronic reduction on vascular NO bioavailability is the main mechanism underlying microvascular rarefaction in the metabolic syndrome, this is not completely clarified (64). One possibility is that insulin, acting on insulin and IGF receptors, associated with angiotensin II, stimulates vascular remodeling (65).

Obesity also leads to formation of hypoxic areas in the adipose tissue; Regazzetti and cols. (66) showed that adipocytes from human and murine origins, under hypoxic conditions, developed a state of insulin resistance, pointing to hypoxia as one of the mechanisms participating in insulin resistance in adipose tissue of obese subjects.

MECHANISMS INVOLVED IN MICROCIRCULATORY DISTURBANCES IN OBESITY

Studies on obese Zucker rats also showed that microvessel rarefaction in obesity is closely related to a chronic reduction in NO bioavailability (57). Several factors might contribute to the observed rarefaction: increased oxidative stress (67), with its NO scavenging affect (68); increased activity and expression of protein kinase C, that reduce NO bioavailability in mesenteric microvessels of Zucker diabetic fatty rats (69); and reduction in tetrahydrobiopterin (BH_4), a necessary cofactor for NO production (70).

Excess of adiposity produces chronic vascular inflammation with production of several inflammatory cytokines such as tumor necrosis factor-α (TNF-α) (71). Ijzerman and cols. have showed a negative correlation between TNF-α and capillary recruitment in adults, suggesting a relationship between TNF- α and insulin resistance (72).

Ijzerman and cols. (72) proposed that increased adipose mass generates cytokine signals to blood vessels, by perivascular fat, resulting on impaired perfusion and insulin resistance.

The rennin-angiotensin system (RAS) can also be an important component for microvascular dysfunction viewed in obesity since all necessary components needed to generate the vasoconstrictor angiotensin II are present in the adipose tissue (73) and increased activity in RAS is present in obesity (74) (Figure 4).

Microvascular impairment in obesity
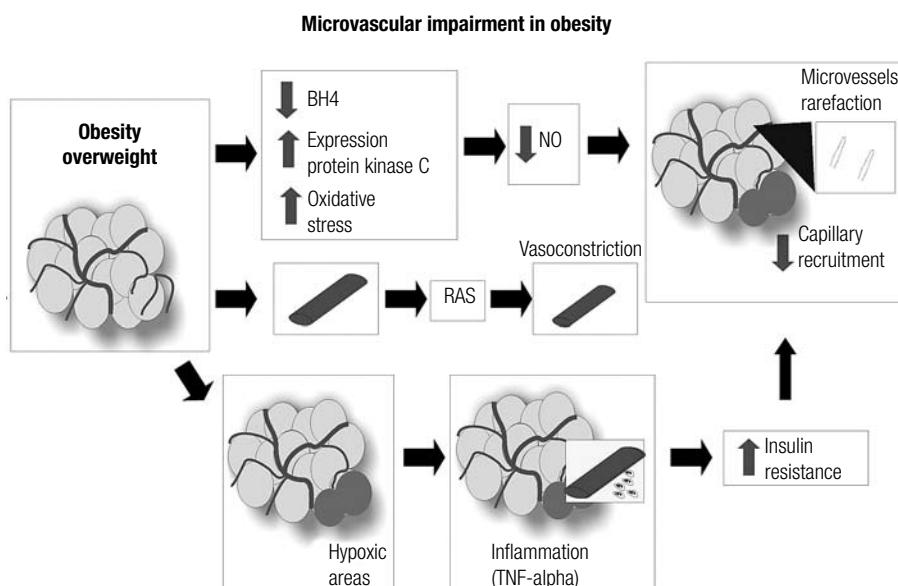
BH$_4$ = tetrahydrobiopterin; NO = nitric oxide; RAS = renin-angiotensin system; TNF-α = tumor necrosis factor alpha.

Figure 4. Microvascular dysfunction due to overweight/obesity.

CONCLUSIONS

Obesity is associated with reduction on tissue perfusion secondary to either endothelial dysfunction or capillary rarefaction. Endothelial dysfunction is an early process in obesity, present even in the absence of hypertension or hyperglycemia, associated with visceral obesity, suggesting that obesity *per se* is an important risk for endothelial dysfunction. The microcirculatory impairment present in obesity may result from increased levels of oxidative stress, inflammatory cytokines or increased activity of RAS, suggesting an association between obesity and obesity-related disorders to insulin resistance and hypertension.

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