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OBESITY AND VASCULAR DYSFUNCTION

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Abstract

One of the most profound challenges facing public health and public health policy in Western society is the increased incidence and prevalence of both overweight and obesity. While this condition can have significant consequences for patient mortality and quality of life, it can be further exacerbated as overweight/obesity can be a powerful stimulus for the development of additional risk factors for a negative cardiovascular outcome, including increased insulin resistance, dyslipidemia and hypertension. This manuscript will present the effects of systemic obesity on broad issues of vascular function in both afflicted human populations and in the most relevant animal models. Among the topics that will be covered are alterations to vascular reactivity (both dilator and constrictor responses), adaptations in microvascular network and vessel wall structure, and alterations to the patterns of tissue/organ perfusion as a result of the progression of the obese condition. Additionally, special attention will be paid to the contribution of chronic inflammation as a contributor to alterations in vascular function, as well as the role of perivascular adipose tissue in terms of impacting vessel behavior. When taken together, it is clearly apparent that the development of the obese condition can have profound, and frequently difficult to predict, impacts on integrated vascular function. Much of this complexity appears to have its basis in the extent to which other co-morbidities associated with obesity (e.g., insulin resistance) are present and exert contributing effects.

Keywords

Adiposity; models of obesity; metabolic syndrome; vascular dysfunction; inflammation

INTRODUCTION

Obesity is a national and global epidemic [1,2], and ongoing investigation has demonstrated that the numbers of individuals categorized as overweight or obese have increased over the last three decades and are continuing to rise, especially in developed economies [3]. Obesity is defined by the Centers for Disease Control as a body mass outside the range of that which

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has been determined to predict healthy outcomes; a determination made through the use of the body mass index (BMI), which is based on height and weight, and which correlates strongly with an individual's adiposity. The BMI classification by the National Heart, Lung, and Blood Institute for adults (age 18–85) defines an individual as being overweight for BMI between 25 and 29.9, and obese for BMI greater than 30. The estimated economic impact of obesity, its “quality of life” implications and related treatment, cost Americans over 117 billion dollars in 2001, while the World Health Organization has estimated that the treatment of obesity represents up to 7% of total global health care expenditures [4].

Obesity is a complex pathology with interacting and confounding causes proposed from the environment, hormonal signaling patterns, adipogenic pathogens, genetic predispositions, adipokine receptor defects, and numerous behavioral aspects such as eating disorders, inadequate portion control, and decreased physical activity [5–16]. Although the etiology of obesity can be extremely complicated, a central imbalance in caloric homeostasis is the primary contributing factor to this condition [17].

The progression of obesity has been associated with an increased predisposition for the development of additional pathological conditions, including a wide array of cardiovascular disease risk factors (e.g., diabetes, hypertension, dyslipidemia, prothrombotic and pro-inflammatory environments), as well as the development of respiratory dysfunction (obstructive sleep apnea), arthritic disorders, and a wide array of adverse psychological conditions [18–24]. When multiple other cardiovascular disease risk factors, in addition to the progression of obesity, are present, this combination leads to the creation of a condition termed “metabolic syndrome”, which can dramatically increase the likelihood of negative health outcomes in afflicted individuals [25–27].

GENETIC FACTORS

Nearly 400 genes have been associated with human obesity [28]. While genetic factors clearly play a key role in the development of obesity, few individuals afflicted with a rare dysfunctional gene express a profoundly obese or lean phenotype; therefore, the widespread frequency of obesity cannot be explained via a monogenic obesity model [12,28,29]. In addition, “susceptibility genes”, or candidate genes that underlie the development of obesity have also been previously described in the literature [30,31]. These “susceptibility genes” may best be conceptualized as those genes promoting adiposity given the appropriate environmental conditions, which include physical activity and diet [32]. However, neither rare nor susceptibility genes can effectively explain the significant increases in both incidence and prevalence within world-wide populations, notably, the increase in obesity prevalence since 1990 [33]. It is more likely that the prevailing form of obesity can be described by numerous genes and gene-gene interactions, which under environmental influences, contribute to an obese phenotype [12].

