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HYPERTENSION AND OBESITY (EFRAIN REISIN, SECTION EDITOR)

Microvascular Endothelial Dysfunction in Patients with Obesity

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Abstract

Purpose of Review To examine the state of the art on the pathogenesis of endothelial dysfunction in the microcirculation of patients with obesity, focusing on the complex relationship between the consolidated and the novel mechanisms involved in this alteration.

Recent Findings Human obesity is associated with vascular endothelial dysfunction, caused by a reduced nitric oxide availability secondary to an enhanced oxidative stress production. Pro-inflammatory cytokine generation, secreted by perivascular adipose tissue, is a major mechanism whereby obesity is associated with a reduced vascular NO availability. Vasculature also represents a source of low-grade inflammation and oxidative stress which contribute to endothelial dysfunction in obese patients. Recently, a direct influence of arginase on endothelial function by reducing nitric oxide availability was demonstrated in small vessels from patients with severe obesity. This effect is modulated by ageing and related to the high levels of vascular oxidative stress.

Summary Oxidative stress, inflammation, and enzymatic pathways are important players in the pathophysiology of obesity-related vascular disease. The identification of new therapeutic approaches able to interfere with these mechanisms will result in more effective prevention of the cardiovascular complications associated with obesity.

Keywords Cytokines · Endothelium · Microcirculation · Obesity · Oxidative stress

Introduction

It is well established that the vascular endothelium is the key regulator of vascular homeostasis, in that it has not merely a barrier function but also acts as an integrative signal transducer for circulating and genetic influences that modify the vessel wall phenotype. This function is ensured by the production of a wide range of factors that regulate vascular tone, cellular adhesion, thromboresistance, smooth muscle cell proliferation, and vessel wall inflammation in response to physical and chemical signals.

The homeostasis of the vasculature is guaranteed by the integrity of vascular endothelial tissue, which represents the central player in the regulation of the complex balance between substances with vasodilating/anti-thrombogenic activities and vasoconstricting/prothrombotic properties [1]. Nitric oxide (NO) represents the major compound in the regulation of vascular homeostasis produced by endothelial cells, deriving from the transformation of L-arginine into citrulline by the activity of the constitutive endothelial enzyme NO synthase (eNOS) secondary to several stimuli, including shear stress or endothelial agonists [2]. Apart from its vasodilating effect, NO exerts its vascular protective role by preventing other key events in the development of atherosclerosis such as platelet adhesion and aggregation, leukocyte adhesion and migration as well as muscle cell proliferation [1, 3].

Obesity represents a major public health concern, as it is associated with high morbidity and mortality because of several chronic diseases. It has been estimated that 4 million deaths and 120 million disability-adjusted life years worldwide are related to excess body weight and, although the trend

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appears to have stabilised in some developed countries, the problem is spreading in the developing world [4••].

On the cardiovascular system, obesity accelerates atherosclerosis progression, inducing pathophysiological changes that are detectable already from young adults. Among these, endothelial dysfunction is one of the earliest vascular alterations observed in obesity, a condition in which endothelial cells undergo activation and switch to a pro-atherosclerotic phenotype. This is characterised by a reduced NO availability because of both its accelerated degradation due to the overwhelming dominance of vascular generation of reactive oxygen species (ROS) and its altered production by the eNOS.

Arginase 1 and 2 are intracellular enzymes of the urea cycle hydrolysing L-arginine to urea and L-ornithine. Upregulation of arginases has been documented in the vasculature of several experimental models of early atherosclerosis and with ageing. By substrate competition for L-arginine, the increased activity of these enzymes uncouples the eNOS and reduces its ability to produce NO. Thus, an upregulation of arginase 1 and 2 is thought to contribute to the development of vascular disease by promoting endothelial dysfunction [5–10]. More recently, a pivotal role of arginase 1 and 2 in human obesity also emerged. Indeed, an increased expression of arginase 1 and 2 has been described in small resistance vessels of patients with obesity and its downregulation by a selective antagonist was able to attenuate the obesity-related endothelial dysfunction. A specific paragraph of the present review is dedicated to this issue.

Beyond the perturbation of intracellular pathways, endothelial dysfunction in obesity is also promoted by autocrine, paracrine and endocrine signals. Among these, low-grade vascular inflammation is strongly involved in favouring endothelial dysfunction and vascular atherosclerosis [11]. In particular, the proinflammatory cytokine TNF-α is a pivotal mechanism involved in reducing NO availability mainly by inducing ROS generation in human obesity [12]. These above-mentioned mechanisms have been mostly demonstrated at the level of microcirculation, thanks to the sophisticated methodological techniques that enable exploration of molecular pathophysiological pathways involved.

