

Review Article

Metabolic Syndrome, Chronic Kidney, and Cardiovascular Diseases: Role of Adipokines

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Obesity is a chronic disease, whose incidence is alarmingly growing. It is associated with metabolic abnormalities and cardiovascular complications. These complications are clustered in the metabolic syndrome (MetS) leading to high cardiovascular morbidity and mortality. Obesity predisposes to diabetic nephropathy, hypertensive nephrosclerosis, and focal and segmental glomerular sclerosis and represents an independent risk factor for the development and progression of chronic kidney disease (CKD). Albuminuria is a major risk factor for cardiovascular diseases (CVDs). Microalbuminuria has been described as early manifestation of MetS-associated kidney damage and diabetic nephropathy. Obesity and MetS affect renal physiology and metabolism through mechanisms which include altered levels of adipokines such as leptin and adiponectin, oxidative stress, and inflammation. Secretory products of adipose tissue also deeply and negatively influence endothelial function. A better understanding of these interactions will help in designing more effective treatments aimed to protect both renal and cardiovascular systems.

1. Introduction

The prevalence of obesity, among both adults and children, has worldwide increased over the past two decades; a phenomenon which is predominantly attributed to the change in dietary habits and lifestyle modifications [1, 2]. It is clearly known that central obesity is an independent risk factor for CVD and is associated with Mets. Insulin resistance (IR) is a key feature of the Mets and consists in a decreased sensitivity or responsiveness of peripheral tissues to the metabolic action of insulin [3]. IR as well as all components of the Mets are associated with altered functions of endothelium which lead to CVD [4]. Hyperlipemia and coronary artery disease are also consequences of obesity which through a cascade of various reactions lead to kidney dysfunction. Moreover, obesity-induced sleep apnoea activates sympathetic nervous system increasing the tone of the glomerular efferent arterioles and the secretion of renin and angiotensin [5]. In the

last decade, obesity has been suggested as a risk factor for chronic kidney disease, decline of renal function, and low-grade albuminuria, but conflicting results have been reported [6–10]. Yet obesity, per se, even in the absence of the above-mentioned medical complications alters renal physiology and metabolism. In this paper, we will examine the role of adipose tissue-secreted factors and the mechanisms of obesity-induced renal and vascular injury leading to chronic kidney and cardiovascular diseases.

2. Epidemiology of Mets, CKD, and CVD

CVD accounts for premature death in about 50% of dialysis patients [11]. As early as 1974, Lindner et al. demonstrated that dialysis patients have a higher prevalence of CVD compared to the general population [12]. The strong association between mild CKD and CVD has been shown, and recently Henry et al. reported that mild to moderate CKD is strongly

associated with an increase in cardiovascular mortality [13, 14].

Ninomiya et al. recently examined the relationship between Mets and CKD [15]. They performed a slope analysis of the association between the glomerular filtration rate (GFR) slope and Mets by using a multiple regression model. GFR decreased significantly faster in patients with 4 or more Mets components compared with those who had 1 or no components. Moreover the mean of the GFR slope was significantly lower in subjects with 3 Mets components in the 60 year and over group. In a large cohort of the NHANES III study with baseline normal renal function, Chen et al. examined the risk of developing CVD following patients for more than 20 years [16].

Interestingly, there also was a 2-fold increase in the risk of microalbuminuria that correlates with the number of components of Mets. Moreover, even low-grade albuminuria below the conventional cut-off point for albuminuria was associated with increased prevalence of CKD [17]. Data from the MESA [18] and LIFE studies [19] clearly demonstrated that albuminuria is one of the strongest risk factors for cardiovascular disease (CVD).

