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Obesity, Adipose Tissue and Vascular Dysfunction

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Abstract

Cardiovascular diseases (CVD) are the leading cause of death worldwide. Overweight and obesity are strongly associated with comorbidities such as hypertension and insulin resistance, which collectively contribute to the development of cardiovascular diseases and resultant morbidity and mortality. 42% of adults in the US are obese and a total of 1.9 *billion* adults worldwide are overweight or obese. These alarming numbers, which continue to climb, represent a major health and economic burden. Adipose tissue is a highly dynamic organ that can be classified based on the cellular composition of different depots and their distinct anatomic localization. Massive expansion and remodeling of adipose tissue during obesity differentially affects specific adipose tissue depots and significantly contributes to vascular dysfunction and CVD. Visceral adipose tissue accumulation results in increased immune cell infiltration and secretion of vasoconstrictor mediators, whereas expansion of subcutaneous AT is less harmful. Therefore, fat distribution more than overall body weight is a key determinant of the risk for CVD. Thermogenic brown and beige adipose tissue, in contrast to white adipose tissue, is associated with beneficial effects on the vasculature. The relationship between the type of adipose tissue and its influence on vascular function becomes particularly evident in the context of the heterogenous phenotype of perivascular adipose tissue that is strongly location dependent. In this review, we address the abnormal remodeling of specific adipose tissue depots during obesity and how this critically contributes to the development of hypertension, endothelial dysfunction and vascular stiffness. We also discuss the local and systemic roles of adipose tissue derived secreted factors and increased systemic inflammation during obesity and highlight their detrimental impact on cardiovascular health.

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I. Obesity and Cardiovascular Disease

The worldwide prevalence of obesity has tripled since 1975, with a parallel trend in type 2 diabetes[1,2]. Globally, over 1.9 *billion* adults were overweight or obese in 2016 and more than 60% of people with obesity live in developing countries[3]. Today, about two out of three adults (69%) are overweight or obese in the United States and current projections suggest that nearly 50% of adults in the US will be obese by 2030[4]. Predictions made in 2008, estimated up to 3.3 *billion* individuals to become overweight and obese by 2030, if adjusted for secular trends[5]. Non-adjusted predictions for 2030 generated by the same study predicted only 1.35 billion overweight and 573 million obese individuals for 2030[5], a number that was outdated already by 2016[3]. While it is well documented that genetic and epigenetic factors contribute to obesity, environmental factors such as diet, physical activity and environmental toxins also play a major role in the increased prevalence of this disorder (Figure 1). For example, the increase in obesity in the US and other industrialized nations is closely related to increased consumption of high fructose corn syrup and saturated fat and to reduced physical activity[3,4] (Figure 1). Further, there is emerging evidence that consumption of high fructose corn syrup diets by pregnant women programs the offspring for the subsequent development of obesity and associated cardiometabolic and cardiovascular disease (CVD) in later life (Figure 2)[6]. These maternal influences appear to be mediated through adverse effects of metabolic factors such as impaired insulin signaling, dyslipidemia and altered blood supply on placental function and resultant fetal nutrition as well as epigenetic influences that originate from maternal obesity[6].

There is considerable evidence that overweight and obesity and their comorbidities, hypertension and insulin resistance, increase CVD and overall morbidity and mortality rates[7–12]. Indeed, a positive association even exists between a progressive increase in body mass index (BMI) within the normal and overweight range and the risk of CVD[6,7]. In this regard, an analysis of the Framingham Heart Study showed a positive association between overweight (BMI 25–29.9 kg/m^2) and the relative risks of hypertension and CVD[8]. In addition, the presence of childhood obesity has been shown to increase the risk for development of type 2 diabetes, hypertension, dyslipidemia, and atherosclerosis and related CVD in adulthood[9–11]. This review discusses the various factors that promote vascular dysfunction and CVD in obesity, with a focus on the role of dysfunctional adipose tissue.

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II. Types of Adipose Tissue

Functionally distinct adipose tissue depots in mice and humans

Adipose tissue (AT) is a dynamic organ distributed throughout the body with an almost unlimited capacity to expand during obesity. Several distinct depots can be defined by their location, size, cellular composition and function. While many functions of AT are conserved between mouse models and humans, their location and abundance can vary broadly. Mammals possess two major types of AT: white and brown (Figure 3). White adipose tissue (WAT) represents the largest proportion of whole-body AT and can be found around major organs and blood vessels in the abdominal cavity and subcutaneously (Figure 4). WAT stores excess energy in the form of triglycerides, and increased accumulation of WAT, particularly in visceral depots, is a key determinant of the relative risk for cardiometabolic disorders, hypertension and CVD[12–17]. To this point, fat distribution dictates CVD risk such that individuals with higher visceral AT and ectopic fat deposition have an increased prevalence of cardiometabolic disorders including hypertension[18,19], dyslipidemia and insulin resistance[15–17] compared to equally obese individuals with less visceral AT and relatively more subcutaneous fat. Thus, measurements limited to determination of BMI do not reflect the actual risk for CVD conferred by obesity.

In contrast to WAT, brown AT (BAT) represents only approximately 4.3% of all AT in adult humans and can be found in cervical, supraclavicular, axillary, paraspinal, mediastinal and abdominal depots[20–22] (Figure 4). In addition, newborns possess interscapular BAT that decreases in size over time and is no longer detectable in adults[23]. BAT protects animals from hypothermia by dissipating energy as heat, via a process called non-shivering thermogenesis, and has more recently been found to also have anti-obesity and anti-diabetes properties and to confer broad cardiometabolic health benefits[24].

The main functional cell type of AT is the adipocyte or fat cell. White adipocytes contain a single large lipid droplet (unilocular) and only possess a small number of mitochondria. Brown adipocytes, on the other hand, have multilocular lipid droplets and contain a large number of cristae-dense mitochondria, which uniquely express uncoupling protein-1 (UCP1) in the inner mitochondrial membrane (Figure 3). UCP1 uncouples oxidative phosphorylation from ATP production, ultimately resulting in the generation of heat[25]. More recently, several UCP1-independent thermogenic mechanisms have also been described[26].

In addition to developmentally preformed brown adipocytes, mice and humans also have inducible brown adipocytes, referred to as beige or brite adipocytes. These multilocular fat cells come from a distinct developmental lineage and tend to be interspersed within WAT, but also express UCP1[27] (Figure 3). At baseline or during thermoneutrality, beige adipocytes display a more white-like phenotype with large lipid droplets and low expression of thermogenic genes[28], but activation by cold exposure, beta-adrenergic stimulation or exercise results in the robust upregulation of a thermogenic program in a process commonly called “browning.” While these cold-inducible brown-like adipocytes were first described almost 40 years ago[28–32], their developmental origin, molecular properties, and physiological roles have only more recently been investigated. In mice, beige adipocytes are enriched within subcutaneous fat depots, and are rarely detected in visceral depots.

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Intriguingly, due to their temperature dependent epigenomic plasticity, beige adipocytes also have the capacity to "whiten" in a warm environment[33].