A MODEL FOR THE STUDY OF OBESITY

The obese Zucker rat (OZR), offers a reliable animal model for the study of an obesity-based induction of metabolic syndrome. This genetic mutation (*fa*–/*fa*–) is autosomal recessive with a locus on chromosome 5, leading to improper encoding of the leptin receptor gene [34,35]. As such, heterozygotes (*fa*–/*fa*+) are generally not physiologically distinguishable from the control (*fa*+/+/*fa*+) lean Zucker rat (LZR). Due to the impairment of the leptin receptor, OZR manifests an impaired satiety reflex, resulting in a profound, consistent hyperphagia, from which the considerable obesity develops. With both hypertrophy and hyperplasia of adipocytes, OZR begins to manifest many of the characteristics of human obesity: moderate hypertension, hypertriglycemia, insulin resistance, and the evolution of a pro-inflammatory state; suggestive that OZR may represent a viable model to study human obesity [35–38].

The initiating stimulus for the development of obesity in OZR is a chronic hyperphagia, leading to an imbalance of caloric homeostasis, making the model extremely relevant to the general human population. The development of type II diabetes mellitus, following a prolonged period of hypertriglyceremia and insulin resistance, in addition to the development of a proinflammatory state within the OZR model, also mimics the human condition [39].

The *ob/ob* mouse is an additional well established model for the study of human obesity that owes its pathology to a deficiency in leptin production as a result of a genetic mutation [40]. The *ob/ob* manifests a pronounced non-insulin dependent diabetes mellitus and obesity observed within 28 days of birth, when compared to their lean littermates [41]. The strain is used as a model for human obesity in a variety of pulmonary, cardiovascular, and metabolic function studies [42–44].

Canine models can viably mimic human obesity without genetic modifications through simple dietary manipulations. This model allows for accurate methods for metabolic assessment *in vivo*, longitudinal studies, and fat deposits assessment [45].

VASCULAR DYSFUNCTION ASSOCIATED WITH OBESITY

Many diagnosed co-morbidities have been positively correlated to overweight/obesity, translating across race, gender, and age. While dyslipidemia, glucose intolerance, insulin insensitivity, hypertension, pro-thrombotic and pro-inflammatory environments play an important role in the pathophysiology of obesity, it is very difficult at this time to separate the disorders and the specific roles each play through the disease progression; therefore, these conditions will be referred to within the context of this review, but not specifically addressed.

Vascular Disease/Coronary Artery Disease/Perfusion abnormalities

Specific to cardiovascular health, a significant effect of obesity is the increase in the development of peripheral vascular disease, a condition identified by decreased perfusion to peripheral limbs and tissues, causing edema, and leading to a decrease in function and progressive loss of tissue viability [46]. In humans, this can lead to loss of mobility, chronic pain, and development of psychological depression [47]. Chronically, these complications can manifest with venous stasis leading to lower limb ulcerations, increases in venous thromboembolism, and a higher rate of pulmonary embolism [48,49].

Studies of the direct physiological effects of peripheral vascular disease have been limited in humans in the past due to the invasive nature of some procedures. However, ultrasound techniques with advanced Doppler technologies have translated to non-invasive means to investigate and track peripheral and coronary disease states [50,51]. Carotid intima-medial thickness (IMT) is a good predictor of adult obesity and cardiovascular events [52,53]. As subjects age, the cholesterol deposits in the macrophage foam cells of the vascular intima become more extensive, and the resulting plaques become linked to acute coronary syndromes; this thickening of the intima-medial layer is highly correlated with adiposity, plaque lesions, and future cardiovascular events [54–56].

In a recognized experimental model of metabolic syndrome, OZR, the perfusion of multiple tissues has been shown to be compromised [35–37,57]. The direct mechanism of this decrease in perfusion, found in both humans and the OZR, seems to be multi-faceted: a combination of altered responsiveness to vasodilator and vasoconstrictor mechanisms, changes to the mechanical properties of the perfusing arteries, or a limit in the density/number of available microvessels to supply the tissue [58].