3. Adipose Tissue As an Active Endocrine Organ

There are multiple changes in adipose tissue in obesity including increase in numbers and size of adipocytes, infiltration of adipose by mononuclear cells, rarefaction of blood vessels, increases in adipocyte turnover rate, differentiation, and apoptosis [20]. The capillary diffusion capacity is reduced in patients with obesity and, in contrast with the response of lean subject, the adipose blood flow does not increase in response to food in obese patients [21]. Since the discovery of leptin as an adipocyte-derived satiety factor, adipose tissue is increasingly being considered as an endocrine organ. Adipose tissue secretes into the circulation a number of proteins and nonprotein factors that regulate glucose and lipid metabolism throughout the body. Among these bioactive adipokines, only adiponectin (ADN), leptin, adipisin, and visfatin are almost synthesized exclusively by adipocytes. In obese patients, the production of ADN is reduced [22–24]. ADN is a 30 kDa protein present as oligomers in the blood stream and has insulin-sensitizing, antiatherogenicity, and anti-inflammatory properties. Reduction of ADN levels is a consistent feature among obese patients who have evidence of IR and often develop diabetes mellitus. ADN plasma levels also negatively correlate with coronary artery disease and dyslipidemia in both mice and humans [25–28]. Overexpression or AND administration reduces oxidative stress, inflammation, IR, and vascular damage. Becker et al. found that low ADN levels in mild to moderate kidney disease were correlated with cardiovascular events [29]. The potential link between ADN levels and low-grade albuminuria was first observed in a clinical study where essential hypertensive patients had a negative correlation between ADN levels and low-grade albuminuria [30]. Later on, similar results were also obtained in obese patients from different ethnic groups [31, 32]. Despite some controversial observations [33, 34], clinical data strongly suggest the

potential causative role of ADN in the development of albuminuria in obese patients. An important contribution in understanding the potential link between obesity and kidney damage comes from the work by Sharma [32]. In a recent study, he showed that ADN knockout mice had baseline increased albuminuria (twice normal values) with podocyte foot process effacement. Morphologically, the endothelium appeared to be normal under electron microscopy. Podocytes expressed the AdipoR1 receptor and ADN regulated an isoform of NADPH oxidase through the AMPK pathway [32]. When treating ADN knockout mice with ADN, proteinuria was reversed and foot processes were normalized. In mice, Sharma et al. [32] also demonstrated that ADN deficiency was a susceptibility factor for early diabetic kidney disease. Consequently, the podocyte may play an important role in determining albuminuria associated with obesity [35]. The role of endothelial dysfunction may be important for albuminuria as well. At the present time, no data are available to document the presence of glomerular endothelial dysfunction in the presence of microalbuminuria. On the other hand, it has been established that podocyte dysfunction contributes to endothelial dysfunction [36, 37].

The increase of visceral fat promotes synthesis of proinflammatory adipokines which cause tissue-specific increase in reactive oxygen species derived from NADPH oxidase. Adipose tissue oxidative stress results in the development of systemic oxidative stress and inflammation, which further lead to the development of metabolic abnormalities. Leptin, a 167 amino acid polypeptide, is expressed mainly by adipocytes; leptin concentration positively correlates with adiposity [38], and hyperleptinemia is an independent risk factor for coronary artery disease [39] and a strong predictor of acute myocardial infarction [40]. Additionally, leptin has been implicated in many atherogenic processes, including platelet aggregation and thrombosis [41–43]; production of inflammatory cytokines, for example, TNF- α , IL-6, and IL-12 [44]; calcification of vascular smooth muscle cells [45]. Interestingly, recent reports have demonstrated that leptin possesses cytokine-like properties and that elevated plasma leptin levels occur concomitantly with elevated IL-6 and C-reactive protein in human obesity, the Mets, and noninsulin-dependent diabetes mellitus [46–48]. Animal testing showed that leptin induces proliferation of glomerular endothelial cells, enhances glomerular TGF- β 1 expression, and increases collagen type IV mRNA production [49]. These factors result in focal glomerulosclerosis, glomerular and mesangial glucose uptake, and proteinuria [49]. Additionally, leptin is also associated with adrenergic activation, increased blood pressure and tachycardia, contributing to obesity-related hypertension and kidney damage [50–53].