In light of their morphological and functional differences, it is not surprising that white and thermogenic brown/beige adipocytes are derived from distinct precursors[31,34–37]. White adipocytes arise from mural precursors that are CD24, CD34[38] and PDGFRα positive[12,39], and subcutaneous and visceral white adipocytes appear to originate from distinct progenitor populations[40]. Developmentally preformed or classical brown fat is derived from a myogenic precursor expressing *Pax7*, *Engrailed-1* and *Myf5* around embryonic days 9.5–11.5 in mice, even before white adipocytes develop[35,37,41]. Beige adipocytes, in contrast, originate from a vascular smooth muscle lineage[42]. Despite their distinct origins, the development of both brown and beige adipocytes is dependent on the transcriptional coregulatory protein PRDM16. Adult humans also have inducible thermogenic adipocytes, and evidence suggests that these cells share properties with both murine brown and beige adipocytes[23,27,29,36,43]. The relative proportion of brown vs. beige adipocytes in different human depots in various contexts remains to be fully clarified[44].

Stromal cell composition of AT and impact on physiology

Although adipocytes account for most of the volume of AT, they only make up about 50% of the cellular content[45,46]. Other cell types include immune cells such as macrophages[47–49], lymphocytes[50–53], eosinophils[54,55] and mast cells[49], as well as fibroblasts, adipocyte precursors, vascular cells[45], multipotent mesenchymal stem-like cells[56] and nerve processes[57,58]. Visceral AT, in contrast to subcutaneous AT, tends to have a higher content of macrophages[49], regulatory T cells[52], natural killer T cells[51] and eosinophils[54]. Further, visceral and subcutaneous AT display differences in angiogenesis[59–63] and sympathetic innervation[58,64,65], which can modulate the propensity for energy storage vs. dissipation. Finally, changes in macrophages[66], eosinophils[66–68] and group two innate lymphoid cells (ILC2)[69] can regulate the browning of AT.

Perivascular and epicardial adipose tissue

In addition to the well-described white and brown adipose depots, AT is also located around most large blood vessels including the aorta and mesenteric vessels, but not the pulmonary and brain vasculature or the microcirculation[70] (Figure 4). Perivascular adipose tissue (PVAT) is a specialized local deposit of adipose tissue surrounding blood vessels that also provides mechanical protection and regulation of blood vessel tone[71–73]. *Ex vivo* aortic ring experiments revealed a role for PVAT in relaxation after stretch-mediated stress in mesenteric arteries and the thoracic aorta of rats[74]. The contractile response of isolated murine mesenteric arteries towards norepinephrine is significantly reduced in the presence of PVAT[75]. Further, electrical field stimulation assays of mesenteric arteries demonstrated a role for sympathetic nerve activation[76] and sensory neurons[77] in the vasodilatory effects of PVAT. The anti-contractile effects of sympathetic stimulation are mediated by the stimulation of β_3-adrenoreceptors in PVAT, and treatment with an antagonist of β_3-adrenoreceptors reduces these effects[76].

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Interestingly, PVAT is itself heterogeneous, with its phenotype strongly location-dependent[78–80]. Due to its close proximity to the vasculature and direct contact with the adventitia[81], PVAT is thought to play a role in vascular function and pathology. PVAT surrounding the abdominal aorta and the mesenteric arteries displays a mostly white phenotype in humans[82] and mice, with almost no UCP1 expressing thermogenic adipocytes[28]. On the other hand, rodent PVAT surrounding the thoracic aorta has a brown-like phenotype with multilocular adipocytes and UCP1 expression similar to classical brown adipocytes[83–86]. This is supported by patterns of BAT detected by positron emission tomography – computed tomography (PET-CT) in the para-aortic area and around the heart of humans[87]. In addition, autopsy studies of Siberian adults revealed clear UCP1 expression and multilocular and paucilocular appearance of about 40% of mediastinal periaortic vascular AT, with some individuals displaying up to 73%[88]. Long-term moderate cold exposure (16°C) of mice results in further browning of thoracic PVAT with a markedly increased expression of *Ucp1* and *Pgc1α* and *β*[84].

Thermogenesis of PVAT through cold exposure or genetic manipulation in mice supports a protective role of thoracic PVAT in inflammation and atherosclerosis. Overexpression of the mitochondrial membrane protein MitoNEET induces browning of WAT and thermogenic gene expression[89,90]. Ucp1-driven overexpression of MitoNEET in BAT and PVAT prevented mice from an intravascular temperature drop during cold exposure and increased energy expenditure even after removal of interscapular BAT[90]. Further, cold exposure of atherosclerosis-prone ApoE-deficient or ApoE-MitoNEET double deficient mice with removed interscapular BAT resulted in reduced atherosclerotic lesion sizes[84,90]. Likewise, lack of PVAT in ApoE-deficient mice with an additional smooth muscle-specific deletion of PPARy (peroxisome proliferator-activated receptor y) had increased atherosclerotic lesions and cold exposure had no protective effect[84]. Although, the potential contribution of cold-induced browning of WAT was not excluded, these studies imply a contribution of PVAT to whole-body thermogenesis and protection from atherosclerosis.

Several studies in humans have examined the phenotype of perivascular fat surrounding the internal thoracic arteries. While human internal thoracic artery PVAT has been reported to have a white phenotype in one study, importantly 84% of the individuals were overweight or obese, which might affect the appearance of AT[91]. Nevertheless, PVAT of human internal thoracic arteries attenuated the contractile response to the thromboxane A2/prostaglandin H2 receptor agonist U46619 and phenylephrine[91]. Similar effects were observed in PVAT stripped arteries through the transfer of PVAT-incubated supernatant[91]. Detailed analysis of human thoracic PVAT is limited due to difficulties with sample acquisition and is often isolated from patients with underlying cardiovascular complications, complicating phenotypic assessment.

Despite the close morphological relationship between BAT and tPVAT in mice, proteomics data revealed a depot specific clustering and an only 43% overlap of their proteome on a standard diet[92]. This is comparable to the overlap of 44% of detected proteins between tPVAT with visceral WAT or the overlap of 53% between visceral WAT and BAT, two very distinct depots with different functions[92] suggesting a potentially unique PVAT composition. Interestingly, PVAT has been shown to regulate vascular tone[83,93] through contact dependent

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and paracrine functions that are impaired during obesity in mice and humans[91,94,95]. The contractile response of mesenteric arteries to norepinephrine, for example, is reduced in the presence of PVAT but compromised in diet-induced obesity[95]. Further, the expression of vasodilatory factors, such as angiotensin (1–7)[96–98], adiponectin[75,76] and nitric oxide[99] is inhibited during obesity[94,95,99,100], and the expression of the vasoconstrictor angiotensin II is induced in PVAT[70]. Finally, a recent single cell RNA sequencing study demonstrated the existence of two main clusters of mesenchymal stem/stromal cells in PVAT of the thoracic aorta of mice[101]. One of the clusters was associated with angiogenic and adipogenic potential, whereas the other cluster was enriched for genes associated with vascular smooth muscle cell differentiation[101]. Transplantation of those PVAT-derived mesenchymal stem/stromal cells to a vein graft model significantly promoted neointima formation demonstrating a possible role of PVAT in vascular remodeling[101].