Vasodilation

Conditions that result from obesity, such as metabolic syndrome, manifest compromised vasodilation in response to physiological or pharmacological challenges, for example, elevated metabolic demand or infusion of endothelium-dependent agonists. One of the most heavily studied endothelium-dependent mechanisms studied has been the changes associated with nitric oxide (NO) production and release from the endothelium [59,60]. In a 2006 study of humans by Van Guilder, obese subjects were observed to have a reduced reaction to the vasodilator acetylcholine after intra-arterial infusion, relative to age matched lean subjects, while there were no differences to an intra-arterial infusion of sodium nitroprusside, a direct NO donor [61]. Patients with metabolic syndrome also show blunted endothelium-dependent dilation responses to infused vasodilators, relative to control patients, while endothelium-independent mechanisms remained intact [62]. These results have been shown in animal studies as well, as both OZR and lean rats fed a high fat diet have been shown to have an impaired vasodilatory response of isolated microvessels to endothelium-dependent NO agonists [63, 64].

This lowered response is mediated by a NO signaling mechanism which can lead to a condition that can also impact muscle cell proliferation, platelet aggregation, macrophage action, and inflammatory markers. The NO signaling mechanism is based upon a balance of NO production, via NO synthase and NO removal systems, which can include the presence of scavenging via reactive oxygen species. While NO synthase activity has been maintained, or possibly increased under obese conditions; however Eringa, 2007 shows a decreases in eNOS protein levels in resistance arteries, which may link obesity with several confounding disease states [65–68]. In addition, the obese animal has been shown to exhibit higher levels of oxidative stress markers than their lean counterpart [69–71]. These animal models of obesity have shown improvements in the patterns of vasodilator reactivity when treated with antioxidants such as vitamin E, or an array of superoxide dismutase mimetics [72,73]. Thus the decreased levels of NO noted in obesity may primarily reflect an increased scavenging via reactive oxygen species, resulting in the production of substances such as peroxynitrite [71, 74]. When arachidonic acid is introduced to the system, vasodilatory responses are attenuated in both gracilis and spinotrapezius arterioles of the OZR in comparison to the LZR [73,75]. The impaired responses appear to operate partially via an elevation in oxidant stress, but additional signaling pathways independent of acute alterations in oxidant tone appear to also be involved.

Flow-mediated dilation initiates the release of endothelium-derived relaxing factors, causing an increase in vessel diameter and therefore an increase in volume perfusion [76]. This dilation, an endothelium-dependent mechanism, has been shown to be impaired in obese patients, due to changes within the endothelium, which may be strongly linked to signaling mechanisms associated with chronic and evolving inflammation [77]. Patients with metabolic syndrome have an impaired brachial artery flow-mediated dilation relative to normal control subjects while their response to an exogenous NO-donor was uncompromised [78]. Amelioration of the condition of metabolic syndrome through weight loss and exercise improves conduit reactivity, via brachial artery flow mediated dilation, although improvements to indices of resistance vessel reactivity are less sensitive to these improvements [78,79].

Vasoconstriction

Vasoconstriction is occasionally described in the literature as a non-vasodilation, or a decrease in a vasodilatory mechanism, specifically relating to a diminished NO production or signaling and leads to decreased muscle tissue perfusion. This is also the case within the realm of obesity-related vasoconstriction.

Vasoactivity and vascular tone are based on a balance of circulating vasodilatory and vasoconstrictive factors; diabetic patients have shown increases in vascular constrictive factors and decreases in vasodilatory agents [80]. Vasoconstriction to angiotensin-II is amplified in the obese animal (OZR), while reactivity to norepinephrine remains similar to the reactivity of the LZR; a similar pattern of reactivity has also been described in humans [81]. Metabolic syndrome patients have shown increased levels of endothelin-1 (ET-1), a potent vasoconstrictor, and an overall increase in response to vasoconstrictive agonists [82,83]. The profound impact mediated by prostanoid species and other metabolites of arachidonic acid on basal perfusion/resting vascular tone as well as on hyperemic responses has been well established [84–87]. More recently, increased levels of vasoconstrictor prostanoids have also been suggested as a possible mechanism for the decreased vascular perfusion and dilator reactivity within obesity and the metabolic syndrome [88]. In the OZR, an increase in vasodilation was noted when the prostaglandin H2/thromboxane A2 receptor antagonist SQ-29548 was administered, suggesting that a chronic basal vasoconstrictor influence, mediated via the PGH2/TxA2 receptor may contribute to impairments in organ perfusion and dilator reactivity [75]. These changes to endothelial vasoconstrictor response with obesity may show an initial effect, while neurological mechanisms may show a longer lasting systemic role [89].

