# Obesity-Induced Perivascular Adipose Tissue Dysfunction in Vascular Homeostasis

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Perivascular adipose tissue (PVAT) is an additional special type of adipose tissue surrounding blood vessels. Under physiological conditions, PVAT plays a significant role in regulation of vascular tone, intravascular thermoregulation, and vascular smooth muscle cell (VSMC) proliferation. PVAT is responsible for releasing adipocytes-derived relaxing factors (ADRF) and perivascular-derived relaxing factors (PDRF), which have anticontractile properties.

obesity perivascular adipose tissue exercise endothelial dysfunction

## 1. Introduction

Today, an increasing prevalence of obesity is observed in many countries, since a third of the worldwide population is described as obese or overweight [1]. National survey data from 2000 to 2018 in the USA reported that obesity prevalence increased to over 42% among adults, and the prevalence of severe obesity (BMI ≥ 40 kg/m 2) doubled to 9.2% over the study period [2]. Weight problems and obesity are increasing at a rapid rate in most of the EU Member States, with estimates of 52.7% of the EU's population being overweight in 2019 [3]. According to the Global Burden of Disease study, 4.7 million people died prematurely in 2017 as a result of obesity [4]. Obesity is a risk factor for developing many disorders such as diabetes mellitus, hypertension, cardiovascular events, obstructive sleep apnea syndrome, certain cancers, and musculoskeletal diseases [5]. Obesity also has a negative impact on quality of life and increases the costs of healthcare [6][7].

Adipose tissue is known as an endocrine organ. By producing adipokines, it regulates various metabolism pathways and processes such as insulin sensitivity, energy metabolism, blood flow, and even inflammatory stage [8][9]. Adipose tissue is divided into two main subtypes: white (WAT) and brown (BAT), according to their characteristic and different properties. WAT is responsible for storage of the excess of energy as fatty acids, while BAT mostly specializes in thermogenesis [10]. There is also a third type of adipocyte, termed the "beige" adipocyte. It is a brown adipocyte that arises within white adipose depots and also has thermogenic capacity [11].

Perivascular adipose tissue (PVAT) is an additional special type of adipose tissue surrounding blood vessels. PVAT is located around the aorta, coronary arteries, small and resistance vessels, and vasculature of the musculoskeletal system [12][13][14] On the contrary, PVAT is absent among cerebral vessels [15]. It consists of stem cells, adipocytes, mast cells, and nerves [16][17]. PVAT lies outside the adventitia, with no laminar structures or any organized barrier separating them from each other. Although PVAT characteristics resemble both brown and white

adipose tissues, recent evidence suggests that PVAT develops from its own distinct precursors, implying a closer link between PVAT and the vascular system [18]. PVAT at different anatomical locations presents different phenotypes. PVAT demonstrates WAT, BAT, and mixed phenotypes, depending on their anatomical placement [19]. In the abdominal PVAT, white adipocytes are more abundant, whereas thoracic PVAT contains more brown adipocytes. These regional differences in PVAT could explain the higher susceptibility of the abdominal aorta to atherosclerosis compared to the thoracic aorta [20][21][22]. Moreover, gender influences differences in PVAT. After menopause in women, there is an increase in perivascular and pericardial adipose tissue, and additionally, the volume of aortic PVAT positively correlates with the reduction in estradiol [23][24]. Additionally, in obesity experimental models, the PVAT mass and adipocyte size are increased [25]. PVAT, similar to every other adipose tissue, secretes cytokines, hormones, growth factors, and adipokines. It plays a beneficial role as long as adipokine levels with opposing properties remain in equilibrium. In obesity, PVAT becomes dysfunctional and exerts detrimental effects on vascular homeostasis [26].

## 2. The Influence of PVAT-Derived Factors on Vascular Function

Under physiological conditions, PVAT plays a significant role in the regulation of vascular tone, intravascular thermoregulation, and vascular smooth muscle cell (VSMC) proliferation ( **Figure 1** ) [27][28][29]. PVAT exhibits an anticontractile effect as a response to several factors such as endothelin-1, phenylephrine, angiotensin II, and serotonin [30][31][32]. PVAT anticontractile factors are divided into adipocytes-derived relaxing factors (ADRF) and perivascular-derived relaxing factors (PDRF) [30][31][32][33]. On the other hand, PVAT induces vasoconstriction by releasing angiotensin II [34] and the superoxide anion [35]. These factors affect vascular tone via endocrine and paracrine mechanisms. Moreover, VSMCs play a significant role in maintaining the balance between vasoconstriction and vasodilator signals. However, PVAT, as a special adipose tissue, is not only a mechanical support for the vasculature but plays a vital role in the homeostasis of the vascular system, sharing a status no less important than that of the endothelium [36].

Hydrogen sulfide (H 2S) is a gaseous factor, which is produced by PVAT, endothelial cells, and VSMCs, controlling the vascular tone. H 2S-induced vasodilation is caused by activation of BK channels in VSMCs, which leads towards cell membrane hyperpolarization, inactivation of voltage-dependent l-type Ca 2+ channels, and a decrease in intracellular Ca 2+ concentration [37]. In addition, H 2S leads to a dose-dependent decrease in intracellular pH, which causes the vasodilation. It is suggested that the Cl − /HCO 3− ionic exchanger is engaged in this process [38]. The shortage of H 2S is important in the development of various cardiovascular diseases, such as hypertension, atherosclerosis, and heart failure [39].