This review will examine the pathogenesis of endothelial dysfunction in the microcirculation of patients with obesity, focusing on the complex links between the consolidated and the novel mechanisms involved in this.

Consolidated Mechanisms of Endothelial Dysfunction: ROS and Inflammation

A large body of experimental and human evidence has documented that obesity is associated with endothelial dysfunction, regardless of concomitant CV risk factors commonly detected in this condition [13]. This finding was homogeneously obtained in different vascular districts, being firstly demonstrated as reduced endothelium-dependent vasodilation to methacholine in the leg microcirculation of obese patients [14]. Similar results were documented in the forearm microcirculation, in which it was also seen that intra-arterial infusion of ascorbic acid led to an ameliorated response to the endothelial agonist acetylcholine, indicating a role of ROS in mediating endothelial dysfunction [15].

The adverse and independent impact of obesity on the homeostasis of the peripheral microcirculation was confirmed in a more recent study conducted in patients with metabolic risk factors and suspected coronary artery disease. Using laser Doppler flowmetry the authors documented that body mass index was significantly associated with decreased endothelium-dependent vasodilatation, an association that remained significant also after adjustment for confounding risk factors, including diabetes mellitus, hypertension, hypercholesterolemia and smoking [16••].

Through the in vitro ex-vivo myographic technique it has been possible to demonstrate the negative impact of obesity on endothelial function in isolated small vessels of abdominal fat of obese patients, also identifying the potential mechanisms underpinning this alteration. All the studies reported a concordant reduction of endothelial function in this vascular district [12, 17, 18]. In details, the reduced endothelium-dependent vasodilation resulted to be unaffected by the eNOS inhibitor Nω-nitro-L-arginine methylester (L-NAME) and potentiated by an antioxidant compound, thus demonstrating a central role played by ROS in reducing NO availability [12]. These findings convincingly demonstrate that microcirculation represents a major target for obesity-related endothelial dysfunction, which is mainly dependent from a downregulated NO activity secondary to oxidant excess.

The discovery that obesity is associated with a systemic low-grade vascular inflammation led to a substantial progress in the knowledge of the obesity-related cardiovascular disease. In particular, the adipose tissue emerged as a central source of pro-inflammatory cytokine production. Indeed, Hotamisligil et al. [19] firstly reported that TNF-α was overexpressed in perivascular adipose tissue (PVAT) from obese patients. From this, many studies confirmed that human obesity is an inflammatory disease and that the specific chemokines produced by visceral fat, called adipokines, have a major role in controlling the inflammatory exposure. The generation of adipokines by fat cells can be regarded as an endocrine function and makes the adipose tissue the largest endocrine organ of the body, particularly in patients affected by severe obesity. Major adipokines generated by fat cells include leptin, resistin and adiponectin [20], all of which can affect, by different mechanisms, vascular homeostasis. Leptin, the main protein produced by adipocytes, may stimulate the secretion of TNF-α and interleukin-6 (IL-6) which, in turn, favour endothelial dysfunction [21] through their direct

activity or inducing an increment of ROS production in endothelial cells [22]. Resistin, produced by adipogenesis, is involved in the development of insulin resistance and obesity [23]. When incubated with human recombinant resistin, endothelial cells enhance their production of endothelin-1 and the expression of adhesion molecules, suggesting its direct impact on vascular endothelium [24]. Adiponectin is produced in mature adipocytes and exerts opposite effects than other adipokines. It can reduce the endothelial expression of adhesion molecules, the proliferation of smooth muscle cells and the transformation of macrophages into foam cells [25]. In patients affected by arterial hypertension, the circulating levels of adiponectin are inversely related to the severity of endothelial dysfunction measured at the level of the forearm microcirculation [26]. Reduced production and activity of adiponectin was demonstrated in obesity [27], and the reduced protective effects of this adipokine represent an important mechanism contributing to the development of endothelial dysfunction and the atherosclerotic process in this condition.

