Published in final edited form as:
Curr Opin Nephrol Hypertens. 2010 May ; 19(3): 227–234. doi:10.1097/MNH.0b013e3283374c09.

Scope and Mechanisms of Obesity-Related Renal Disease

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Abstract

Purpose of review—Obesity is established as an important contributor of increased diabetes mellitus, hypertension, and cardiovascular disease, all of which can promote chronic kidney disease (CKD). Recently, there is a growing appreciation that even in the absence of these risks, obesity itself significantly increases CKD and accelerates its progression.

Recent findings—Experimental and clinical studies reveal that adipose tissue, especially visceral fat, elaborates bioactive substances that contribute to the pathophysiologic renal hemodynamic and structural changes leading to obesity-related nephropathy. Adipocytes contain all the components of the renin-angiotensin-aldosterone system, plasminogen activator inhibitor, as well as adipocyte-specific metabolites such as free fatty acids, leptin, and adiponectin which affect renal function and structure. In addition, fat is infiltrated by macrophages that can alter their phenotype and foster a pro-inflammatory milieu which advances pathophysiologic changes in the kidney associated with obesity.

Summary—Obesity is an independent risk factor for development and progression of renal damage. While the current therapies aimed at slowing progressive renal damage include reduction in weight and rely on inhibition of the renin-angiotensin system, the approach will likely be supplemented by interventions aimed at obesity-specific targets including adipocyte-driven cytokines and inflammatory factors.

Keywords

Obesity; kidney; CKD

Introduction

Obesity is now a worldwide epidemic, with overweight, obesity, and extreme obesity all increasing. The number of patients with CKD and end stage renal disease (ESRD) has also risen. Potentially linking these two epidemiologic observations is that many obesity-induced derangements are themselves nephrotoxic. Thus, diabetes mellitus is a common cause of renal dysfunction and ESRD and occurs with greater frequency in the obese [1] Likewise, adiposity contributes to hypertension, hyperlipidemia and cardiovascular disease, all of which promote

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The authors report no conflicts of interest.

renal disease. [2] Recently, there is increasing support that obesity *per se* can initiate and accelerate progression of kidney disease. [3] [4] [5]Among 75,000 Norwegians followed over 21 years, increased BMI dramatically correlated with initiation of renal replacement or death with CKD (Figure 1). Interestingly, prehypertension only adversely affected outcome in those with obesity. [5]

Clinical Characteristics

In 1974, Weisinger et al. first reported an association between obesity and nephrotic syndrome that remitted with weight loss and returned with weight gain.[6] The renal histology was that of idiopathic focal segmental glomerulosclerosis (FSGS). The term obesity-related glomerulopathy (ORG) is now used to describe this secondary form of FSGS. Although proteinuria has been the clinical hallmark of obesity-related renal disease, ORG is now observed at lower thresholds of proteinuria. Thus, Kambham et al. documented a ten fold increase in ORG between 1986–1990 and 1996–2000. This study importantly noted that ORG was less likely than idiopathic FSGS to present with nephrotic-range proteinuria or edema, and was frequently associated with little to no hypoalbuminemia. [7] Among a Chinese cohort with ORG, half had proteinuria <1 gm/day, and a third <400 mg/day.[8] Even among extremely obese patients with normal renal function prior to bariatric surgery, majority had glomerular lesions, including glomerulomegaly, podocyte hypertrophy, increased mesangial matrix and mesangial cell proliferation.[9] Despite these structural changes, only 4% had macroalbuminuria, and 41% had only microalbuminuria. Thus, 96% of this group had no dipstick definable proteinuria. Such observations illustrate a shift in the concept of ORG as a nephropathy that does not hinge on the manifestation of proteinuria for diagnosis.