Components of the renin–angiotensin–aldosterone system (RAAS) are present in the aortic and mesenteric PVAT, except renin [40]. The effect of factors on vascular tone is different. Angiotensin 1–7 induce vasodilation by endothelium-dependent mechanisms. After the activation of the Mas receptors, located in the endothelium, the synthesis of NO is increased, which leads to vasodilation by the activation of BK channels [41]. On the contrary, angiotensin II, which is also produced by PVAT, induces vasoconstriction. There are regional differences in

angiotensin II synthesis by PVAT, while it is greater in mesenteric adipose tissue than in the periaortic adipose tissue [35]. Moreover, angiotensin II in increased concentration activates immune cells, which can produce cytokines and proinflammatory mediators [42].

Nitric oxide (NO) is a well-known endogenous gas with vasodilative properties, which is produced in almost all human cells. There are three isoforms of NOS: neuronal NOS (nNOS), inducible NOS (iNOS), and endothelial NOS (eNOS) [43]. Each of them is characterized by different attributes. nNOS is present in cells of the central and peripheral nervous system, where produced NO acts as a neurotransmitter and plays a role in the central regulation of blood pressure [44]. iNOS is activated by inflammatory cytokines and plays a role in inflammation; additionally, iNOS is Ca 2+ independent, unlike other isoforms [43]. eNOS, which is located in endothelial cells, regulates blood pressure locally and has an antiatherosclerotic effect [44][45]. PVAT is responsible for increased production of NO by a direct mechanism, while eNOS isoform is also present in PVAT, where NO is directly produced and released affecting vasculature [46]. In addition, NO produced in PVAT positively regulates adiponectin release by PVAT [47]. On the other hand, PVAT-derived factors, mentioned in previous sections, increase NO production, which is responsible for activations of BK channels and stimulating cGMP synthesis endothelium and smooth muscle cells.

## 3. The Role of Inflammation, Oxidative Stress, and Hypoxia in Obesity

Obesity is characterized by an excessive level of triglycerides and lipids, which are stored in adipocytes. It leads to their hyperplasia and hypertrophy, where hyperplasia is a well-tolerated complication. In contrast, it is suggested that the capacity of lipid storage and subsequent growth in adipocyte size is limited, and exceeding this threshold induces serious molecular changes and induces cellular dysfunction and death of adipocytes [48]. Moreover, enlarged adipocytes induce elevation of IL-6, IL-8, and leptin and decrease the level of adiponectin, which leads to consequent accumulation of inflammatory factors in PVAT [49][50]. Cytokines, fatty acids, and cell-free DNA, which are excreted after adipocytes apoptosis, induce migration of macrophages to the adipose tissue. Adipose tissue macrophages are divided into two subgroups, which differ from each other by type of secreted cytokines and cell markers: M1 with an inflammatory profile and M2 with an immunosuppressive feature [51]. The M1 subclass secretes cytokines such as TNF-α, IL-6, and IL-1β and plays a significant role in inducing an inflammatory state in adipose tissue, which is important in the development of vascular disorders. Obesity is accompanied by a chronic low-grade inflammatory state, which is confirmed by an elevated level of inflammatory markers, especially C-reactive protein and IL-6, which are significantly higher among obese nonmorbid patients and positively correlates with BMI [52][53].

The excess of carbohydrates, fatty acids, and hyper nutrition induce oxidative stress activation by various pathways such as glycoxidation, oxidative phosphorylation in mitochondria, and NADPH oxidase (NOX) activation with consequent reactive oxygen species (ROS) production [54][55]. The increase in NOX activity leads to excessive production of the superoxide anion ($O^{2-}$), which can react with DNA, lipids, and proteins leading to their destruction [56]. Moreover, $O^{2-}$ leads to the alteration of NO activity and consequent endothelial dysfunction and

cardiovascular events among obese populations [57]. In addition, an elevated level of ROS induces VSMC proliferation and remodeling, which contribute to hypertension development and increased risk of cardiovascular events [58][59].

Moreover, hypertrophy of adipocytes does not proceed hand in hand with angiogenesis, and the demand of tissues for oxygen is greater than the supply. As a result, hypoxia and consequent necrosis and inflammation occur [60]. Hypoxia-inducible factor (HIF-1α), which is increased in adipose tissue among obese individuals, plays the role of mediator in hypoxia. HIF-1α induces the elevation of IL-6 and TNF-α activity and reduces adiponectin concentration [61].