Over the last decade, several reports demonstrated that the major mechanisms whereby PVAT induces vascular changes include the secretion of TNF-α and IL-6 [28]. TNF-α might stimulate ROS production via activation of NAD(P)H oxidase [29], or by the activation of nuclear transcription factor-kappa B (NF-kB), leading to activation of macrophages, migration and proliferation of smooth muscle cells and induction of adhesion molecule expression by the endothelial cells [30]. IL-6 increases the ROS production by activating xanthine oxidase and NAD(P)H oxidase. In patients with obesity-related metabolic syndrome, Tesauro et al. [31] assessed the effects of TNF-α neutralisation by infliximab, a monoclonal antibody blocking the TNF-α signalling, on vascular reactivity during hyperinsulinemia. At baseline, patients showed a reduced relaxation to endothelium-dependent relaxation, an effect reversed by infliximab. Ascorbic acid was also able to improve the vasodilator response to acetylcholine in obese patients, with no further potentiating effect when infliximab was concomitantly administrated. These results convincingly indicate that TNF-α inhibition ameliorates endothelial function in obese patients, an effect consequent to a decreased ROS activity [31]. A specific role played by PVAT-derived inflammation in the pathogenesis of vascular dysfunction is highlighted by a more recent study conducted in isolated resistance vessels, assessed in the presence or in the absence of PVAT. While in vessels of lean controls PVAT generated factors that potentiated NO availability, in obese patients the presence of PVAT did not improve vasodilation [32]. Acute injection of TNF-α and IL-6 around healthy blood vessels reduced dilator activity of PVAT, resulting in no longer differences compared to the obese group. Pre-incubation of ROS scavengers or cytokine antagonist prevented these alterations [32]. These results demonstrate that in physiological conditions adipocytes contribute to the regulation of local vascular tone by favouring NO availability. This important regulation is lost in obese patients, whose PVAT is characterised by adipocyte hypertrophy, ROS generation and increased production of TNF-α. These data highlight the central role of inflammation as a promoter of vascular dysfunction, being an important mechanism through which the pathological PVAT exerts a deleterious effect on the surrounding vasculature.

Small Vessels in Obesity: Target and Source of TNF-α

Based on the above-mentioned demonstrations, PVAT can be considered a direct regulator of vascular homeostasis throughout the generation of pro-inflammatory cytokines, including TNF-α, with direct effects toward the vasculature. Thus, in obesity, the adipose tissue-derived inflammatory cytokines regulate the vascular physiology not only by their endocrine activities (related to the systemic increase in chronic inflammation) but also via their local paracrine function. In a study conducted in our laboratory, small arteries were isolated from visceral fat immediately after collection of a biopsy sample during laparoscopic surgery, in patients with and without severe obesity. Vessels from the obese group showed a reduced endothelium-dependent relaxation, which was resistant to L-NAME. Such defect was reversed by the superoxide scavenger tempol and, to a similar extent, by infliximab [12]. In agreement with these functional results, the direct measure of intravascular superoxide anion concentration by the confocal microscope evidenced that vessels from the obese group showed higher levels of superoxide anions compared to the control group, an alteration that was reversed completely upon incubation of the obese vessels with tempol or infliximab. These data were further supported by immunohistochemistry, which indicated a marked upregulation of TNF-α mainly in the media layer of these vessels, demonstrating for the first time that the vascular wall may also be a source of TNF-α involved in endothelial dysfunction [12] (Fig. 1). In conjunction, these results corroborate the concept that in human obesity small vessels show a reduced NO activity due to an excess of ROS generation which, in turn, is secondary to excessive expression of vascular TNF-α. In the same study, potential pathways involved in TNF-α-induced vascular ROS generation were also explored. To address this issue, specific inhibitors of major enzymatic sources were utilised (apocynin, S-methylisothiourea and allopurinol to inhibit the NAD(P)H oxidase, iNOS and xanthine oxidase, respectively). The inhibition of NAD(P)H