PVAT is an important contributing factor to hypertension[18,19], endothelial dysfunction[102] and other vascular abnormalities in obesity[71–73,94,103,104] (Figure 5). PVAT normally releases vasodilatory mediators, including adiponectin[75,76], and yet to be fully characterized molecules often acting on K^+ channels, that exert an anti-contractile activity and promote vascular relaxation[70]. However, in the setting of obesity and insulin resistance, oxidative stress and inflammation are increased in PVAT, thereby resulting in an increase in pro-inflammatory adipokines including tumor necrosis factor alpha (TNF-α), and interleukins (IL-6 and IL-8), leading to vascular insulin resistance, impaired relaxation, and vascular stiffness[71]. Il-6 and TNF-α also attenuate the vasodilation of mesenteric arteries *ex vivo*[94]. Other cytokines such as interleukin-18 (IL-18) are thought to have protective effects on PVAT and vascular function, and loss of IL-18 results in elevated blood pressure in mice associated with the whitening of thoracic PVAT[105]. However, the specific impact of IL-18 in PVAT needs to be addressed in AT-specific conditional knock out animals. The Framingham Offspring and Third Generation cohort studies showed that increased PVAT volume is associated with higher thoracic and abdominal aortic dimensions and increased arterial stiffness, even after adjusting for age and CVD risk factors including BMI and visceral AT volume[104].

The heart is also directly associated with specific AT depots. Epicardial AT is located on the surface of the myocardium in direct contact with the coronary arteries, and pericardial AT is in contact with the pericardial sac[106]. Under physiological conditions, epicardial AT may supply energetic substrates to the heart and has a greater capacity for free fatty acid turnover than other visceral AT depots[107]. Although its cold-induced UCP1 expression does not reach levels of classical BAT[28], human epicardial AT has a thermogenic phenotype and has been suggested to regulate the temperature of the myocardium[108]. Other studies described the portion of epicardial AT surrounding the coronary arteries in humans as a white-like depot despite the expression of some classical brown fat marker genes such as UCP1, PRDM16 and CPT1β[109]. The same study found a lower expression of adipogenic marker genes PPARγ, FABP4 and C/EBPα but an increased expression of pro-inflammatory cytokines compared to subcutaneous AT[109]. This discrepancy might be explained by the reported whitening of epicardial AT after birth in humans, with only distinct subset of multilocular UCP1 positive cells[110]. Epicardial AT secretes polypeptides, such as adiponectin[111] and adrenomedullin[112], which have cardioprotective effects, with low expression of adiponectin

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in epicardial AT being associated with hypertension[113]. Healthy epicardial AT accounts for approximately 5–20% of the heart weight[114], and the thickness of epicardial AT is increased in hypertensive individuals[115–117]. Under pathological conditions, epicardial AT becomes infiltrated with immune cells expressing pro-inflammatory genes (IL-1β, Il-6 and TNF-α)[118] and can contribute to structural changes in the heart[119–121]. Studies from epicardial AT derived from coronary artery bypass grafts showed significantly lower adiponectin expression compared to other visceral adipose depots and a marked increase in CD45 expression, suggesting increased immune cell infiltration compared to omental AT[122]. Studies of mild cold exposure in humans and the analysis of epicardial AT could be beneficial to understanding the role of epicardial AT thermogenesis for CVD[110]. Since mice do not have a comparable epicardial AT depot, a mechanistic understanding of how epicardial AT contributes to blood pressure modulation is lacking.

III. Cardiovascular consequences of obesity and adipose tissue dysfunction

Impact of AT on blood pressure regulation

One of the central modes of blood pressure regulation is via the renin-angiotensin-aldosterone system (RAAS). The major bioactive component angiotensin II is produced from its precursor angiotensinogen by the activation of angiotensin-converting enzymes 1 and 2. Angiotensin-converting enzyme 2 can further process angiotensin II to generate angiotensin 1–7, which has vasodilatory properties[96–98]. Angiotensin II[83] and aldosterone are also secreted by adipocytes and can directly activate vascular smooth muscle cells (VSMC) via the angiotensin type 1 receptor[123]. Angiotensin II is a prominent regulator of vascular tone,[124] and its expression is spatially regulated in PVAT, with higher expression in mesenteric PVAT compared to thoracic PVAT[83]. Interestingly, studies in rats have demonstrated that fasting reduces angiotensinogen expression in visceral AT, whereas refeeding significantly induces its expression and results in elevated blood pressure[125]. A similar effect can be observed by overexpression of angiotensinogen in mice, which also results in hypertension[126].

All of the components of the RAAS are also secreted by human WAT[127]. However, there are conflicting data as to whether the basal expression of RAAS components differ in visceral and subcutaneous AT in lean individuals. One study reported a higher general expression of angiotensinogen, the precursor of angiotensin II, in visceral AT compared to subcutaneous AT[128]. A more recent, larger study, however, reported no changes in angiotensinogen expression between the two depots in lean individuals[129]. Nevertheless, visceral AT expressed higher amounts of renin, angiotensin-converting enzyme 2 and both angiotensin receptor types 1 and 2 in the same study, whereas ACE1 was not changed[129]. In rats, mesenteric PVAT expresses higher levels of angiotensin II and both angiotensin receptor subtypes than thermogenic thoracic PVAT[83]. This is in line with the reported downregulation of angiotensinogen after beta-adrenergic stimulation of murine adipocytes *in vitro*[130].

Thermogenic brown and beige AT is considered to have protective effects on the vasculature, as individuals with detectable thermogenic AT have lower odds for hypertension and

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coronary artery disease relative to individuals without thermogenic AT[24]. Moreover, coding variants in PRDM16, the master regulator of thermogenic AT, are associated with hypertension in humans[131]. Interestingly, components of the RAAS cascade can directly affect AT, and angiotensin 1–7, besides its vasodilatory actions[96–98] also induces BAT and reduces diet-induced obesity in mice[132,133]. Surprisingly, pharmacological activation of angiotensin receptor 2 and angiotensin II treatment can induce browning of subcutaneous white adipocytes *in vivo* and stimulation of brown precursor differentiation *in vitro*[134,135]. This protective impact on BAT is assumed to be either mediated by increased sympathetic nerve activation[135] or through increased conversion of angiotensin II to angiotensin 1–7. Moreover, deletion of the type 1 angiotensin receptor results in increased appearance of multilocular beige adipocytes[136]. Taken together, it appears that angiotensin 1–7 and activation of the angiotensin receptor 2 or inhibition of the type 1 angiotensin receptor can stimulate BAT, which in turn has beneficial effects on blood pressure and attenuates development of CVD. Further studies will be needed to investigate the direct impact and molecular basis of the protective impact of thermogenic AT on hypertension.

Adipose tissue remodeling during obesity

Obesity results in a chronic low-grade inflammatory state in adipose tissue[137,138]. Visceral obesity in particular, is strongly associated with the development of CVD[13,14]. Defining and understanding remodeling of different AT depots during obesity is thus of utmost importance to ultimately preventing deleterious sequelae. During obesity, AT can expand by either enlargement of existing adipocytes (hypertrophy) or by increasing the number of adipocytes (hyperplasia) (Figure 3), with the relative importance of either mechanism varying based on depot, sex and age[31]. At baseline, fed a standard diet, neither visceral nor subcutaneous AT exhibit significant new adipogenesis in adult humans or mice[31,139]. Long-term high fat feeding of mice, on the other hand, resulted in increased adipogenesis and hypertrophy in the visceral AT, including mesenteric PVAT, whereas subcutaneous AT adapts to the higher energy intake by hypertrophy[31]. The individual impact of hypertrophy versus hyperplasia in the development of the metabolic syndrome is still under debate[140]. Maximum hypertrophy in adipocytes in established obese conditions can result in the exhaustion of the lipid storing capacity in adipocytes, which in turn can induce ectopic storage of fat in other organs such as the liver, supporting the development of the metabolic syndrom[141]. On the other hand, visceral AT is more susceptible to AT inflammation, which in turn contributes to metabolic and CVD outcomes[142]. Sex-dependent differences in AT distribution have been reviewed elsewhere[143–145], but in short, females most often accumulate AT in the subcutaneous depot, whereas men and post-menopausal women tend to accumulate AT in central visceral depots[143]. Hormone replacement therapy in postmenopausal women prevents this central AT distribution[146], highlighting the role of sex hormones in fat distribution. However, recent studies, using an elegant separation of gonadal sex and sex chromosomes demonstrated that the XX chromosomal sex results in increased weight gain independent of the gonadal sex[147,148]. This was mediated through the X-chromosome-escaped dose-dependent expression differences of the histone demethylase KDM5C in females compared to males, and lowering KDM5C levels in females to the same extend seen in males resulted in weight loss and body fat content[148].