Glomerulomegaly is the primary histopathologic feature which distinguishes ORG from primary FSGS as well as obese patients with other renal diseases. [8] [10] [11] [12] [13] Increased glomerular size may be a manifestation of processes that promote cell proliferation and matrix synthesis (see below). Additionally, the link of glomerulomegaly and sclerosis may reflect the limited capacity of mature podocytes to divide. Indeed, glomerulomegaly with ORG was accompanied by a 45% reduction in podocyte density.[14] Thickening of the glomerular basement membrane (GBM) which has previously been considered an early manifestation of hyperglycemia and diabetic nephropathy, may be an additional pathologic finding associated with obesity. Obesity promotes hyperinsulinemia which may transition to hyperglycemia and type II diabetes. In obese patients with IgAN, GBM was ~25% thicker despite similar HgbA1c to the non obese.[12] Thicker GBM was also seen in biopsies from patients with benign nephrosclerosis related to essential hypertension and patients with ORG, with no data on glucose, though triglycerides and cholesterol were higher in the obese.[15] Another series found thicker GBM in obese patients, as well as direct correlation with HgbA1c in the normal range. [16] GBM thickness also correlated directly with circulating levels of cholesterol and triglycerides. Thus, glycemic and lipid abnormalities of obesity may contribute to GBM thickening which may not achieve the level seen in overt diabetes.

Obesity dramatically alters renal hemodynamics. A recent study found that glomerular filtration rate (GFR) was higher obese adults than in normal weight controls.[17,18] The renal plasma flow (RPF) was also elevated, though not to the same degree. As a result, the filtration fraction (FF) increased, a hemodynamic adjustment that paralleled the degree of BMI and adipose mass. Even renal allografts adjust their function to the body habitus of the recipient. [19] Molecular sieving experiments in obese individuals suggest that afferent arteriolar vasodilatation, together with efferent arteriolar vasoconstriction, contribute to increased FF. [17,20] In experimental animals, even mild adiposity enhances the antinatriuretic response. [21] By lowering tubular NaCl relative to GFR, obesity-dependent mechanisms disrupt the tubuloglomerular feedback (TGF) response, preventing suppression of GFR.[22] Given the

high rate of hypertension in obesity, TGF inadequacy may allow transmission of systemic BP to the glomerulus contributing not only to increased GFR but to deleterious structural consequences.[23] Importantly, obesity-induced GFR increase is not fixed, with studies documenting improvement in hyperfiltration after gastroplasty.[24] [25]

Pathophysiology

Obesity induces several pathophysiologic disturbances that contribute to renal injury.

Renin-angiotensin-aldosterone system (RAAS)

The RAAS is a major regulator of vasomotor tone and cellular proliferation that affect renal function and structure. Adipocytes and adipose-infiltrating macrophages comprise an important source of RAAS (Figure 2). Indeed, visceral fat expression of angiotensinogen (Aog) approximates that of the liver, classically considered the chief source of Aog.[26] Circulating levels of Aog increase with increasing BMI.[27] Relevant to obesity and CKD, infusion of angiotensin II (AngII) in obese mice resulted in a dramatic increase in adipocyte-derived and circulating, but not liver, Aog.[28] The AngII type 1 receptor (AT1), primarily responsible for post-glomerular vasoconstriction, is elevated in the renal cortex of obese Zucker rats.[29] Renal AT1 is also upregulated in transgenic mice overexpressing Aog exclusively in adipocytes (aP2-Agt).[30] Overall, adipose-derived increase in circulating RAAS ligands together with adipose-driven increase in renal AT1 provide a powerful combination for increasing efferent arteriolar vasoconstriction, glomerular pressure, FF, as well as cellular proliferation that culminate in renal damage. As with other proteinuric glomerulopathies, inhibition of RAAS has been used to treat ORG. Notably, although escape from the antiproteinuric benefits of angiotensin converting enzyme inhibition has been observed, it coincided with weight gain, further underscoring the prominent role of adipose tissue RAS.[31] Fasting decreases Aog and can reduce AngII production and AT1 density.[26] Such mechanisms may have contributed to decreased proteinuria observed in an obese teenager soon after bariatric surgery with negative caloric balance but minimal weight loss.[32]