## 4. The Potential Influence of Diet on PVAT-Derived Factors among Obese Patients

Besides exercise, an adequate diet is another beneficial intervention in weight loss and obesity treatment. Nowadays, there are a wide variety of diet strategies, which differ from one another in terms of the percentage content of macronutrients, such as carbohydrates, proteins, and fats. However, a reduction in daily calorie intake is a universal rule and a recommended strategy in weight loss [62]. Some data that present the influence of dietary intervention directly on PVAT are available. Nevertheless, the association between diets and PVAT are not clearly understood. Reports mainly refer to animal models, in which high-carbohydrate (HC) diets induce obesity and the consequent loss of the anticontractile effect of PVAT by an imbalance in PVAT-derived factor secretion [63]. In contrast, Costa et al. have shown that consuming an HC diet for 4 weeks enhanced the release of vasodilatory factors from PVAT, suggesting that this could be a compensatory adaptive characteristic in order to preserve the vascular function during the initial stages of obesity [64]. Additionally, it is suggested that imbalanced diets can cause PVAT inflammation and dysfunction as well as impaired vascular function. The recent published study has showed that a high-fat (HF) and a high-sucrose (HS) diet affected PVAT at different sites. Sasoh et al. have presented characteristic differences in the effects of HF and HS diets on PVAT and aortae [65]. A HF diet induced an increased number of large-sized lipid droplets and increased cluster of differentiation (CD) 68+ macrophage- and monocyte chemotactic protein (MCP)-1-positive areas in the abdominal aortic PVAT (aPVAT). Furthermore, a HF diet caused a decreased collagen fiber-positive area and increased CD68+ macrophage- and MCP-1-positive areas in the abdominal aorta. In contrast, a HS diet induced an increased number of large-sized lipid droplets, increased CD68+ macrophage- and MCP-1-positive areas, and decreased UCP-1 positive area in the thoracic aortic PVAT (tPVAT). Moreover, a HS diet caused a decreased collagen fiber-positive area and increased CD68+ macrophage- and MCP-1-positive areas in the thoracic aorta. However, there were some factors that did not follow the trend to this variation. For example, angiotensinogen levels were increased in both tPVAT and aPVAT of the HF group. The authors concluded that the potential mechanisms underlying these effects may be related to the different adipocyte species that comprise tPVAT and aPVAT [65]. Victorio et al. reported that the effect of HF and HS diets on PVAT differs depending on sex [66]. The anti-contractile effect of PVAT was measured by comparing the phenylephrine-induced contraction in mesenteric arteries after 3 and 5 months of HF or HF+HS diet among male and female mice. The results showed that anticontractile function was impaired after 3 months of both obesogenic

diets among females, while among males, the anti-contractile effect remained comparable during the experiment. Moreover, the assessment of PVAT-derived endothelial function after acetylcholine administration likewise demonstrated differences between sexes, while obesogenic diet among females induces endothelial dysfunction after 3 months and only after 5 months among males.

However, there are many reports that relate the positive impact of different diets on inflammatory state, oxidative stress, NO, adiponectin, or leptin concentration. Thus, one could conclude that similar changes could be observed in PVAT; however, further studies should be conducted.

The Mediterranean diet (MD) is the most popular diet and is commonly known as a healthy, balanced diet with proven efficiency in reducing the cardiovascular risk among high-risk patients and reducing overall mortality [67][68]. A typical MD contains 55–60% carbohydrates, mainly complex ones, 25–30% polyunsaturated and monounsaturated fats, and 15–20% proteins, and meals are generally based on fish, nuts, olive oil, and plant-based foods [69]. Luisi et al. reported that the implementation of an MD for 3 months among overweight/obese patients, with high-quality extra virgin olive oil, induced weight loss and the significant elevation of adiponectin levels [70]. Interestingly, among normal weight controls, the MD has no impact on weight, and the increase in adiponectin concentration was not as considerable as that found among overweight/obese patients. It can be concluded that weight loss and the consequent reduction in adipose tissue contribute to a size reduction in adipocytes and an improvement in adiponectin synthesis and release. Among both groups, the concentration of IL-6 significantly decreased after dietary intervention, which provides proof of the anti-inflammatory properties of MD [70]. Moreover, it is suggested that the higher the amount of fiber in one's diet, the greater the adiponectin concentration in one's blood [71].

Recently, the ketogenic diet has become very popular due to its therapeutic properties in relation to different diseases. It has been widely used in drug-resistant epilepsy with good outcomes and is increasingly being used in metabolic disorders such as obesity or diabetes mellitus [72][73]. The ketogenic diet is characterized by low carbohydrates and high fat, inducing changes in the metabolism of energy substrates, with a switch from glucose to fatty acids [72]. A very low-calorie ketogenic diet (VLCKD) is a special type of caloric reduction diet characterized by a very low or extremely low daily food energy intake, circa 800 kcal per day [74]. It provides 30–50 g of carbohydrates, about 30–40 g of fats, and 0.8–1.5 g/kg of ideal body weight (IBW) of proteins [75]. Monda et al. reported that obese patients who consumed a VLCKD diet for 8 weeks presented with a significant body mass reduction, a decreased concentration of inflammatory markers such as IL-6, TNF-α, and CRP, and a significant elevation in the level of adiponectin in their blood [74]. This relatively short period of intervention induced a significant multifactorial improvement; however, the main limitation of the aforementioned study is the small sample size. In other reports, the ketogenic diet has also been proven to have anti-inflammatory properties [76][77].

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