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In obesity, the immune cell composition of different AT depots demonstrates dynamic changes[70,142,149] (Figure 4). For example, adipose tissue macrophages increase in obesity and their ablation improves insulin sensitivity and reduces inflammation[47,150–152]. The recruitment[47] and proliferation[153] of pro-inflammatory macrophages during obesity is greater in visceral than in subcutaneous AT[154,155]. Obesity further results in the loss of protective CD4 helper[156] and regulatory T cells (Tregs)[52,157] and in the enrichment of CD8 T cells in visceral AT[53]. These variations in immune cell infiltration between visceral and subcutaneous AT results in a low-grade inflammatory environment that can contribute to CVD[158,159]. Recently, eosinophils have gained attention for their role in promoting beige adipocyte activation[67,68], and their loss during obesity, especially in visceral and mesenteric AT, renders mice susceptible to diet-induced obesity[54] and abolishes the anti-contractile effect of PVAT to norepinephrine[95]. However, some of these findings require further clarification and together with detailed information on PVAT immune cell content and changes during obesity are discussed elsewhere[70].

Thermogenic brown and beige fat, on the other hand, have anti-obesity effects in humans[160,161], and depletion of UCP1 itself or ablation of UCP1 expressing thermogenic AT results in weight gain[162,163]. In contrast to WAT, classical BAT of obese mice expresses lower levels of genes associated with immune cells, suggesting that thermogenic AT is resistant to diet-induced inflammation[86]. However, other studies have shown that macrophages[164] and B lymphocytes[165] infiltrate thermogenic AT during obesity, and together with increased inflammatory cytokines[109] are thought to suppress UCP1 expression in brown adipocytes[164]. Further, mice fed a HFD for 12 weeks, show reduced expression of some thermogenic marker genes, and adipocytes shifted from a multilocular to an unilocular appearance with increased lipid accumulation in BAT and thoracic PVAT[92]. The increased body and PVAT weight also impair anti-contractile effects of PVAT[91]. High fat feeding further results in a tPVAT-specific upregulation of Notch1 compared to WAT or BAT[92]. Genetic adipocyte-specific induction of Notch1 resulted in morphological changes of tPVAT comparable to HFD induced effects[92]. This is supported by another study showing that adipocyte-specific overexpression of Notch1 impairs thermogenesis and insulin sensitivity and results in whitening of classical BAT, whereas pharmacological inhibition of Notch1 results in browning of WAT and ameliorates HFD-induced obesity[166].

Remodeling of AT during obesity and its impact on blood pressure homeostasis

Obesity is strongly associated with the development of hypertension[13], a major risk factor for CVD morbidity and mortality[167,168]. Compared to normal weight individuals, obese individuals also carry a greater risk for coronary artery calcification, carotid artery intimal media thickening and left ventricular hypertrophy, even after adjustment for traditional CVD risk factors[169]. Weight reduction significantly improves blood pressure[19,170,171], and therefore, suggests a direct link between AT phenotype and odds of developing CVD and hypertension. Visceral obesity in rodents and humans is particularly associated with the metabolic syndrome[172], which consists of several risk factors for CVD, including hypertension[173]. On the other hand, humans with thermogenic AT have lower odds for hypertension, coronary artery disease and congestive heart failure, even when obese[24].

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Angiotensinogen expression is significantly elevated in obese individuals and is also higher in visceral AT compared to subcutaneous AT[128,174,175] (Figure 4). Interestingly, expression of angiotensin II is increased in subcutaneous AT in obese individuals with hypertension compared to normotensive obese individuals[128]. Diet-induced obesity did not affect angiotensinogen levels in BAT, liver, kidney or heart in wild-type mice or in mice expressing the human angiotensinogen gene under its own promoter[175]. Importantly, adipocyte-specific deletion of angiotensinogen prevents increased angiotensin II in the circulation and blocks elevation of BP in obese mice[176], suggesting a direct impact of AT-derived angiotensinogen on blood pressure. Moreover, angiotensin receptor type 1 inhibition reverses obesity-induced blood pressure elevation in rats[177]. Finally, angiotensinogen levels are negatively regulated by PRDM16, and deletion of PRDM16 and ablation of beige adipocytes results in increased angiotensinogen expression[178,179]. Ablation of BAT in mice results in obesity as well as elevated blood pressure[180]; however, whether this is a consequence of obesity induced changes in RAAS or can be directly linked to factors secreted by brown AT needs to be further determined. Aldosterone, another component of the RAAS secreted by adipocytes[123], also positively correlates with BMI, and weight loss reduces serum aldosterone levels and reduces hypertension[181]. Components of the RAAS can therefore affect VSMC and endothelial dependent regulation of vascular tone, both of which are adversely affected during obesity.

Leptin, an adipocyte-derived hormone that regulates food intake and energy expenditure, is significantly increased in obesity in mice and humans[182,183] (Figure 4). In contrast to angiotensinogen, it may be expressed at higher levels in subcutaneous than in visceral AT[184–186], and its expression is correlated with adipocyte size[185]. Nevertheless, diet-induced obesity results in elevated leptin levels and attendant increases in heart rate and blood pressure in rodents[92,187,188]. This induction is mediated by a leptin-stimulated increase in sympathetic nerve activity[189,190], and antibody blockade of leptin or inhibition of leptin receptors on hypothalamic neurons normalized blood pressure in obese rodents[187]. Finally, leptin deficient mice[191] and humans with loss of function mutations in leptin or the leptin receptor have lower blood pressure despite severe obesity[187]. It is not well understood how the chronic increase of leptin in obese subjects results in leptin-resistance[192] and whether this affects blood pressure. Based on the above-mentioned data, reduced leptin signaling ameliorates blood pressure in mice, and therefore, leptin-resistant obesity should be beneficial in regard to blood pressure. Indeed, leptin also has some vasodilatory effects in healthy rodents, via induction of nitric oxide expression in endothelial cells[77,193] and in healthy humans by a mechanism independent of nitric oxide[194]. Further, leptin resistance was demonstrated to selectively affect neurons in the hypothalamus that regulate food intake, while affecting other neuronal circuits to a lesser extent[195,196], which could explain how obese individuals do not have beneficial effects on blood pressure when leptin resistant. In detail, agouti obese mice were resistant to food intake and body weight effects of systemic leptin administration, but had a preserved induction of leptin-induced renal sympathetic activation[196,197]. Similar results in diet-induced obese mice showed the preservation of leptin-induced renal sympathetic activation and blood pressure regulation despite the resistance to weight-reducing actions of leptin[188].