Neural mediated vasoconstrictors have also been shown to play a part in basal vasoconstriction in hypertensive patients, due to a hyperactivity of the sympathetic nervous system [90]. Baseline and maximal diameters and arteriolar blood flow of obese animals are reduced compared with the lean counterparts, suggesting an increase in adrenergic tone and structural mechanisms to increase vascular resistance [91]. Systemic adrenergic activity has not been found to be elevated when normalized to blood volume, instead, these changes may indicate a redistribution and possible remodeling of adrenergic activity within the obese animal, allowing increases in perfusion of the mesenteric system and decreases in perfusion of the skeletal muscles [92].

Functional Hyperemia/Muscle Blood Flow

Functional hyperemia is defined as an increase in tissue/organ perfusion in response to metabolic demand. This increase can be modified at rest or with activity through the release of metabolic factors from skeletal muscle, myogenic responses, conducted vasodilation, and the release of the endothelium-derived factors nitric oxide and prostaglandins [72]. Humans and animal models, in a condition of obesity, have shown a reduced blood flow response to exercise or any increase in local metabolic activity [72,93].

In addition to impairments to vasodilator reactivity discussed above, and the potential for enhanced vasoconstrictor responses to constrain perfusion, myogenic (intraluminal pressure-induced) control of the blood vessel may be augmented in obese animals, as OZR are seen to respond to these changes with a significantly greater constriction than in lean animals. It has been hypothesized that the generation of peroxynitrite, through the progressive scavenging of nitric oxide by pressure-induced increases in superoxide anion may play a key role in antagonizing calcium-activated potassium channels, thus enhancing myogenic activation [71, 94,95].

Sympathetic neural hyperactivity, associated with obesity, has been shown to reduce vasodilation, increase vascular resistance and decrease blood flow [96,97]. In addition, it seems that obesity may be associated with either an increased reactivity to adrenergic neurotransmitters, also leading to a reduction in blood flow or possibly an increased sympathetic nerve activity as a result of obesity [98–101].

Microvessel Density/Rarefaction

In addition to a constrained functional hyperemia, and therefore the inability to provide an adequate blood supply to active tissue in an obese setting, there is an additional restriction within the peripheral tissue that becomes increasingly relevant with elevated metabolic demand. With the development of the obesity-associated metabolic syndrome, previous studies have demonstrated that a progressive microvascular rarefaction (a reduction in microvascular density) develops within multiple tissues/organs [58,102–104]. This rarefaction can lead to tissue hypoxia and ischemia leading to a predisposition to cellular dysfunction, in addition to, reductions in nutrient transport, blood supply, and exchange capabilities.

Capillary Recruitment

Insulin action and glucose transport can be varied by skeletal muscle capillary recruitment, and while specific mechanisms associated with insulin-mediated capillary recruitment are not fully understood, the presence of “obesity-mediated insulin resistance” has been demonstrated to impair this process [105,106]. Additionally, isolated vascular smooth muscle cells from obese animals and subjects demonstrate a profound impairment in insulin-signaling mechanisms [107,108]. Addressing this, it has recently been hypothesized that the presence of excess abdominal adipose tissue may interrupt the glucose-insulin signaling/transport mechanisms of surrounding tissues and organs by an increased production of fatty acid metabolites, adipokines and chemokines, thus leading to an impaired capillary recruitment via insulin-mediated avenues, as described in obese humans and obese Zucker rats [106,109,110].

Vascular Structure and Remodeling

In addition to microvessel number and recruitment disturbances, structural alterations also take place in the environment of obesity. These modifications are described and well known within the diabetic literature, but the appearance of these changes is now being expressed in association with peripheral artery disease and metabolic syndrome, a link that could be mediated by the theory of an “obesity-mediated insulin resistance” [106,111,112].

