Chapter 12
Mechanisms for Obesity Related Kidney Disease

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Abstract Obesity is a major cause for the initiation and progression of kidney injury resulting in chronic kidney disease (CKD) and end stage renal disease. High body mass index is a major risk factor for new-onset CKD as well. The well recognized kidney disease secondary to obesity is glomerulopathy. Typical histological features of obesity related glomerulopathy include glomerulomegaly and focal segmental glomerulosclerosis. In obese individuals, excess excretory load induces hyperperfusion and hyperfiltration by the kidneys leading to glomerulomegaly. Lipid accumulation in the kidney which accompanies excessive fat deposition in the body is implicated in the development of CKD. Obesity is associated with metabolic abnormalities in the adipose tissue such as increased free fatty acids, hyperinsulinemia, insulin resistance, pro inflammatory conditions, reduced adiponectin, leptin resistance and activation of the renin-angiotensin-aldosterone system, all of which mediate injury to the cells of glomeruli and tubules leading to CKD. Despite much progress in our understanding of the mechanisms of obesity related kidney disease, several questions about the pathogenesis of nephropathy associated with obesity remain to be answered. Delineating obesity linked factors, which lead to adaptive and maladaptive changes in the kidney and predispose patients to renal disease could lead to identification of molecular targets and reno-protective and therapeutic strategies to improve outcomes for obese patients with CKD.

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Introduction

Obesity is currently an epidemic in developed countries and a global health challenge.
A significant association has been noted between obesity and initiation and pro-
gression of chronic kidney disease (CKD) in population-based studies [1–6]. The
incidence of obesity-related renal disease has increased ten times in recent years.
Prevalence of obesity which is estimated to rise by 40% in the next decade is expected
to result in a parallel escalation in the incidence of obesity related CKD [7, 8].

High body mass index (BMI) is a major risk factor for new-onset CKD [1, 2, 9].
In a study of 75,000 Norwegians, who were followed up for 21 years, increased
BMI was found to correlate with initiation of kidney disease or CKD related
mortality [5]. A 600% increase in end stage renal disease (ESRD) was observed in
those with a BMI more than 40 kg/m^2 in a survey of more than 3 lakhs individuals
enrolled in the Kaiser Permanent Health System between 1964 and 1985 [8, 10].
Obese individuals are at a greater risk for acute kidney injury, for nephrolithiasis
and kidney cancer as well [7].

Until recently, obesity related kidney disease was thought to be linked to obesity
associated hypertension, diabetes and cardiovascular disease, which are all common
causes of renal disease. There is increasing evidence that even without other risk
factors, obesity can initiate kidney disease and also accelerate progression of pre-
existing renal disease [5, 11, 12]. Several obesity-induced disorders are nephrotoxic
[13].

Obesity Related Glomerulopathy

The first record on the link between obesity and massive proteinuria was by
Weisinger et al. [14]. Later, many reports confirmed the association of obesity with
proteinuria, glomerulomegaly and frequently, focal segmental glomerulosclerosis
(FSGS) [15–18]. FSGS is not observed in all cases of obesity related kidney dis-
ease; its presence may depend on the degree of obesity or renal impairment. Among
various sub-types of FSGS, the perihilar variant is more common [17].

In 2001, Kambham and colleagues proposed the term 'obesity-related
glomerulopathy' (ORG) for the microscopic lesions observed in kidney biopsies
from obese individuals [17]. The diagnostic criteria for ORG are: BMI values of
30 kg/m^2 or greater and absence of clinical as well as biopsy evidence of other renal
diseases [17]. The concept of ORG as a nephropathy does not for its diagnosis,
depend on the manifestation of proteinuria. Patients with ORG may also not have

edema [17]. Kambham et al. noted that ORG is less likely than idiopathic FSGS to present with edema or the degree of proteinuria as seen in nephrotic syndrome. ORG is however frequently associated with hypertension and dyslipidemia [17].

Isolated proteinuria of unknown onset with or without renal impairment, is the initial symptom in most cases. Even with relatively high excretion of protein in the urine, hypoalbuminemia may not be present [17]. The mechanism for this remains obscure. Typically, the clinical condition is stable. Alternately, the patient may have slowly progressive proteinuria. Significantly, weight loss can strikingly reduce proteinuria associated with obesity [18, 19]. In 10–33% of patients diagnosed with ORG, long-term outcomes include progression to ESRD [17].