In recent years, a great deal of attention has been focused on the orexigenic peptide ghrelin which is predominantly secreted by the stomach [54, 55]. Patients with obesity-related Mets have reduced ghrelin circulating levels. Ghrelin has important vascular actions; it acutely stimulates production of NO in vascular endothelium through a PI3-kinase-dependent mechanism involving phosphorylation of Akt which directly phosphorylates and activates eNOS leading to increased production of NO [56]. This signaling pathway

is similar to that used by insulin to promote increased production of NO in vascular endothelium. Moreover, we have demonstrated that intra-arterial ghrelin administration acutely improves endothelial dysfunction by increasing nitric oxide (NO) and decreases ET-1-dependent vasoconstriction, thereby restoring the physiological balance between these opposing vascular mediators in patients with central obesity [57, 58].

Thus, therapeutic interventions including weight loss, exercise, or pharmacological therapies that increase plasma ghrelin levels could contribute to this strategies by mimicking and/or augmenting beneficial effects of increased insulin sensitivity.

Dysregulation of adipokines synthesis and release into the blood stream occur in obese patients and play a critical role in promoting IR [59–61]; diabetes and dyslipidemia are characterized by low adiponectin levels and elevated levels of inflammatory adipokines such as TNF- α (TNF- α) [62].

Adipose tissue also expresses a local renin-angiotensin system (RAS). Adipocytes express RAS receptors and synthesize and secrete angiotensinogen and angiotensin peptides [63]. RAS is a hormonal cascade that governs vascular tone, fluid-electrolyte balance, and blood pressure [64].

4. Adipokines and Cardiac Function

Many studies have shown effects on the heart of various adipokines. TNF- α has been considered to be a critical factor in the pathogenesis of cardiac contractile dysfunction and heart failure. Transgenic mice with overexpression of TNF- α develop severe dilated cardiomyopathy [11], and TNF- α directly depresses cardiomyocyte contractility and induces apoptosis of cardiomyocytes *in vitro* [65]. TNF- α has negative inotropic effects on cardiomyocytes *in vitro*, and leads to heart failure in mice [66–72]. In addition, elevated serum TNF- α levels have been associated with the progression of heart failure in patients [66].

Experimental findings have shown that adiponectin has several beneficial effects in the cardiovascular system. Adiponectin plays an essential role in the maintenance of heart architecture, as the cytokine may attenuate angiotensin II-induced cardiac hypertrophy [73] and attenuate cardiomyocyte contractile dysfunction in *db/db* diabetic obese mice via a mechanism possibly related to c-Jun and IRS-1 phosphorylation [74].

Moreover, adiponectin represses atherosclerotic lesions in a mouse model of atherosclerosis, and adiponectin-deficient mice exhibit an accelerated vascular remodeling response to injury [75]. In addition, adiponectin stimulates nitric oxide production in endothelial cells through AMPK-dependent and AMPK-independent phosphorylation of endothelial nitric oxide synthase (eNOS) [76, 77] and hypoadiponectinemia is associated with the progression of left ventricular hypertrophy (LVH), which is accompanied by diastolic dysfunction [78].

An association between serum leptin concentrations and various cardiovascular risks, including myocardial infarction [79], coronary heart disease [40], stroke [39], chronic heart

failure [80], and left cardiac hypertrophy [81], has been observed.

Several works suggested that leptin could be an important link between obesity and development of cardiovascular disease [82]. This might be mediated through various effects of leptin including effect on blood pressure [83], inflammatory vascular response [42, 84], and platelet aggregation [85, 86]. High levels of leptin are associated with lower arterial distensibility [87] and have also been shown by several investigators to promote angiogenesis, enhance the calcification of vascular cells, and potentiate the prothrombotic platelet aggregation [86, 88] moreover, obese individuals possess higher plasma levels of prothrombotic factors such as fibrinogen, von Willebrand factor, factor VII, and plasminogen activator inhibitor-1 (PAI-1), which lead to a higher risk of thrombosis and atherosclerosis. The levels of pro-thrombotic factors such as fibrinogen, von Willebrand factor, factor VII, and plasminogen activator inhibitor-1 (PAI-1) are shown to be directly correlated with leptin levels [89].

Ghrelin is not produced by the adipose tissue; however, the functions of this gastric peptide are closely related to those of adipokine regarding metabolic and cardiovascular function.