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Resistin is enriched in visceral AT[198], including epicardial AT[199] and PVAT[200], and is markedly increased during obesity[200,201]. Resistin has an important role in type 2 diabetes and insulin resistance in mice[201]. In humans with type 2 diabetes, resistin expression was only elevated in combination with hypertension and not in patients without hypertension[202]. In hypertensive patients without type two diabetes, resistin levels did not correlate with blood pressure indicating a more complex connection of obesity, insulin resistance and blood pressure regulation by resistin. In mice, resistin treatment induced hypertension through the induction of angiotensinogen[203]. Finally, resistin treatment of isolated human VSMC similar to angiotensin, resulted in increased proliferation[204].

Visfatin is also expressed in visceral AT, including PVAT[200], and increased through hypoxia induced expression of HIF1α[205] in obesity[200]. Hypertensive patients have elevated serum visfatin levels[206] however, newly diagnosed, non-obese hypertensive men did not show any association of plasma visfatin levels and hypertension[207]. Importantly, visfatin is mostly enriched in adipose tissue macrophages in mice[200] and humans,[208] and therefore, its role in adipocyte specific regulation of blood pressure might be a secondary cause of increased immune cell infiltration in obesity. Nevertheless, it was shown that hypoxic conditions can induce visfatin in murine adipocyte cell lines and its adipocyte specific role in blood pressure regulation should be determined by adipocyte-specific deletion of visfatin.

Adiponectin is another endocrine factor secreted by AT that tends to be reduced during obesity[209,210] (Figure 4). In humans, visceral adiposity inversely correlates with adiponectin secretion, whereas secretion of adiponectin by subcutaneous AT is not affected by adiposity[209]. Serum adiponectin levels are reduced in obese individuals with hypertension[211], and lifestyle intervention[212] or anti-hypertensive therapy[211] resulted in increased adiponectin levels and improved blood pressure[212]. In addition, lower adiponectin levels correlate with the risk for development of hypertension in humans[213,214], independent of body fat distribution[215]. Mice on a standard diet that lack adiponectin display elevated blood pressure despite similar body weight[76], whereas adiponectin overexpression in obese mice ameliorates elevated blood pressure[210]. To understand the direct impact of adiponectin without secondary metabolic effects such as insulin resistance, mice lacking adiponectin were fed a high salt diet. These mice developed hypertension, which could be rescued by adiponectin administration[210]. The observed elevation in blood pressure was associated with reduced endothelial eNOS and prostaglandin I_2 synthase[210], indicating a role for adiponectin in endothelial cell mediated vasodilation[216]. Further, *ex vivo* stimulation of murine mesenteric arteries with norepinephrine was significantly reduced in the presence of PVAT or PVAT-derived supernatant and could be blocked by adiponectin blocking peptide or in vessels derived from adiponectin-deficient mice[95]. Adiponectin blocking peptide also blocked electrical field stimulation of mesenteric arteries depending on the presence of PVAT[76]. Adiponectin treatment of isolated mesenteric arteries stripped of PVAT restores the anti-contractile effects[75,76], depending on the vascular large-conductance Ca^{2+}-activated K^+ channel on VSMC[75]. Finally, AMPKα1-deficient mice secrete less adiponectin, and *ex vivo* stimulation of thoracic aortic rings from these mice displayed an impaired vasodilatory effect of PVAT after U46619 treatment[217].

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Another factor enriched in human omental AT and detected in human serum is omentin[218]. Like adiponectin, it is reduced in obese conditions[219] and induced through weight reduction[220]. In rats, omentin treatment ameliorates angiotensin II or noradrenalin-induced hypertension and reduces blood pressure in normotensive rats[221,222]. Interestingly, omentin suppressed inflammatory mediators in various vascular cell types[222–224] and induced adiponectin levels, which might result in the indirect regulation of blood pressure. This is also the case for adipolin[225], which is reduced in obese mice[226] and has a protective role in vascular remodeling through the inhibition of VSMC proliferation and macrophage activation[227], and although associated with protective effects on CVD, its role in regulation of blood pressure needs to be further determined.

Several other factors secreted by different adipose tissue depots have been associated with a role in blood pressure regulation; however, functional and mechanistical proof is still sparse and will be required to understand the independent impact of those AT-derived mediators in the regulation of hypertension. Interleukin-33 (IL-33), for example, plays a pivotal role in the activation of eosinophils, and genetic loss or obesity-induced reduction of eosinophils in PVAT results in a reduced anti-contractile response[95]. Further, activation of eosinophils by IL-33 treatment rescues obesity-induced high blood pressure to the level of control mice, dependent on an endothelial cell and nitric oxide synthase-mediated effect[228]. Of note, patients with pulmonary hypertension showed elevated IL-33 levels[229], and deficiency of the IL-33 receptor attenuates the progression of pulmonary arterial hypertension in mice[230]. Therefore IL-33 could play a differential role in blood pressure regulation of vasculature with and without PVAT.

Vascular stiffening and CVD risk

While vascular stiffening is a normal phenomenon with increasing age, obesity and associated insulin resistance accelerates this process. To this point, a population study showed that skin-fold thickness is a predictor of arterial stiffness in hypertensive patients[231]. Another study found an association between abdominal obesity and increased vascular stiffness[232,233]. Epidemiological studies have demonstrated that hyperinsulinemia or insulin resistance, as exists in overweight and obese individuals, is an independent risk factor for vascular stiffening. This vascular stiffening in association with obesity and insulin resistance has been observed in all age groups, including children[234,235].

There is considerable evidence that the vascular stiffening that is increased in obesity is a powerful risk factor for CVD. Data from the Framingham Heart Study have established an increased incidence of CVD events with increasing weight in both men and women[8], and CVD has been strongly associated with vascular stiffness[235,236]. Importantly, arterial stiffening is especially striking in obese and diabetic premenopausal females who tend to lose the normal protection afforded by female sex hormones against vascular disease and show an increase in CVD events relative to lean, non-diabetic, age-matched women[237]. Indeed, vascular stiffness independently predicts heart disease, cerebrovascular disease and renal disease, as increased vascular stiffness is significantly associated with damage to target organs such as the heart, kidney, and brain[238]. For example, stiffening of central arteries increases systolic pressure and decreases diastolic pressure, resulting in increased pulse

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pressure and afterload leading to an increase in left ventricular mass and myocardial oxygen demand. Further, the decrease in diastolic pressure is associated with reduced coronary blood flow during diastole. These changes have been consistently associated with left ventricular remodeling and fibrosis together with left ventricular diastolic dysfunction and associated heart failure with preserved systolic function (HFpEF)[239,240] (Figure 5). While early detection of arterial stiffening in obese individuals certainly helps to identify a powerful risk factor for CVD, definitive studies on the impact of weight loss on reversal of vascular stiffness have yet to be conducted.

Mechanisms in CV stiffness with Obesity

Development of arterial stiffness is a complex process that is driven by the interaction of endocrine factors and AT-derived cytokines, as well as interactions between different vascular cellular components, the extracellular matrix (ECM), PVAT, and immune cells in the vasculature[6,94]. The paragraphs that follow focus on mechanisms involved in CV stiffness in conditions of overnutrition and obesity. This includes a discussion of the role of vascular endothelial abnormalities which lead to impaired endothelial nitric oxide (NO) synthase (eNOS) activation and associated increases in vascular stiffness. We also discuss the emerging role of vascular cell-specific mineralocorticoid (MR) and insulin receptor (IR) activation in promoting endothelial stiffness via endothelial Na^+ channel (EnNaC) activation, and the impact of a decrease in bioavailable NO in mediating vascular stiffness in diet induced obesity (Figure 5).