Clinical and basic science studies have demonstrated that changes in insulin resistance and increases in BMI are frequently associated with stiffness of resistance arterioles, thickening of basement membranes, and increases in diameter [113,114]. Increases in the level of insulin can contribute to increased arterial wall thickness by direct trophic effects of smooth muscle cells, by generation of reactive oxygen species, protein kinase C, and by activation of NF- κ B, which acts to stimulate growth and proliferation of vascular smooth muscle cells. There has also been a positive correlation between structural peripheral vascular changes and insulin resistance [115]. The documented decrease in microvessel density found with obesity and its consequences could also mediate this correlation.

In structural remodeling, the factors which influence upstream must be separated from the local alterations to microvessel environment. Obesity, diabetes, insulin resistance, atherosclerosis, hypertension, and stenosis are all conditions that have significant effects on conduit arteries, but have a severe effect on the autoregulation of the microvasculature; thus, leaving it severely compromised, thereby threatening downstream vessels and surrounding tissues with ischemia and hypoxia. In an attempt to accommodate, the microvessel creates a thickened basement membrane to acclimatize to the increase in pressure and a transition in the shunt system normally used to redirect blood during meals or exercise [111,116]. As the disease progression of metabolic syndrome continues, the walls of the microvessels begin to atrophy, decreasing the size of the lumen, decreasing the ability to shunt, thereby increasing the risk of ischemia, and increasing the risk of peripheral vascular disease [111].

Coronary Dysfunction

The continuous supply and distribution of fully oxygenated blood throughout the myocardium is essential for maintaining cardiac performance, with any significant ischemia leaving the myocardial mass at profound risk for injury and dysfunction. While resting coronary perfusion shows little difference with increasing BMI, a reduced capacity for perfusion with elevated metabolic demand has the potential to widen the gap between metabolic supply and demand, putting the heart at risk of ischemic injury [89].

Disease states such as obesity and insulin resistance can cause or exacerbate a series of impairments within control mechanisms of the coronary vasculature, including endothelial function, neurohumoral control, and smooth muscle ion channel behavior, while additional effects of obesity can include an increased inflammatory state, vascular permeability, cell adhesion and an increased predisposition for coagulation events [59,89,117,118]. Endocrine and neural control of the vasculature may be modified due to an increase in activity of the renin-angiotensin system [119]. Additionally, recent studies have suggested that altered function of ion channels and calcium handling within the vascular smooth muscle may contribute to the dysfunction expressed in the coronary vasculature of obese dogs [89].

Inflammation

Attempting to understand the relationship between obesity and inflammation can be a daunting task in that inflammation is simultaneously its own independent risk factor while also being an integral component in the pathways by which other obesity related risk factors manifest themselves as disease. Adipokines, cytokines secreted by adipose tissue, released in excess in an obese state can create an environment susceptible to inflammation. In obese animal models, many adipokines are amplified above a normal level, but are lower than a traditionally described inflammatory state, leading many investigators to describe a chronic state of low-grade obesity-associated inflammation [120,121]. These white adipose derived signaling molecules can be classified as non-esterified fatty acids (NEFA), cytokines, chemokines, or hormones and can influence insulin dependent and independent signaling, insulin mediated glucose uptake and numerous aspects of vascular function [18,58,89,106,122,123]. The inflammatory markers to be briefly covered in this review include: TNF α , endothelin, angiotensinogen, adiponectin, MCP-1, IL-1 β , IL-8, Leptin, IL-6, and resistin. It is important to note that this list constitutes only a sampling of white adipose derived signaling molecules and further fails to account for a great deal of the cross talk between the signaling molecules. The scope of the topic would demand a separate review of its own and thus, we only hope to present a general picture of the crucial role of inflammation in the pathogenesis of obesity.