Less easily conceptualized is the role of the AngII type 2 receptor (AT2). Obese Zucker rats treated with an AT2 receptor antagonist showed dramatic increase in blood pressure and renal cortical renin.[33] Similarly, when AT2 null mutation was introduced into the aP2-Agt strain of mice overexpressing Aog in adipocytes, exacerbation of hypertension, higher renal renin, and higher circulating AngI were observed.[34] AT2 KO/ aP2-Agt mice showed significant amelioration of elevated adipocyte levels of several angiogenic/inflammatory cytokines than aP2-Agt mice with intact AT2, including TNF-α, IL-6, IL-1β, and vascular endothelial growth factor (VEGF). These data thus suggest a role for AT2 in mediating the considerable adipose inflammatory response associated with increased Aog.[34]

Aldosterone blockade lessens renal injury. These benefits are independent of antihypertensive effects and instead, may relate to blocking aldosterone effects on plasminogen activator inhibitor (PAI-1) and transforming growth factor-β (TGF-β, reactive oxygen intermediates, inflammatory mediators, and podocyte function.[35] [36] [37] Adipose tissue is capable of AngII-independent aldosterone production and at least one oxidized derivative of linoleic acid is able to stimulate aldosterone production.[38] Further, complement-C1q TNF-related protein 1 (CTRP1), which in part mediates AngII stimulation of aldosterone, is also prominently expressed by adipose tissue where it may mediate AngII-independent aldosterone production.[39] Treatment with eplerenone in a mouse model of metabolic syndrome increases podocyte nephrin, reduces proteinuria and normalizes urinary markers of oxidative stress.[35] In this connection, the transgenic Ren2 rat shows podocyte foot process effacement which is normalized by treatment with spironolactone accompanied by a reduction in albuminuria as well as attenuating NADPH oxidase activity.[40] Overall, elevated aldosterone which prevails

in obesity may be injurious to glomeruli through indirect effects to increase GFR as well as through direct podocyte effects.

Plasminogen activator inhibitor-1 (PAI-1)

PAI-1, as the primary physiological inhibitor of plasminogen activators, inhibits fibrinolysis and proteolysis and has a key role in obesity and insulin resistance. [41,42] [43] [44] Obesity induces PAI-1 in adipose tissue and glomerular cells where it is an independent risk factor for renal damage through its effects to decrease protease-dependent matrix degradation and cellular migration.[45] In a podocyte injury-associated glomerulosclerosis model, renoprotection conferred by PPAR-γ agonist is achieved, in part, through decreased PAI-1. [46] Interestingly, preliminary studies suggest PAI-1 also modulates podocyte injury. Thus, renal ablation in PAI-1 deficient mice caused less proteinuria, glomerular sclerosis, podocyte damage/loss. These *in vivo* findings were paralleled by decreased angiotensin-induced apoptosis in cultured PAI-1 deficient podocytes compared with PAI-1 intact cells. These results are of interest because of the highly differentiated nature of podocytes, which once lost, are not replenished and thought to promote intraglomerular injuries that lead to glomerular sclerosis. (Unpublished data.)

Melanocortin

The central nervous melanocortin system plays a pivotal role in regulating body weight and energy homeostasis.[47] Melanocortin 4 receptor (MC4-R) has been identified as the cause of rare forms of monogenic obesity and heterozygous mutations in the MC4-R gene account for about 6% of early onset or severe adult obesity.[48] Novel non-selective melanocortin receptor agonists improve obesity, hyperinsulinemia and fatty liver disease in obese C57BL/6 mice. [49] Recently, the effects of melanocortin-4 receptor in obesity-associated renal injury were studied in MC4R−/− mice.[50] Although MC4R−/− mice exhibited many characteristic of the metabolic syndrome, including increased weight, hyperinsulinemia, and hyperleptinemia, they were not hypertensive. Although treatment with L-NAME caused a similar increase in systemic blood pressure in both MC4R−/− and age-matched wild type mice, the MC4R−/− developed more renal injury including greater elevation in urine albumin, renal TGF-β content and renal macrophage infiltration. These results emphasize that hypertension is an important risk factor for obesity related kidney injury in MC4R−/− mice.