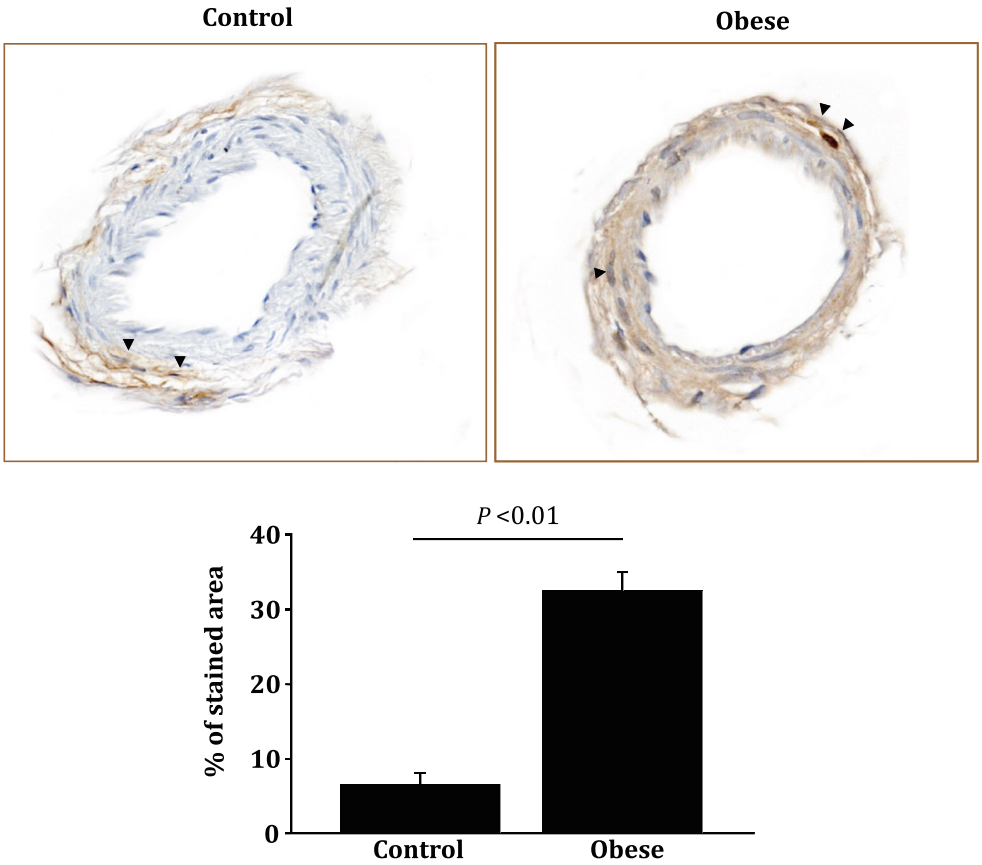

Fig. 1 Immunostaining for TNF-α in small arteries from obese patients and controls. The panels display representative images (original magnification × 400) and column graphs refer to the densitometric analysis of immunostained areas. Specific TNF-α immunostaining is detected in the outer layers of vessel wall in control samples. TNF-α expression is enhanced and evident throughout the muscle layer in a vessel from obese patients (arrowheads). Adapted from reference [12]

oxidase and iNOS led to a significant reduction of the intravascular superoxide generation [12]. Based on these findings, it is conceivable that both NAD(P)H oxidase and iNOS are the two major enzymatic pathways that, once simultaneously activated by TNF-α, mediate vascular ROS production in obesity, whereas xanthine oxidase does not seem to be implicated.

To strengthen the strict cross-talk between between inflammation and vascular changes in obesity, there is the demonstration that bariatric surgery-induced weight loss leads to a reduced inflammation, which in turn is associated with a fall in the circulating levels of molecules with a negative effect on vascular homeostasis, including components of the renin-angiotensin system and endothelin-1 [33••].

Novel Mechanism of Endothelial Dysfunction: Arginase

Arginase is a manganese metalloenzyme that hydrolyses L-arginine to urea and L-ornithine. It exists in 2 distinct isoforms, arginase I and II, both of which are widely expressed in many tissues, including the cardiovascular system. The fact that arginase and eNOS utilise L-arginine as their common substrate results in important reciprocal interactions between these enzymes. An increased concentration or activity of arginase may reduce the amount of L-arginine available for eNOS, reducing production of NO and inducing endothelial dysfunction [5, 34]. An increased vascular activity and expression of arginase has been detected in experimental models of hypertension, accelerated atherosclerosis [9, 10, 35, 36], including obesity [37••]. Several observations indicate that arginase activity is upregulated with increasing age and is involved in the development of endothelial dysfunction in blood vessels of aged rats and mice, as it results in uncoupling of the eNOS due to lack of substrate [38]. Arginase inhibition, in turn, improves endothelial function and increases NO formation in old rats [39], suggesting that the contribution of arginase to endothelial dysfunction might be modified by ageing. For these reasons, in a recent study, we explored the possible influence of arginase on endothelial dysfunction in small vessels from obese patients, its relationship with ageing and the potential pathways accounting for this variable influence.