Renal Changes in Obesity

Structural Changes

Much is currently known about the structural and hemodynamic changes in the kidneys of the obese (Table 12.1) [20–23].

Autopsies have revealed an increase in kidney weight in those with a high BMI [22]. Increase in kidney weight may result from hypertrophy of individual nephrons secondary to increased tubular and glomerular functions related to increase in BMI.

Table 12.1 Structural and functional changes in kidney in obesity

A. Structural changes	
1.	Increase in kidney weight
2.	Intra cellular (mesangial and tubular cells) and extracellular lipid accumulation
3.	Glomerulomegaly
4.	Thickening of glomerular basement membrane
4.	Focal segmental glomerulosclerosis
5.	Enlargement of podocyte foot processes
6.	Podocyte detachment
7.	Decreased podocyte density
8.	Increased cross sectional area of tubular epithelial cells
9	Tubulointerstitial damage
10.	Increased microvessels
B. Hemodynamic changes	
1.	Increased glomerular filtration rate
2.	Increased plasma flow
3.	Increased filtration fraction
4.	Afferent arteriolar vasodilatation
5.	Efferent arteriolar vasoconstriction
6.	Disrupted tubuloglomerular feedback

Intracellular or extracellular accumulation of fluid and lipid components may also contribute to a larger kidney.

Glomerular sizes are larger in the obese, even without obvious renal disease [23–25]. There is no unanimity on the definition of glomerulomegaly in ORG. A morphometric study found that in patients with ORG and preserved renal function, when compared to control subjects, the mean glomerular volume is increased about 3-fold [26]. The glomerular capillaries are increased in number. The increase in vascular endothelial growth factor (VEGF) expression in the glomeruli of patients with ORG may contribute to the formation of new micro vessels [27]. Cell proliferation and matrix synthesis could also contribute to glomerular enlargement. Glomerulomegaly is accompanied by a 45% reduction in podocyte density [24]. Thickening of the glomerular basement membrane (GBM) considered as an early manifestation of diabetic nephropathy, is seen with obesity as well. Both glycemic and lipid abnormalities in obesity may contribute to GBM thickening, which may not be as severe as seen in patients with type 2 diabetes.

Obesity-induced glomerular hypertrophy and glomerulomegaly may cause glomerular podocytes to enlarge their foot processes to cover the expanded glomerular surface area. Consistent with this, a relative reduction in the coating area of glomerular podocytes on the glomerular surface is found in patients with ORG [28]. This may cause changes in podocyte function and a consequent loss in protein selectivity, podocyte detachment, and replacement by matrix deposition, leading to FSGS. Incidence of foot process fusion among glomerular podocytes is significantly lower in ORG than in idiopathic FSGS [17].

Focal lipid vacuoles are occasionally seen in the cytoplasm of glomerular mesangial cells and tubular epithelial cells [29]. A study comparing the kidney biopsies from obese patients with proteinuria and biopsies from non-obese patients with proteinuria found a 33% increase in the cross-sectional area of proximal tubular epithelial cells and 54% increase in the lumen of the proximal tubules [30].

Changes in Hemodynamics

Hemodynamics in the kidney is markedly altered by obesity. In obese individuals, there is compensatory hyperfiltration to meet the high metabolic needs of the larger fat mass.

A recent study found that glomerular filtration rate (GFR) is higher in obese adults than in those with normal body weight [30, 31]. Renal plasma flow (RPF) is also increased, though not to the same degree. As a result, the filtration fraction (FF) increases, a hemodynamic adjustment that parallel the degree of BMI and adipose tissue mass. Studies in obese individuals suggest that afferent arteriolar vasodilatation, together with efferent arteriolar vasoconstriction, contribute to the increase in FF [31–34]. By lowering tubular sodium chloride relative to GFR, obesity-dependent mechanisms disrupt the tubuloglomerular feedback (TGF) response, preventing suppression of GFR [35]. Given the high rate of

association of hypertension with obesity, inadequate TGF may result in the transmission of systemic blood pressure to the glomerulus contributing not only to increased GFR but also to structural changes in the kidney [35]. Increase in obesity-induced GFR is not however permanent [36, 37].