Metabolic/adipose factors

Obesity causes lipid disturbances that may directly contribute to renal damage. Young C57BL/6 mice fed a HFD became heavier, developed hyperglycemia, hyperinsulinemia, elevated triglycerides and cholesterol and lower circulating adiponectin. They became proteinuric and had morphological abnormalities including, glomerulomegaly, expanded mesangial matrix, GBM thickening and podocyte effacement.[51] A dramatic increase in mesangial area was also observed in young obese Zucker rats fed a HFD, an abnormality which normalized by treatment with rosuvastatin.[52] Lipid moieties can directly injure renal parenchymal cells. Human mesangial cells exposed to LDL, oxidized LDL, and glycated LDL at concentrations approximating those in circulation dramatically increased synthesis of mesangial matrix components, fibronectin and laminin.[53] The lipid moieties also promoted mesangial production of macrophage migration inhibitory factor, and increased expression/release of inflammatory activators, CD40 and IL-6.[53] Treatment of hyperlipidemic mice with anti-IL-6 monoclonal antibody ameliorated lipid-induced renal toxicity, including glomerular lipid accumulation, mesangial cell proliferation and matrix accumulation, resulting in normalization of proteinuria.[54] Lipids also directly damage podocytes. [14] Oxidized LDL causes redistribution and loss of nephrin as well as podocyte apoptosis by decreasing phosphorylation of Akt, a prominent pathway for cell survival.[55,56] Additional podocyte metabolic pathways

may be altered by lipids. Thus, podocytes cultured with the saturated fatty acid, palmitate, increased ceramide production resulting in blockade of insulin-stimulated glucose uptake.[57] Fatty acid-induced insulin resistance in podocytes appears to represent a novel nexus where lipid abnormalities and altered glucose metabolism may interact directly to foster nephropathy.

Sterol regulatory element binding protein-1 (SREBP-1) appears to play a critical role in the renal lipid accumulation, subsequent inflammatory/fibrotic response, and resultant injury.[58] [59] Thus, renal effects of a HFD were not seen in SREBP-1c −/− mutant mice, while SREBP-1a transgenic mice had increased glomerular lipid accumulation, markers of glomerulosclerosis as well as increased albuminuria. Ameliorating effects were recently observed for farnesoid X receptor.[60] Lending credence to these data for human disease are observations that glomerular expression of SREBP-1 is up-regulated two fold in glomeruli from patients with obesity related glomerulopathy.[61]

Adipose tissue produces a number of bioactive substances. Leptin was originally identified as a murine obesity gene product abundantly produced by adipose tissue and regulates the hypothalamic-pituitary axis involved in food intake, energy expenditure and intracellular lipid homeostasis. Circulating levels of leptin parallel fat stores and absence of leptin or mutation in the leptin receptor gene causes massive hyperphagia in animals and humans. Despite severe obesity, these mutations are not accompanied by renal dysfunction. Contrasting adipose-originating cytokines which are elevated, adiponectin levels are depressed in obesity. Low adiponectin levels have been associated with inflammation, atherosclerosis, insulin resistance, and augmentation of blood pressure.[62] Experimental and clinical hypoadiponectinemia is associated with endothelial cell dysfunction, impaired endothelium-dependent vasodilation, disinhibition of leukocyte-endothelium adhesion, and activation of RAAS. Adiponectin also supports normal function of the podocyte[63] and hypoadiponectinemia may impair the pivotal role of podocytes in maintaining an intact glomerular sieving barrier and promote intraglomerular injuries that lead to glomerular sclerosis. Thus, adiponectin null mutant mice have an exaggerated response to renal injury including glomerulomegaly, glomerular collagen deposition, podocyte foot process effacement, increased TGF-β, and albuminuria.[64] Adiponectin treatment normalizes podocyte effacement and albuminuria. At least in part, adiponectin's benefit may be through reduction in oxidant stress.[63] [65] Conversely, adiponectin deficiency leads to augmentation of NADPH oxidase and increase in urinary reactive oxygen species. It is of interest that obese African-Americans show a strong negative correlation between plasma adiponectin levels and albuminuria.[63] Importantly, adiponectin level can increase even with modest weight loss. Only 1 month after bariatric surgery, obese patients had a significant increase in adiponectin.[66]