Arterial stiffness in obesity is associated with structural and functional changes in the intimal, medial, and adventitial layers of the vasculature[241]. Arterial stiffness is regulated by plasma factors such as aldosterone and insulin, as well as factors derived from the different layers of the vascular wall. Moreover, interactive signaling between different cells of the vascular wall modulates structure and function of cellular and non-cellular components. Increased arterial stiffness in obese and insulin resistant states has been related to mechanisms related to both endothelial cell (EC) and VSMC stiffness, leading to the use of such terms as the “stiff endothelial cell syndrome”[241–243] and the “smooth muscle stiffness syndrome”[242]. In addition to the role of ECs and VSMCs, vascular adipose and immune cell dysfunction and ECM remodeling contribute to obesity-associated arterial stiffness. This underscores the importance of understanding the complex cellular and ECM interactions that contribute to obesity-associated arterial stiffness[243,244].

Increased plasma insulin and aldosterone levels lead to heightened activation of vascular MRs and IRs in obesity and insulin resistance states[239–243]. Further, a downstream mediator of MR and IR activation, the ion channel EnNaC, has recently been identified as a key molecular determinant of endothelial dysfunction and CV fibrosis and stiffening[239,243]. Increased activity of EnNaC results in a number of negative consequences including stiffening of the cortical actin cytoskeleton in ECs, impaired endothelial nitric oxide (NO) release, increased oxidative stress meditated NO destruction, increased vascular permeability and stimulation of an inflammatory environment. Such endothelial alterations impact vascular function and stiffening through increases in vascular constriction and stimulation of tissue remodeling including fibrosis. In the case of the myocardium, obesity and associated

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elevations in aldosterone and insulin are associated with coronary vascular endothelial stiffening and related reductions in bioavailable NO leading to heart failure with preserved systolic function (HFpEF).

Recent studies, conducted in female mice fed a diet high in refined carbohydrates and saturated fat showed increased endothelial and aortic stiffness, impaired endothelial-dependent vasorelaxation, aortic fibrosis, aortic oxidative stress and increased vascular expression of EnNaC[239–241]. To gain further insight into the vascular role played by EnNaC, we have characterized a mouse model with endothelial cell-specific deletion of the α, pore-forming, subunit of EnNaC[241]. Obesogenic diet induced abnormalities, along with vascular and cardiac remodeling and fibrosis, were all significantly attenuated in mice with deletion of EnNaC[241–243]. From a mechanistic standpoint, these studies showed that diet induced obesity resulted in a heightened inflammatory response that was associated with reduced endothelial NO synthase (eNOS) activation and NO production and bioavailability. These latter events likely emanated from increased EnNaC activity leading to polymerization of cortical actin fibers, subsequently reducing eNOS activity, and decreasing NO production leading to increased vascular stiffness (Figure 5). This research has further revealed that activation of the endothelial Na^+ channel by aldosterone and insulin leads to endothelial cortical stiffening, impaired NO production and subsequent vascular fibrosis and stiffening in diet induced obesity[244,245]. Additionally, these observations in this obese mouse model also suggest that activation of the endothelial Na^+ channel in the coronary vasculature promotes myocardial fibrosis, myocardial stiffening and impaired diastolic relaxation and HFpEF, a condition that is especially pronounced in obese and insulin resistant females.

Studies performed in epithelial cells have shown that both aldosterone and insulin increase ENaC activity via activation of the ubiquitously expressed serum and glucocorticoid regulated kinase 1 (SGK-1)[246]. Very recent work has shown that SGK-1 represents a point of convergence for insulin and aldosterone signaling in endothelial cells[244]. Consistent with this notion, our preliminary studies have shown that aldosterone and insulin induced increases in EnNaC activity are diminished in isolated ECs from SGK-1 global knock-out mice compared to those of wild-type controls[244]. It is also of relevance that evidence exists in humans for SGK-1 playing an important integrative role in the development of the cardiometabolic syndrome. Specifically, an SGK-1 gain of function gene variant that exists in 5 percent of the population is associated with increased blood pressure and obesity[247] and has a particularly strong effect in increasing blood pressure in states of hyperinsulinemia and obesity[247]. Further, in rodent models, hyperinsulinism sensitizes the blood pressure to high fructose and salt intake, an effect involving increased activity of SGK-1[248]. Indeed, SGK-1-knockout mice are protected against salt-induced hypertension in the context of obesity caused by a high-fat and high-fructose diet[248]. Finally, increased SGK-1 activity in obesity and hypertension has also been demonstrated in adipocytes[249] and immune cells[250]. Thus, multiple lines of evidence point towards important contributions of SGK-1 signaling in promoting the cardiometabolic syndrome, vascular stiffness and associated CVD in obesity.

In summary, obesity is increasing in prevalence and these increases in obesity are associated with increased consumption of refined carbohydrates and saturated fat and reduced physical activity. These and other environmental factors interact with genetic and epigenetic factors

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to promote obesity and related CVD (Figure 1). Obesity also negates the CVD protection normally afforded in premenopausal women. The earliest sign of obesity related CVD is impaired NO mediated relaxation which leads to CV stiffness. Recent studies indicate that insulin and mineralocorticoid receptor activation of the EnNaC is important in the pathogenesis of CV stiffness, especially in obese females who lose the protection against CVD normally afforded in premenstrual women.

IV. Unanswered questions and future directions

While recent research has highlighted key links between obesity, adipose tissue, and vascular function, a number of important unanswered questions remain. From a basic standpoint, a more complete understanding of the developmental origin and cellular and molecular components of perivascular fat is necessary. Moreover, a comprehensive inventory of the secreted polypeptides and metabolites released by adipose tissues in normal physiology and the obese state will help further illuminate how excess adiposity contributes generally to vascular dysfunction and more specifically to the pathogenesis of hypertension and vascular stiffening. Future studies will also need to uncover the role of environment, genetics, epigenetics, and the microbiome on modulating the interactions between adipose tissues and the vasculature.