Ghrelin has been demonstrated to have cardiovascular effects, both in animals and humans. Ghrelin protects the heart from ischemia in rats, and chronic administration of the peptide improves cardiac contractility in animals with chronic heart failure [90]. Furthermore, in the heart of rats subjected to ischemia followed by reperfusion, ghrelin reduces the infarct size [91], increases cardiac output, diastolic thickness of the noninfarcted wall, and attenuates the development of cardiac cachexia in rats with heart failure [92]. In humans, ghrelin administration reduces cardiac afterload and increases cardiac output and systemic vascular resistance, without changing heart rate [93]. Moreover, ghrelin administration increases exercise capacity and improves left ventricular function and muscle wasting in patients with chronic heart failure [94–96].

5. Adipose Tissue Inflammation

Recent observations from Kamei et al. [97] on transgenic mice have led to the concept that obesity contributes to IR and diabetes promoting a condition of chronic, low-grade inflammation of the adipose tissue because of additional infiltration and accumulation of inflammatory macrophages [98–102]. The macrophage content of adipose tissue is higher in visceral obesity compared to subcutaneous obesity, leading to the concept that visceral fat more than subcutaneous one plays a central role in the development of IR [103]. Macrophages appear to be recruited from the circulation, and adipocyte-derived factors might be involved in this process.

Monocyte chemoattractant protein-1 (MCP-1) is produced predominantly by macrophages and endothelial cells and is considered one of the most important potent chemotactic factors for monocytes. The increase of MCP-1 expression in adipose tissue contributes to the macrophage infiltration and IR associated with obesity.

The general low-grade chronic inflammatory state, closely related to obesity, may affect insulin action by suppressing insulin receptor signalling via serine phosphorylation of insulin receptor substrates at metabolically relevant sites [104]. Because favourable metabolic and hemodynamic actions of insulin share common intracellular transduction pathways [105], inflammation may simultaneously contribute to both IR and vascular dysfunction, two cardinal and interrelated features of the Mets. Moreover, macrophages become activated and secrete inflammatory cytokines such as TNF- α and IL-6 which in turn decrease insulin action on adipocytes, determine hypoadiponectin, and increase leptin production [98, 106]. TNF- α indeed plays a central role in the pathophysiology of IR and vascular damage in patients with obesity; the deletion of the TNF- α gene or the TNF receptors has proven effective to improve insulin action in both genetic and dietary models of rodent obesity. Overexpression of TNF- α has previously been reported in obese adipose tissue [62, 107], as well as in the skeletal muscle of insulin-resistant animals and humans and exposure to TNF- α acutely inhibits insulin-stimulated glucose uptake. Additionally, TNF- α -induced vasculopathy is characterized by increased vascular reactive oxygen species.

We have previously demonstrated that TNF- α neutralization with the monoclonal antibody infliximab ameliorates insulin-stimulated vascular reactivity in Mets [108]. Our findings suggest that increased oxidative stress is involved in mediating the effects of TNF- α on insulin-stimulated vasodilator capacity. The beneficial action on vascular reactivity demonstrated in our study proposes a novel mechanism by which TNF- α activation might be involved, via increased oxidative stress, in the pathophysiology of vascular dysfunction in patients with obesity-related MetS.

The degree to which any particular adipose-derived inflammatory mediator enters the blood stream and plays a role in metabolic and cardiovascular disorders has not yet been established [109].

An emerging area of interest is the role of perivascular adipose tissue (PVAT) in regulating local vascular tone [110]. The presence of adipose tissue around the heart and the great vessels has been recently recognized as an independent cardiovascular risk factor. The perivascular adipose tissue (PVAT) is the potential source of the mediators leading to obesity-related vascular damage.

Because of the absence of the fascial boundaries, epicardial adipose tissue may locally interact and affect the coronary arteries and myocardium through paracrine actions of pro- and anti-inflammatory adipokines and other bioactive molecules [111].

Thus, the epicardial and perivascular adipose tissue could mechanically and functionally modulate the function of the myocardium and vasculature thereby possibly playing a role in obesity-related atherosclerosis [112].

Several studies demonstrated that epicardial fat produces a number of bioactive molecules as well as TNF- α , IL-6, IL-1, resistin, free fatty acid, and adiponectin that could affect cardiovascular morphology and function [113–117].