Adiposity-driven proinflammatory cytokines

Fat distribution, specifically visceral adiposity, is a key determinant of renal dysfunction, even in normal weight individuals.[67] The role of the visceral fat relates not only to secretion of bioactive substances, but also to promote a low grade chronic inflammatory state. Visceral fat is infiltrated by macrophages which constitute an important source of pro-inflammatory mediators. Macrophages also have a reciprocal relationship with adipocytes. For example, fatty acids released by adipocytes stimulate TNF-α release by macrophages which, in turn, can stimulate production of IL-6 by fat cells further amplifying the inflammatory response in adipose tissue as well as the kidney.[68] TNF-α is a key mediator of progressive renal fibrosis. Gene expression profiles in glomeruli obtained from renal biopsy samples of patients with ORG showed increased TNF-α and its receptors, suggesting TNF-α's role in development of ORG.[61] Interleukin-6 is secreted by adipose tissue and circulating levels increase with obesity, with as much as 30% derived from adipose tissue.[69] Glomeruli from patients with

ORG show increased expression of IL-6 signal transducer, pointing to the possibility of IL-6 pathogenicity in glomeruli.[61] Many of the bioactive substances produced by macrophages also inhibit preadipocyte differentiation, further expanding a population of large, dysfunctional, insulin-resistant adipocytes that fuel the vicious cycle between obesity and renal injury.

Adiposity-driven macrophage infiltration and phenotypic switch

Obesity-related macrophage infiltration of adipose tissue is believed to be key in inflammation and insulin resistance.[70] [71] Importantly, depending on the local microenvironment and stage of tissue injury, macrophages display heterogeneity in functions.[72] [73] [74] Thus, M1 or "classically activated" macrophages are induced by classical immune pathways and function to enhance proinflammatory cytokine production (IL-1β, TNF-α, IL-6). By contrast, M2 or "alternatively activated" macrophages function in the resolution of inflammation and tissue repair through synthesis of anti-inflammatory cytokines IL-10 and IL-1 decoy receptor and possess high endocytic clearance capacities.[75] [74] [73] Obesity induces macrophage phenotypic switch in adipose tissue,[76] shifting from M2 phenotype predominating in lean rodents to a robust increase in proinflammatory M1 macrophage population in obese animals. [77] [78]

Experimental approaches to inhibit proinflammatory macrophages have been successful in reducing kidney injury.[79] [80] [81] The possibility that phenotypic alteration of macrophages modulate obesity-associated CKD has recently been evaluated. Using AT1a receptor knockout mice (AT1aKO) and a high-fat diet-induced obesity model, we recently found that HFD feeding augmented renal injury, including mesangial expansion and tubular vacuolization in AT1aKO (submitted for publication). There was significantly greater macrophage infiltration in visceral adipose tissue and kidney of obese AT1aKO. Kidney M1 macrophage activation was markedly induced while kidney M2 activation was reduced by half in obese AT1aKO. Further, M1, but not M2, activation in peritoneal macrophages was enhanced in obese AT1aKO. These data reveal a new role of macrophage AT1 receptor in mediating macrophage polarization and suggest that AT1a deficiency reduces the population of potentially beneficial M2 macrophages and promotes obesity-related renal damage.

In conclusion, new evidence indicates that in addition to promoting diabetes, hypertension, and cardiovascular disease; obesity per se, causes pathophysiologic disturbances that adversely affect kidney function and structure. These abnormalities are remediable through weight reduction and inhibition of RAS, an approach that will likely be supplanted with interventions that directly target adipocyte-associated cytokines and inflammatory factors.

Acknowledgments

This work has been supported by NIH DK044757 (VK, LM).