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Non-standard Abbreviations and Acronyms

AMPKα1	5’AMP-activated protein kinase catalytic subunit alpha 1
ANG 1–7	Angiotensin 1–7
ANG II	Angiotensin II
ApoE	Apolipoprotein E
AT	Adipose tissue
ATP	Adenosine triphosphate
BAT	Brown adipose tissue
BMI	Body mass index
CD	Cluster of differentiation
C/EBPα	CCAAT-enhancer binding protein alpha
CVD	Cardiovascular disease
EC	Endothelial cells
ECM	Extracellular matrix

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EnNaC	Endothelial Na^{2+} channel
eNOS	Endothelial nitric oxide synthase
FABP4	Fatty acid-binding protein
HFD	High fat diet
HFpEF	Heart failure with preserved ejection fraction
HIF1α	Hypoxia-inducible factor 1 alpha
IL	Interleukin
ILC2	Group 2 innate lymphoid cells
IR	Insulin receptor
KDM5C	Lysine-specific demethylase 5C
MR	Mineralocorticoid receptor
Myf5	Myogenic factor 5
NO	Nitric oxide
Pax7	Paired box 7
PET-CT	Positron emission tomography-computed tomography
PDGFRα	Platelet-derived growth factor receptor alpha
PGC1α	Pparg coactivator 1 alpha
PRDM16	PR domain containing 16
PVAT	Perivascular adipose tissue
RAAS	Renin-Angiotensin-Aldosterone-System
SGK-1	Serum/Glucocorticoid regulated kinase 1
TNFα	Tumor necrosis factor alpha
Treg	Regulatory T cells
UCP1	Uncoupling protein 1
US	United States
VSMC	Vascular smooth muscle cell
WAT	White adipose tissue

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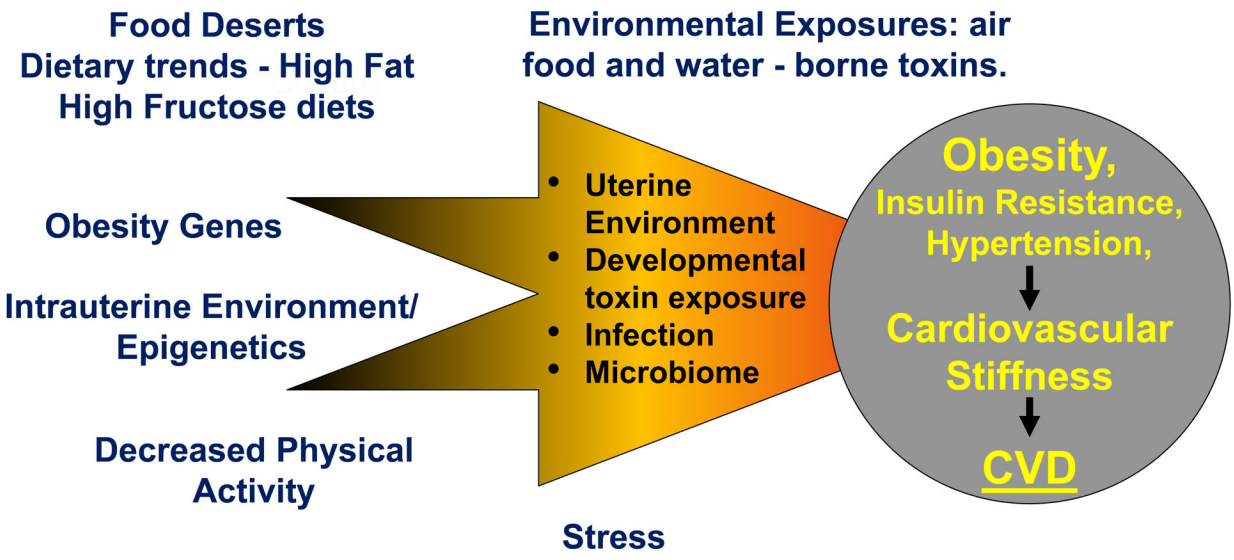

Figure 1. Obesity, vascular stiffness and cardiovascular disease (CVD): genetic/epigenetic and environment interactions.

A food desert refers to an area with limited access to nutritious, affordable food.

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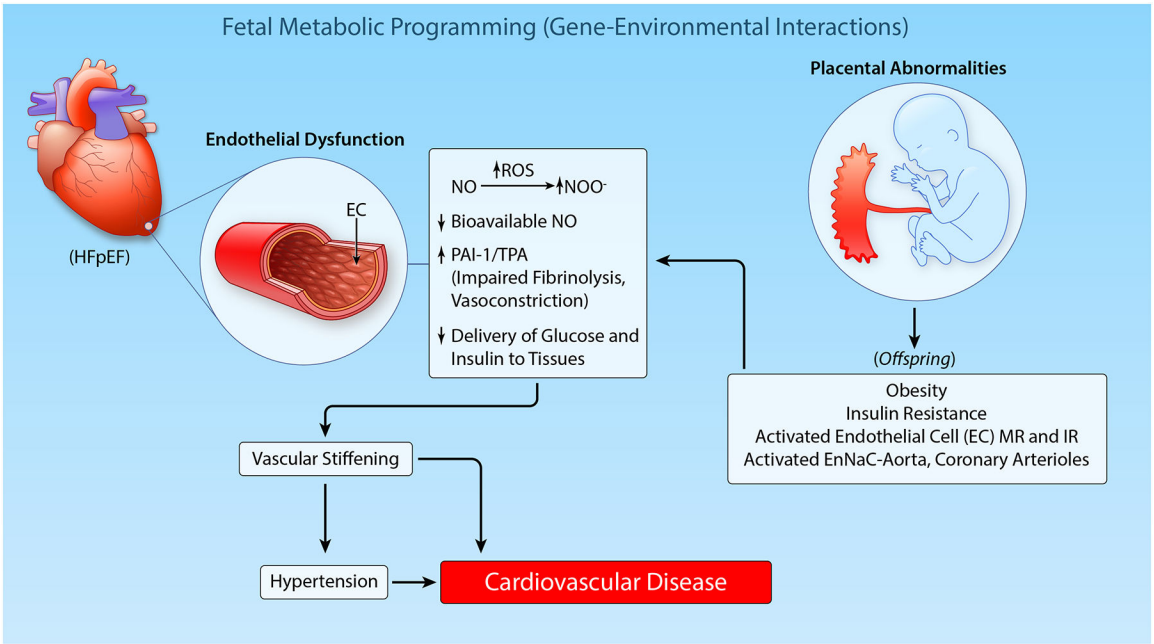

Figure 2. Prenatal programming and epigenetics in the genesis of obesity and cardiovascular disease (CVD) in offspring.

(Illustration credit: Ben Smith)

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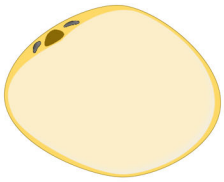
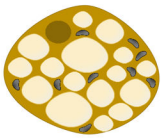
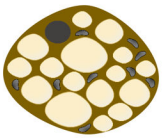

	White Adipocyte	Beige Adipocyte	Brown Adipocyte
Depots	Visceral and subcutaneous and most PVAT depots	Cervical*, supraclavicular*, axillary*, paraspinal*, renal*, thoracic PVAT*, subcutaneous (only rodents)	Interscapular (human only infants), thoracic PVAT*
Function	Storage of triglycerides, endocrine (secretion of adipokines and vasoactive factors)	Thermogenesis, anti-inflammatory properties, cardioprotective	Thermogenesis, anti-inflammatory properties, cardioprotective
Progenitor	$CD24^+$, $CD34^+$, $PDGFR\alpha^+$	Vascular smooth muscle origin	Myogenic origin $Pax7^+$, $En\text{-}1^+$, $Myf5^+$
Changes during obesity	Hyperplasia, hypertrophy, Immune cell infiltration, secretion of vasoconstrictors	"Whitening", loss of UCP1 expression	Potentially resistant to obesity-induced inflammation

* The definition of these thermogenic AT depots in humans as brown or beige is still under debate

Figure 3. Function and localization of different adipose tissue depots.

Comparison of white, beige and brown adipocytes in regard to their localization in specific depots in human and mice. Their major functions and progenitor cells are depicted. Major changes occurring during adipose tissue remodeling in obesity are highlighted. PVAT, Perivascular adipose tissue; CD, Cluster of differentiation; PDGFRα: Platelet-derived growth factor receptor alpha; Pax7, Paired box 7; En-1, Engrailed-1; Myf5, Myogenic factor 5;Ucp-1, Uncoupling protein-1; AT, Adipose tissue.