Moreover, recent studies have shown that perivascular adipocytes physiologically exert anticontractile effects which are both NO dependent and independent.

In particular, adipokines released from fat depots have local rather than systemic vasoregulatory effects, a mechanism defined as vasocrine signaling. In healthy subjects, PVAT seems to mediate an anticontractile effect in medium- and small-sized arteries [118, 119].

Adiponectin is the main candidate for this role based on the finding that the anticontractile properties of the fat are abolished entirely with an adiponectin type 1 receptor blocking fragment [119].

Importantly, this effect of PVAT is lost in patients with obesity-related metabolic syndrome, and conformational changes in perivascular fat have been shown to associate with lots of its anticontractile properties likely due to inflammatory, vasoconstrictor, and oxidative mechanisms. Recent studies has demonstrated a positive correlation between epicardial adipose tissues volume and coronary atherosclerosis using multislice computed tomography [120].

Moreover, Hosogai and colleagues demonstrated that PVAT of obese mice is hypoxic and that hypoxia stimulated an inflammatory phenotype and a loss of the anticontractile properties. This effect is mediated by endoplasmic reticulum stress and posttranscriptional regulation. Because hypoxia is a prominent feature of adipose tissue in obese individuals and is thought to cause adipocyte dysfunction and tissue inflammation [121], these findings further support a prominent role for PVAT-derived inflammatory cytokines in adversely modulating vascular function.

Of note, the obese phenotype could be reproduced by adding the inflammatory cytokines IL-6 or TNF- α to the PVAT around healthy vessels, which in turn could be blocked by cytokine antagonists.

In conclusion, these studies suggest that PVAT in obese individuals predominately exerts influence that contributes to vascular disease and may act both locally (paracrine) and downstream (vasocrine), through outside-to-inside signaling.

6. Renal Effects of Obesity

The most common types of morphological renal lesions observed in renal biopsies of obese patients are mainly focal and segmental glomerulosclerosis and glomerulomegaly [122]. The podocyte foot process effacement described in the ADP knockout mice probably represents an earlier stage of kidney involvement. Early changes occurring in the presence of only mild metabolic abnormalities and mild hypertension in the absence of diabetes mellitus include increased glomerular cell proliferation, increased mesangial matrix, thicker basement membrane, and increased expression of glomerular transforming growth factor- β [50].

In a recent study, Lamacchia and colleagues demonstrated that para- and perirenal fat thickness is an independent predictor of kidney dysfunction and increased renal resistance in patients with type 2 diabetes [123].

The mechanisms of obesity-induced renal injury are not fully understood and are likely to involve a combination of

hemodynamic and metabolic abnormalities. Many factors contribute to the increase in both glomerular filtration rate (GFR) and rise in renal plasma flow (RPF) observed in obese patients. The increased protein intake determines a rise in GFR [124]. Moreover, IR causes increase in the efferent arteriolar pressure because the reduction of noradrenaline-induced efferent arteriolar constriction by insulin action is blunted. Subsequently, the transcapillary pressure gradient increases resulting in hyperfiltration [124]. Augmented filtration determines microalbuminuria. Moreover, insulin stimulates the synthesis of IGF-1 and IGF-2, both promoting glomerular hypertrophy [122, 124]. The rapid and parallel increases in the prevalence of end-stage renal disease and obesity in the past two decades suggest that obesity may be a major risk for kidney disease through other mechanisms than diabetes and hypertension (see Figure 1) [125]. Additionally, obesity increases the risk of development of renal diseases from different aetiologies, such as primary immunoglobulin A nephritis or unilateral nephrectomy [126, 127]. Whether weight loss, in the long term, can slow down the progression of renal damage or reverse it is unknown at the present time. In the short term, weight loss usually leads to reduction of the proteinuria. Antiproteinuric effects of weight loss are also observed in obese patients with nephropathies due to other causes [126].

7. Mechanisms of Vascular Damage in Obesity

Abdominal obesity is well recognized as a major risk factor for CVD, but the underlying mechanisms of vascular damage in obesity remain poorly understood.