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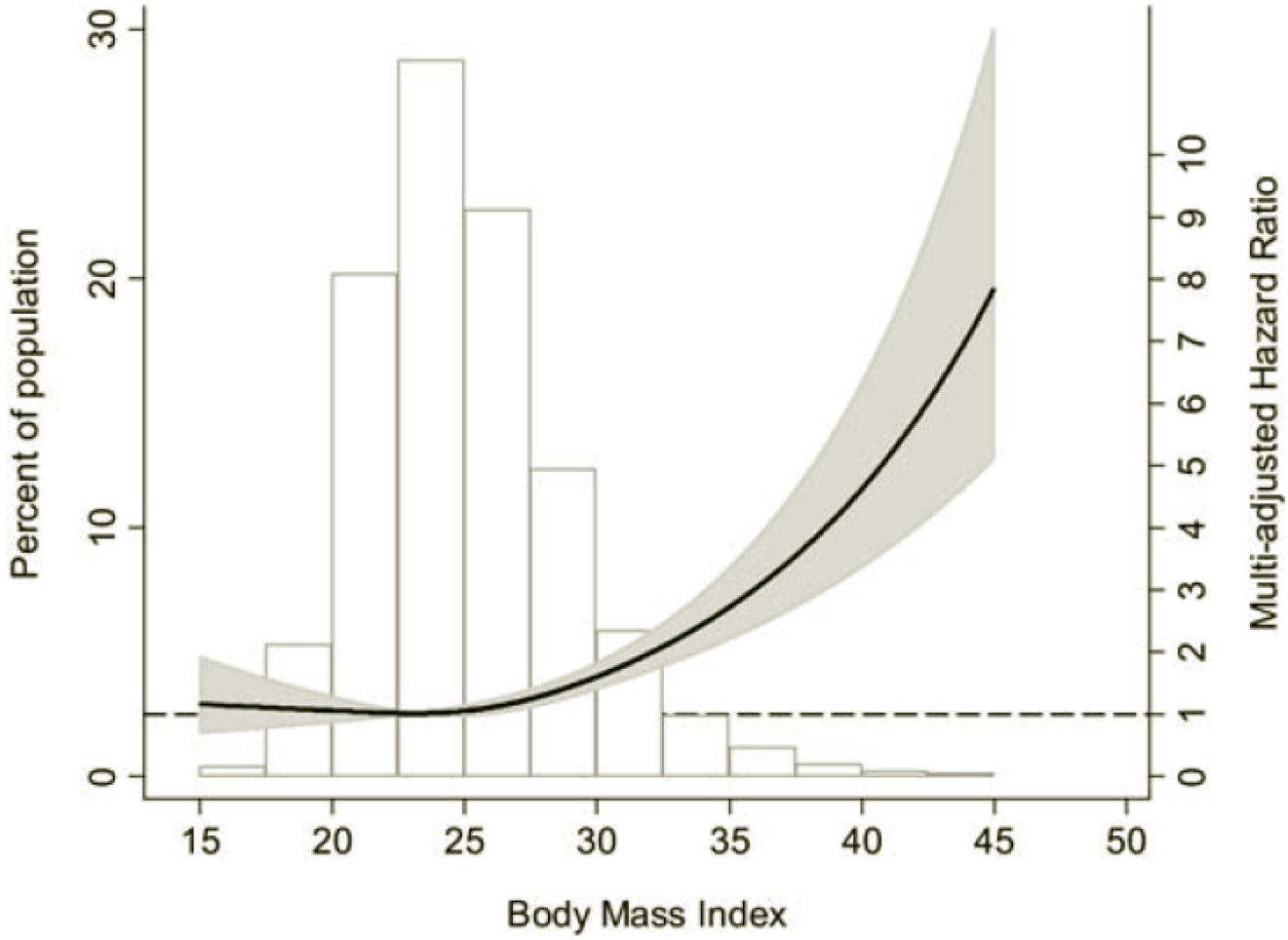

Figure 1.

Left axis and bar graph: Distribution of BMI in the study population of 74,986 adults in the HUNT I Study in Norway. Right axis: Hazard ratio for treated ESRD or CKD-related death by BMI, multi-adjusted for age, gender, smoking status, physical activity, and socioeconomic status. (Adapted from[5]).