Levels of TNF α correlate strongly with adiposity and are associated with impaired capillary recruitment in man, diminished vasodilatory effect in muscle resistance arteries of rats, diminished insulin-mediated glucose uptake in rat skeletal muscle, elevated adhesion of polymorphonuclear leukocytes (PMNs) to microvessels, induction of oxidative stress, upregulation of endothelial cell adhesion molecules, and reduced barrier function [18,89,122,123]. TNF α is produced by neutrophils, macrophages and adipocytes with its production apparently elevated in perivascular adipose tissue leading researchers to believe that the measurements of circulating TNF α may give deceptively low concentrations relative to true site-of-action concentrations [122,123]. TNF α , which works primarily by modifying the effects of insulin, is one of a group of signaling molecules capable of acting directly on the vascular endothelium and the net effect of its apoptotic and pro-inflammatory properties is endothelial dysfunction and decreased insulin sensitivity by the vascular endothelium [18,122,123].

Angiotensinogen is expressed in high levels by visceral adipose tissue with lower levels of expression evident in subcutaneous fat [18]. Angiotensinogen serves as the precursor to

angiotensin II, a powerful vasoconstrictor product of the renin-angiotensin system (RAS). At low levels, the vasoconstriction elicited by angiotensin II is mild and predominately manifested in large, conduit vessels [89]. Chronic activation of the renin-angiotensin system results in drastically elevated angiotensin II levels, leading to significant vasoconstrictive response and ultimately resulting in inflammation, vascular remodeling, thrombosis and plaque rupture [18,89]. The effects of angiotensin II are mediated via a cognate receptor, AT1. Interaction between angiotensin II and AT1 results in the previously stated consequences, mediated through RAS, along with increased oxidant stress at the level of the vascular endothelium [89]. The oxidant stress sensitive transcription factor NF κ B is in turn activated leading to increased expression of the adhesion markers VCAM-1, ICAM-1, E-selectin and IL-8 resulting in increased rolling and adherence of leukocytes within the microcirculation [18].

Another signaling molecule capable of exerting effects directly on the vascular endothelium is adiponectin [122]. Unlike TNF α , adiponectin is associated with improved endothelial function and positive cardiovascular outcomes [18,106,122,123]. Adiponectin is inversely correlated with adiposity and reduces the production of pro-inflammatory cytokines, TNF α , and IL-6 while concurrently increasing expression of the anti-inflammatory cytokines IL-10 and IL-1 receptor antagonist [18,123]. The direct effect of adiponectin on the vascular endothelium is the phosphorylation of eNOS at Ser1177, resulting in increased production of NO [122]. Adiponectin also aids in the prevention of leukocyte rolling in adhesion by reducing expression of endothelial cell adhesion molecules, possibly through an inhibition of NF κ B [18].

The primary function of leptin is classically considered to be regulation of appetite and body weight. This regulation is achieved through diminished appetite via suppression of neuropeptide Y by leptin at the hypothalamus with concurrent increase in melanocyte-stimulating hormone (i.e. satiety signaling) [123]. Leptin action, when associated with the leptin receptor in the vascular endothelium, enhances endothelin-1 production, elicits oxidative stress, and promotes angiogenesis [18,123]. Leptin has also been shown to enhance platelet aggregation, which may lead to platelet adhesion [18]. Leptin levels are directly proportional to adiposity and leptin is capable of exerting a vasodilatory effect on coronary and resistance arteries through endothelium-dependant phosphorylation of eNOS at Ser1177 or directly through uncharacterized endothelium-independent mechanisms [124,125]. Interestingly, leptin levels are elevated in human obesity leading some scientists to postulate the existence of leptin resistance, with C reactive protein (CRP) identified as a possible source of disruption of intracellular leptin signaling [122].

IL-6 is the primary regulator of CRP, with elevations in IL-6 leading to CRP mediated inhibition of eNOS, angiotensin-stimulated production of reactive oxygen species, increases in vascular permeability, elevated expression of adhesion molecules and thrombus formation [18,122,123]. IL-6 levels are directly proportional to adiposity and elevations result in direct impairments of endothelial function [18].