Results indicated that in small arteries of obese patients, arginase contributes to endothelial dysfunction by reducing NO availability. Such influence is attenuated by ageing, and this modulation is related to the high levels of vascular ROS detected in old as compared to young healthy controls and young obese subjects [40••]. Moreover, increased expression of arginase was detected

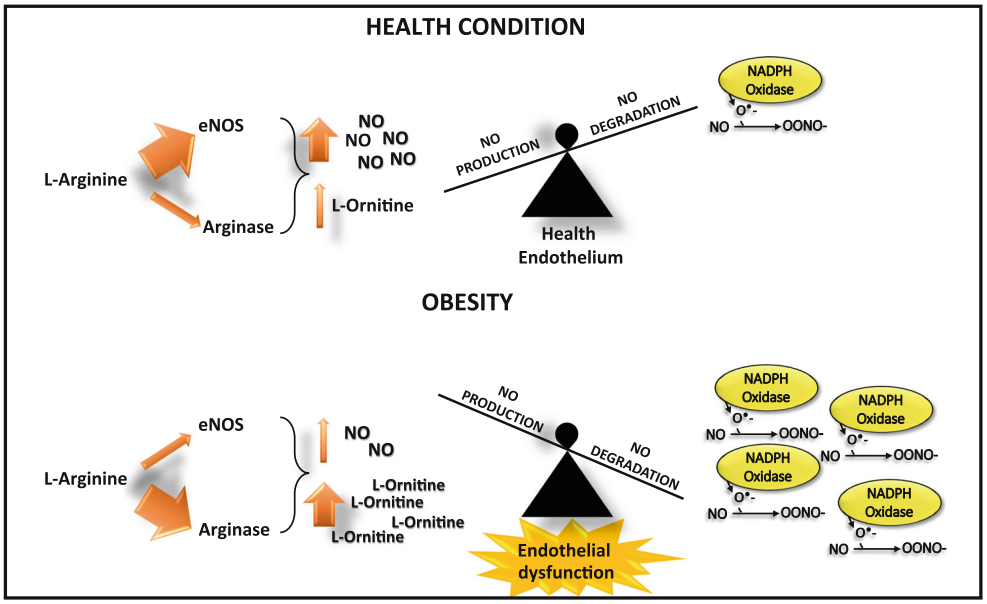

Fig. 2 The contribution of arginase to the obesity-related endothelial dysfunction. Obesity is associated with endothelial dysfunction which results from an unbalance between production and degradation of NO. Among factors influencing degradation of NO in obesity, an increased production of free radicals, and particularly superoxide anions, secondary to hyperactivity of the enzyme NDAPH oxidase represents the most important contributor. Recently, an upregulation of the arginase activity has been documented in obesity. Arginase exists in two isoforms, Arginase 1 and 2, that are widely expressed in human tissues including the cardiovascular system. It uses L-arginine (the same substrate of the eNOS) to produce L-ornithine/urea. Because of substrate competition, the upregulation of arginase activity detected in obesity reduces the production of NO by the eNOS, further contributing to the reduced NO availability. Adapted from reference [40••]

in the vascular wall of obese and aged groups. These findings, while extending previous data of influence of arginase on endothelial function of insulin resistant, morbidly obese patients [41••], suggest that early interventions able to reduce arginase activity may represent a useful strategy to prevent obesity and ageing-related endothelial dysfunction in humans (Fig. 2).

Conclusions

Obesity is characterised by a marked endothelial dysfunction evidenced in several vascular districts including peripheral microcirculation, where a reduced NO availability is detected. In such a scenario, PVAT plays a direct influence on the vascular homeostasis, since it generates pro-inflammatory cytokines, including TNF-α, with a well-demonstrated direct vascular detrimental effect. This is related to the fact that TNF-α promotes superoxide generation in the vascular wall via several pathways, the most important being the hyperactivation of the NAD(P)H oxidase. Of note, vasculature surrounding PVAT not only represents the main target of PVAT-derived pro-inflammatory cytokines but is also considered as an important source of low-grade inflammation and oxidative stress which, together with the PVAT, contribute to endothelial dysfunction which characterises obese patients. Whether the small arteries and adipocytes located within PVAT should be regarded as independent and coexisting sites of TNF-α generation or, by contrast, whether there is a hierarchical relationship or mutual interplay between these two districts is still not established. More recent reports, while confirming the role of ROS and low-grade inflammation as consolidated mechanisms accounting for endothelial dysfunction, were able to put in evidence new lights on mechanisms involved in endothelial dysfunction in obese patients, identified as "new contributor." In detail, an increased activity of arginase may reduce the production of NO and inducing endothelial dysfunction is small vessels from obese patients. Its impact is reduced by ageing because of higher levels of vascular oxidative stress. Of note, the "consolidated" and "new" contributors to endothelial dysfunction are not independent mediators but together conspire to the pathophysiology of endothelial dysfunction in human obesity.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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