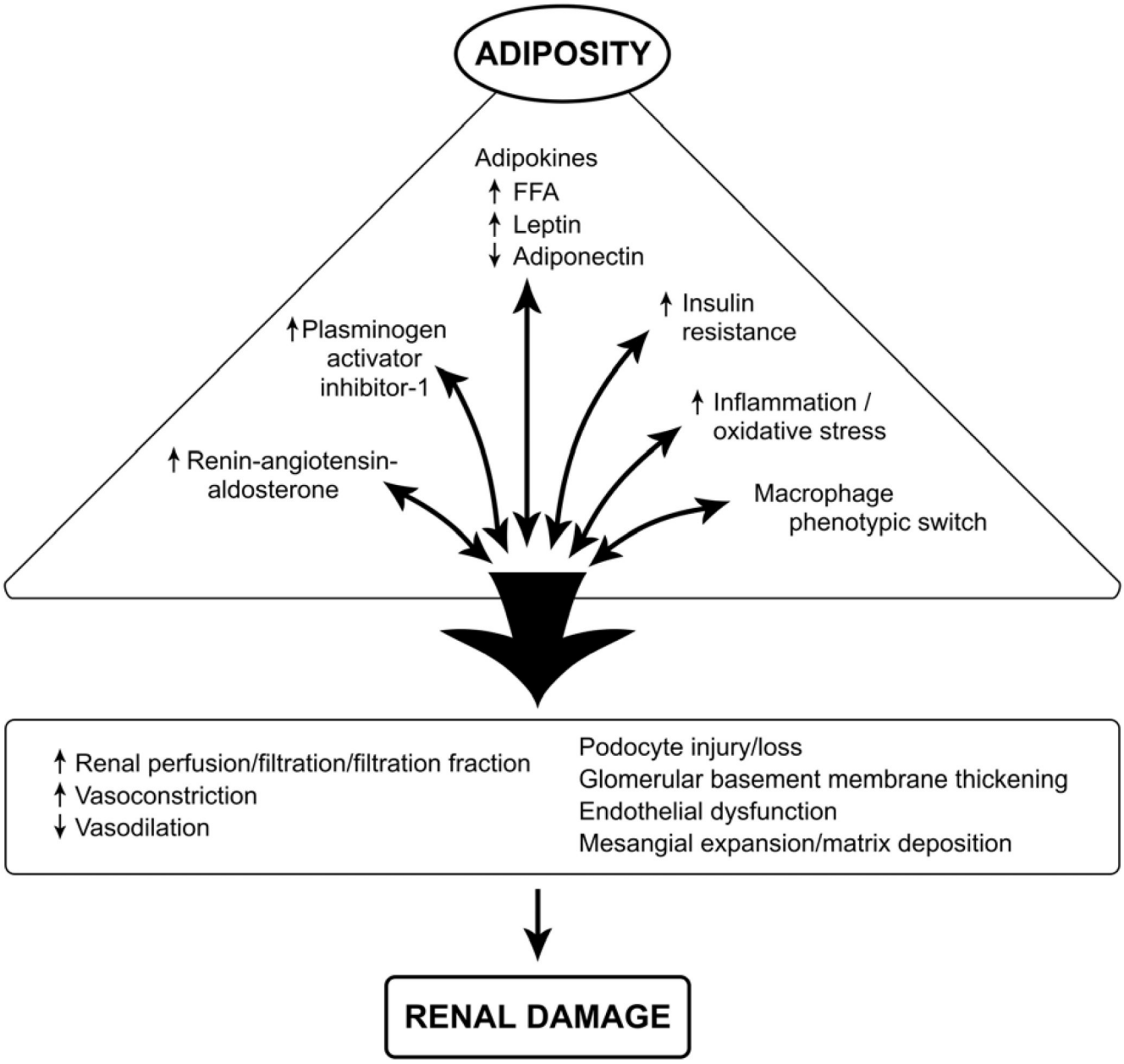

Figure 2.
Mechanisms of obesity related renal disease. Adipose secretes a large number of mediators with impact on renal function and structure, culminating in renal damage.