Resistin is a product of white adipose tissue though its expression in humans borders on undetectably low levels [18]. It has no clear correlation with adiposity though it has been implicated in adipogenesis and in the development of insulin resistance [18,123]. Resistin stimulates the production of TNF α , IL-6 and MCP-1 through NF κ B with a concomitant decrease in the production of IL-10 [18]. Additionally, resistin elevates ET-1 release and expression of adhesion molecules and has been strongly correlated with insulin resistance and chronic kidney disease [122].

Endothelin exerts its potent vasoconstrictor effects through the endothelin type A (ETA) receptor. ET-1 has been recognized as a mediator of endothelial dysfunction in coronary and

peripheral artery diseases due to the prolonged vasoconstrictive effect of ET-1 resulting in a decreased coronary blood flow reserve in humans. Plasma ET-1 concentrations correlate with adiposity and show further correlations with elevated HbA1c (glycosylated hemoglobin, considered to be indicative of glycemic control over extended periods of time), hypertriglyceridemia and increased waist/hip ratio [89].

Both NF κ B and TNF α have been shown to increase production of MCP-1, a signaling molecule whose function through the CCR-2 receptor is, primarily, the recruitment of macrophages into tissues at sites of inflammation [123]. MCP-1 increases monocyte adhesion to the vascular endothelium, has been described as anti-angiogenic and has a strong inverse correlation with NO bioavailability [58,122]. These effects are similar to those seen by increased IL-1 β or IL-8 expression though they are achieved through a different mechanism [58,122,123].

It rapidly becomes apparent that inflammation and obesity is a winding road, with most signaling molecules modifying the actions of other signaling molecules which in turn propagate the process. In some cases, adiposity leads to increased production of a cytokine whereas in other cases, production of a cytokine leads to increased adiposity, leads to increased cytokine production. For this reason, inflammation can never truly be solely a risk factor or an outcome of obesity; rather, it is a multifactorial contributor to the overall pathophysiology of the condition.

Perivascular Adipose Tissue

Adiposity can be described by location, upper body/abdominal or lower body; and most confounding disease states related to obesity are those with profound visceral adipose deposits, within the upper body [126]. This visceral adipose may act to impair function via mechanical compression or enhanced adipokine secretions [127]. The perivascular adipose tissue (PAT) is described as the adipose tissue which surrounds local vasculature, specifically but not limited to the peri-aortic adipose tissue and that surrounding the coronary arteries [127]. There are other adipose deposits, including epicardial adipose tissue, and intramuscular adipose tissue, which produce specific adipokines and have access to local vasculature [122]. Overall a net decrease in vascular tone and relaxation has been attributed to the perivascular adipose tissue of the aorta and mesenteric arteries, as the removal of PAT from these tissues led to an enhanced contractile response [128–130].

In the past, this vascular adventitia has had stabilizing properties, but under further investigation, there are significant endocrine properties that may be mediated by PAT [131–134]. In addition to endocrine properties, PAT has been shown to regulate vascular tone of the smooth muscle via release of perivascular adipocyte-derived relaxation factor (PVAT) which acts to hyperpolarize the smooth muscle and promoting vasodilation [134]. PVAT has also been shown, in obese hypertensive animals, to react with various vasoconstrictors, to locally attenuate the effects of vasoconstrictors, while atorvastatin increased the efficacy of PVAT [135]. PAT has also been shown to release angiotensin and ET-1 when stimulated by angiotensin II, causing a significant vasoconstriction and an increase in reactive oxygen species [136,137].

The low-grade inflammation discussed above may also be mediated by pro-inflammatory cytokines released by PAT. The epicardial adipose tissue, considered to be a localized department surrounding the heart and PAT of the coronary arteries, has been shown to produce TNF- α , IL-1 β , IL-6, MCP-1, and IL-8 [127,138]. In addition to the chemotactic properties of these inflammatory markers leading to the leukocyte migration to the vascular endothelium, inflammation can be mediated and increased by the amount of adipose tissue in the obese environment [127]. As demonstrated in Figure 1, these factors are released throughout the

adipose tissue, however predominantly within the upper body and visceral cavity, easily accessible to the vascular system.