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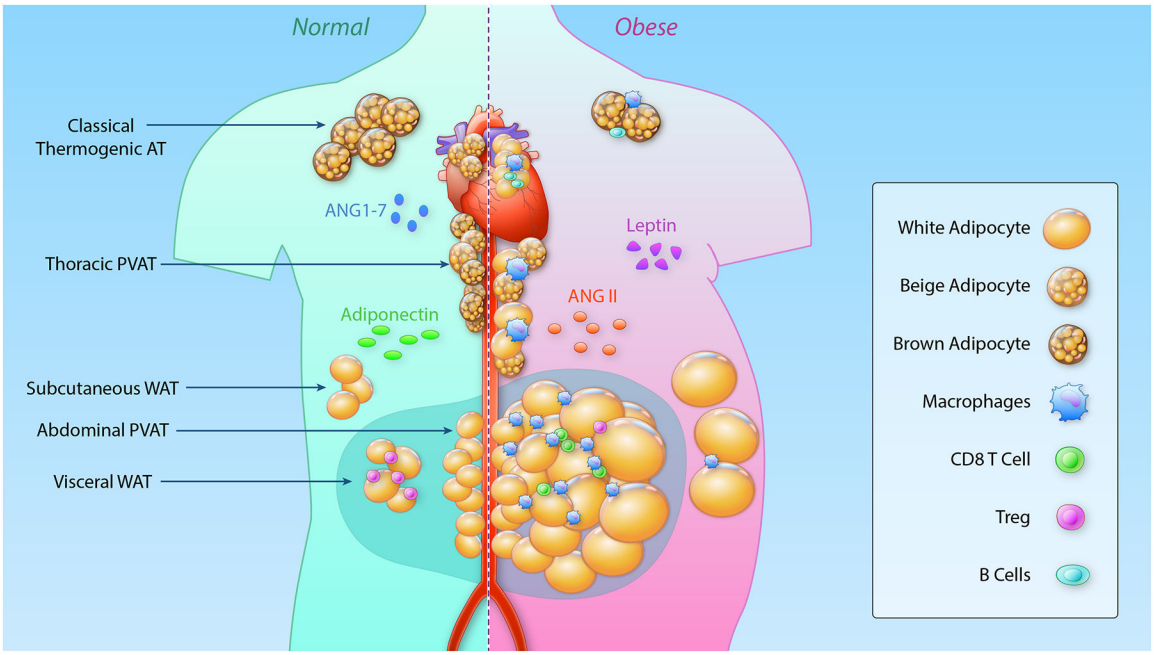

Figure 4. Changes in different adipose tissue depots in homeostasis and during obesity.

In states of normal body weight (left), thermogenic brown and beige adipocytes are found surrounding the thoracic aorta (PVAT) and can be detected in the cervical, supraclavicular, axillary, paraspinal, renal and epicardial area and in infants in the interscapular depot. These cells have a multilocular appearance and due to the high density of mitochondria appear brown. The abdominal aorta and mesenteric vasculature are surrounded by white adipocytes. These unilocular adipocytes are also found in visceral and subcutaneous adipose depots. Adiponectin and angiotensin 1–7 are secreted by adipocytes and have a vasodilating effect on the vasculature. In the lean state, adipose tissue is populated with different immune cells important for homeostasis, that change dramatically during obesity. During obesity (right), T regulatory cells (Treg) are lost in visceral adipose tissue and inflammatory CD8 T cells and macrophages infiltrate the visceral, mesenteric and to a lesser extent subcutaneous adipose depot. Thermogenic adipose tissue in proximity to the heart and the aorta downregulates thermogenic gene expression and becomes infiltrated with immune cells. Classical brown adipose tissue is potentially protected against obesity-induced immune cell infiltration. Secretion of vasodilatory factors from adipocytes are downregulated whereas leptin and angiotensin II (ANGII) are predominantly secreted, resulting in elevations in blood pressure. PVAT, Perivascular adipose tissue; WAT, white adipose tissue; ANG II, Angiotensin II; ANG 1–7, Angiotensin 1–7; CD, Cluster of differentiation. (Illustration credit: Ben Smith)

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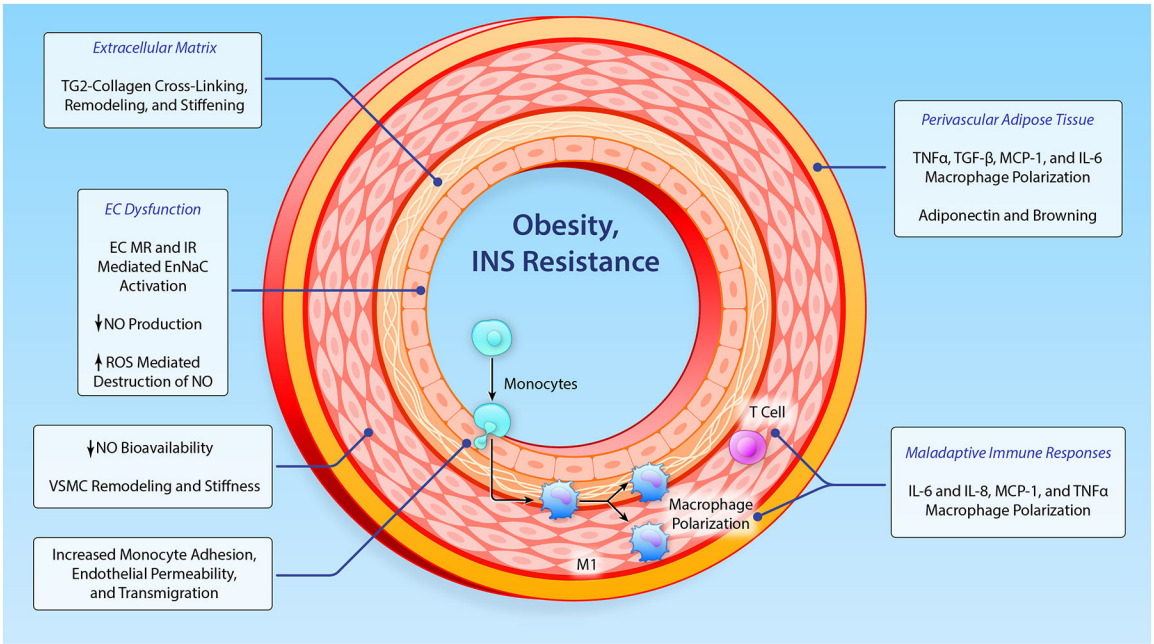

Figure 5. Effects of obesity on the vasculature which promote dysfunctional remodeling and stiffness of the vasculature.

EC, endothelial cell; VSMC, vascular smooth muscle cell; MMPs, matrix metalloproteinase; TG2, tissue transglutaminase; Ang II, angiotensin II; MR, mineralocorticoid receptor; TxA2, thromboxane A2; ENaC, epithelial Na^+ channel; IL, interleukin; TNF, tumor necrosis factor; NO, nitric oxide; MCP-1, monocyte chemotactic protein-1; CRP, C- reactive protein; TGF-β, transforming growth factor-β. (Illustration credit: Ben Smith)