One of the most important mechanisms by which obesity leads to the development of vascular diseases is the development of IR in skeletal muscle, adipose tissue, and liver. The adipose tissue excess, particularly visceral fat, is associated with a continuous production of mediators that impair insulin action in skeletal muscle, like free fatty acids (FFAs), and is associated with a decreased production of adiponectin, a mediator known to improve insulin sensitivity [128]. Plasminogen activator inhibitor-1 (PAI-1) is typically increased in the obesity/IR state and plays an important role in the genesis of vascular abnormalities [129]. In addition, obesity and IR are frequently associated with altered coagulation/fibrinolysis. In combination, all of the above abnormalities create a state of constant and progressive damage to the vascular wall, manifested by a low-grade progressive inflammatory process [130]. Endothelial dysfunction is defined as paradoxical or inadequate endothelial-mediated vasodilation and is characterized by loss of balance between vasoconstrictors and vasodilators, increased oxidative stress, and elevated expression of proinflammatory and prothrombotic factors.

Endothelial dysfunction is a fundamental initial step in the development and progression of atherosclerosis and has been considered an important event in the development of microvascular complications [130].

Adipose tissue can produce a significant amount of compounds able to affect endothelial function; the ability of adipokines to directly affect vascular homeostasis may

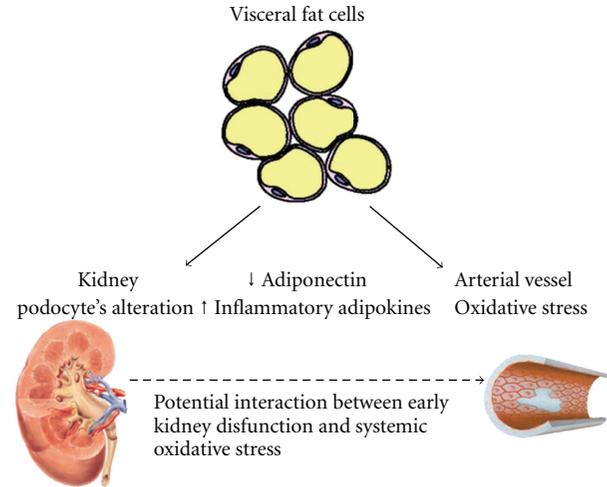


FIGURE 1: Possible dynamic interactions between obesity, CKD, and CVD. The increase of visceral mass determines both decreased production of ADN and increased production of inflammatory adipokines which result in increased insulin resistance.

represent an important mechanistic basis of vascular disease in patients with obesity. Central obesity is associated with increased levels of free fatty acid (FFA) that induces endothelial dysfunction by effect of insulin-mediated vasodilatation in humans and by impairment of nitric oxide-independent mechanism mediated by reduction of potassium-mediated vasodilatation [131]. The increased levels of FFA from the more lipolytically active intra-abdominal adipocytes decreased insulin sensitivity through the intracellular insulin signaling [132].

Moreover, FFAs are capable of utilizing the innate immune receptor TLR4 to induce proinflammatory cytokine expression in macrophages and adipocytes. In particular, the TLR4 signaling appears to be required for a component of insulin resistance induced by FFAs in adipocytes and in vivo after lipid infusion and high-fat diets [133].

Moreover, TNF alpha overproduction in obesity mediates the increased endothelial permeability by activating NADPH oxidase [129] and also inhibits transcriptional, as well as posttranscriptional, eNOS gene expression an effect that can account for the endothelial dysfunction.

In obese patients, an increase in reactive oxygen species has been demonstrated and could be the link between the low-grade inflammation, platelet activation, and nitric oxide destruction.

In IR and obesity, the dyslipidaemia is characterized by a different composition and distribution of LDL cholesterol, resulting in an increased concentration of the more atherogenic small dense LDL. Small dense LDL particles can move through endothelial fenestrations, entering the subendothelial space where inflammation and transformation into plaque can occur [134]. Moreover, the ox-LDL is mostly taken up by macrophage scavenger receptors, rather than the normal LDL receptor pathway, thus inducing atherosclerosis.