NEFA's released from the PAT tissue can interfere with insulin signaling and insulin mediated glucose uptake. This result can filter downstream of the large PAT influenced arteries and cause a reduction in capillary recruitment, through a vasoconstriction of pre-capillary arterioles, thus preventing capillary recruitment and muscle glucose uptake [122]. Insufficient glucose could limit muscle activity, as these downstream fibers would be metabolically inactive, suffering reduction in insulin signaling and possible ischemia [139].

The vasa vasorum represents a vascular network which integrates into the walls of larger arteries, and can facilitate the diffusion and transport of substrate within the arterial wall microenvironment. Recent studies have suggested that this might be an avenue through which inflammatory molecules can be introduced into the arterial wall, and contribute rapidly to alterations in vascular function [140,141]. This issue may be especially important within the abdomen, where fat deposits increase risk for a variety of confounding disease states and the mesenteric vasculature is abundant to aid in digestion. The vasa vasorum physically unites the cofactors related to obesity-related insulin resistance through an insulin resistant reduction in blood flow, impairment of insulin signaling, a reduction in NO dependent vasodilation, an increase of oxidant stress radicals, deposition of lipid into the surrounding tissues, and a chronic low-grade state of inflammation; specifically allowing PAT deposits to release adipokines at vascular beds for easy access to systemic effects, as evident in Figure 1 [37,139,142].

Interventions/Management of Obesity

The principle issue related to obesity is the imbalance between energy expenditure and energy intake. Obesity results from more caloric intake than expenditure [17]. Therefore, the management of the disorder can be determined by changing one of the variables of the equation, either by decreasing caloric intake or increasing energy expenditure. Unfortunately, the obese condition can create additional pathophysiologies that interrupt this resolve.

Weight loss can show dramatic results to the self esteem, cardiovascular function, and arthritic symptoms experienced by an obese individual [143,144]. The cardiovascular effects can cascade throughout the negative cofactors associated with metabolic syndrome. Hodett, 2007, has shown improvements in vascular function of the microvessels of weight loss patients, including increases in eNOS expression, improvements in functional hyperemia, and vasodilation [72]. In addition, studies have shown an improvement in arterial compliance and distensibility [145]. Within the coronary system, weight loss has been shown to improve heart rate variability, left ventricular dysfunction (both systolic and diastolic) and mass, along with decreases in cardiac output, resting heart rate, and EKG intervals [146]. Weight loss has also shown beneficial results within the disease states of hypertension, dyslipidemia, and insulin resistance.

The methods by which individuals choose to lose weight, however, may be detrimental to their overall health. The physiological adaptations to obesity are especially important when exercise programs or medications are introduced. It must be considered that obesity causes persistent disproportionate elevations in cardiac filling pressures during exercise [147–149]. Patients must start slowly, in order to reverse some of the complications that have already developed; these patients have a baseline condition of rarefraction, therefore a limit in functional hyperemia, and increased risk of tissue hypoxia/ischemia, which may cause further muscle damage [58].

There are additional risks with non-exercise related weight loss techniques. Starvation tactics, such as liquid protein or low calorie, can cause tachycardia or an increase the EKG intervals,

specifically of the QT interval [150]. There are many commercially available diet pills, with unknown or dangerous side effects, especially those that prevent absorption of various food products or are stated to increase the resting metabolic rate such as fenfluramine or dexfenfluramine. Surgical options are currently available as well and have shown significant improvements in weight loss, hypertension, insulin resistance, and arthritic conditions; however bariatric surgery can come with significant complication risk [4,151].

Obesity is reaching epidemic levels worldwide; as these this disease state progresses, alterations to the local endothelium and systemic cardiovascular system become evident. Within chronic cases of obesity, changes of the vasodilatory and vasoconstrictive mechanisms due to neural mediated changes, low-grade inflammation, or increases in radical oxidant scavenging accompanying confounding diseases significantly increase the morbidity and mortality rates associated. Future interventions should target the treatment of obesity prior to these systemic effects taking place.

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Figure 1.

A schematic representation of adipose tissue depositions, the adipokines, inflammatory markers and other factors that are released from these tissues, and their identified impact on elements of vascular function. Pointed arrows indicate potentiating effects on vascular outcome, while flat headed arrows indicate inhibitory effects on vascular outcome.