8. Vascular Dysfunction in Insulin Resistance and Metabolic Syndrome

Hyperinsulinemia and IR are established metabolic features of obesity. Vasodilator actions of insulin to stimulate production of nitric oxide (NO) from vascular endothelium lead to increased blood flow that further enhances glucose uptake in skeletal muscle [135, 136]. Insulin binding to its cognate receptor activates two major branches of insulin signal transduction network. Metabolic actions of insulin tend to be mediated by phosphatidylinositol 3-kinase- (PI3K-) dependent signaling pathways, whereas the nonmetabolic insulin signalling pathways (MAPK-dependent insulin signalling pathways) typically regulate growth, mitogenesis, and differentiation [137, 138] and also regulate the secretion of the vasoconstrictor endothelin-1 (ET-1) from endothelium.

The PI3K-dependent metabolic actions of insulin directly promote glucose uptake in skeletal muscle by stimulating translocation of insulin responsive glucose transporters (GLUT4). At the same time, PI3K-dependent vascular actions of insulin to increase blood flow and capillary recruitment substantially contribute to promoting glucose disposal under healthy conditions [3].

ET-1, a potent vasoconstrictor synthesized and secreted by vascular endothelium, plays an important role in endothelial dysfunction.

In humans, insulin-stimulated ET-1 production may influence skeletal muscle glucose disposal, and ET-1 infusion induces peripheral insulin resistance. NO, however, is known to inhibit ET-1 production and action [139]. Consequently, under healthy conditions, the effects of insulin-stimulated ET-1 on the metabolic actions of insulin are likely to be offset by insulin-stimulated production of NO [140].

IR is characterized by selective impairment in PI3K-dependent signalling in both metabolic and vascular insulin target tissues, and the diminished sensitivity to the actions of insulin in vascular endothelium contributes importantly to the clinical phenotype of this condition [3].

In insulin-resistant states, the insulin-mediated ET-1 secretion is augmented, and blockade of ET-1 receptors significantly improves insulin sensitivity and peripheral glucose uptake in the context of IR [141, 142].

Another important mechanism of insulin action is the increased microvascular perfusion of skeletal muscle leading to increased muscle blood flow and glucose uptake.

While the majority of previous studies have focused on the endothelium-dependent effect of insulin, we have suggested that the blunted vasodilator responsiveness to the exogenous NO seen in obese patients during hyperinsulinemia could be related to the facilitatory action physiologically exerted by insulin on vasorelaxation within VSMCs. Indeed, insulin enhances vasodilator responsiveness by reducing Ca^{2+} concentration in VSMCs, via activation of the Na^+ , K^+ -ATPase pump [143]. Similarly, in human VSMCs, insulin inactivates the small GTPase RhoA and its target, Rho-kinase, thereby leading to decreased phosphorylation of myosin light chain and subsequent vasodilation [144].

In a recent study, we have demonstrated that insulin exerts a facilitatory effect on vascular reactivity to a variety of

vasoactive molecules (acetylcholine, sodium nitroprusside, and verapamil) by the increased delivery of substrates in skeletal muscle of healthy subjects, but in contrast with the results obtained in healthy subjects, the responsiveness of these vasodilators was not enhanced during hyperinsulinemia in the group of patients with the metabolic syndrome due to increased oxidative stress [145].

9. Conclusion

The rapid growth of obesity is contributing to an “epidemic” in Mets and diabetes and related renal and cardiovascular complications. Adipose tissue is an endocrine organ which produces a variety of “adipokines.” Clinical management should be aimed to reduce risk factors by encouraging lifestyle modifications such as diet, aerobic exercise, and healthy eating as well as pharmacologic intervention to improve insulin sensitivity, dyslipidemia, and blood pressure control and protect the kidney from further injury. At the present time, there are few drugs available to produce significant long-term weight loss. Weight loss of about 10% can improve insulin sensitivity and lower blood pressure, reduce serum lipid levels, decrease plasma inflammatory cytokines, and increase circulating AND [97, 146]. Finally, an emerging area of interest is the potential role of the podocyte-specific drugs. Further research on adipokines action on renal cells is needed and will lead to novel treatment strategies aimed to fight the increased incidence of obesity-related chronic kidney and cardiovascular diseases.

Conflict of Interest

The authors declare no conflict of interest.

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