The changes in renal hemodynamics found in obesity are closely linked to increased salt sensitivity [38]. Activation of the renin–angiotensin–aldosterone system (RAAS) in the kidney is an important mechanism by which salt sensitivity is increased in obesity [37, 39]. Activation of renal sympathetic nerves may also be involved in the increased salt reabsorption seen with obesity [40, 41]. The glomerulus enlarges in response to increases in GFR, RPF, FF and tubular sodium reabsorption.

Potential Mechanisms of Renal Injury

Kidney disease is initiated with increases in GFR and pressure in glomerular capillaries (P_{GC}), followed by hypertrophy of the glomerulus as well as podocytes [42, 43]. Micro albuminuria ensues and progresses to proteinuria. Mesangial cell proliferation, mesangial matrix expansion, nodular glomerulosclerosis and tubulointerstitial injury contribute to a decrease in GFR culminating in ESRD [44, 45]. The exact mechanisms for obesity associated CKD in humans are not yet completely clear. Current understanding is based upon association studies, cell and animal studies and pharmacological manipulations.

Several obesity-related factors have been implicated in the progression of CKD (Fig. 1). These may act singly or together to cause renal injury. Potential mechanisms are: (i) adverse effects of adaptations to increase in body mass and excretory load, (ii) adverse effects of adaptations to obesity-induced sodium retention [44], (iii) insulin resistance (IR) and progressive hyperglycemia (iv) direct or indirect effects of hyperinsulinemia (v) renal lipotoxicity [46–48] (vi) rise in free fatty acids (FFAs) which may aggravate insulin resistance and (vii) fatty acid/triglyceride accumulation within tissues resulting in cellular dysfunction [49].

The effects of IR, dyslipidemia and oxidative stress are likely to be intensified by dysregulation of adipocytokines such as leptin and adiponectin and proinflammatory cytokines [49]. Resistin, corticosteroids, nutritional status and genetic factors are the other factors implicated.

Excess Excretory Load

Obesity is associated with an excess excretory load resulting from increased body mass and the increased energy intake and tissue turnover required to maintain it. Fat-free body mass also increases in obesity harmonious with functional overload [50]. Organomegaly in obesity includes the kidneys [15]. Chagnac et al. confirmed
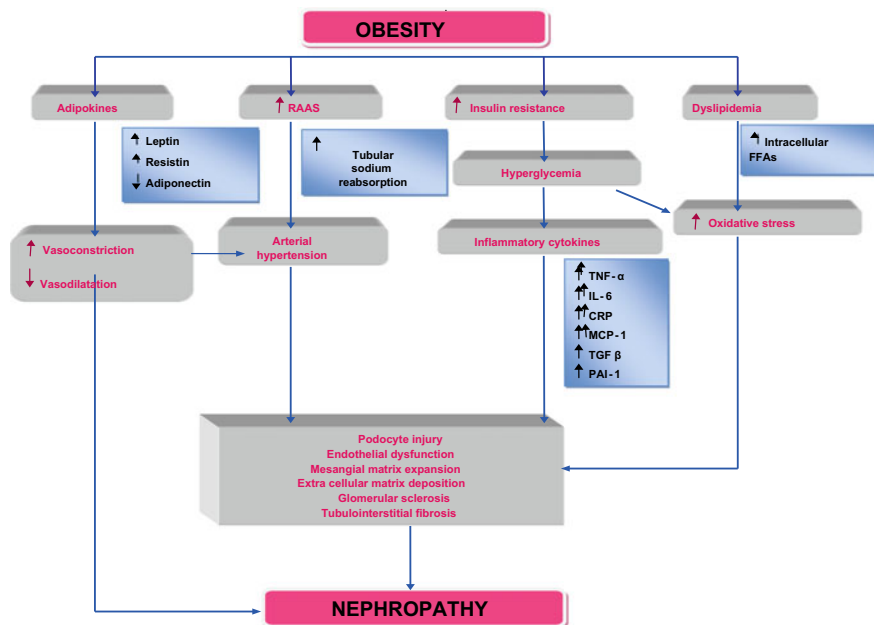
Fig. 1 Mechanisms of renal disease in Obesity. RAAS—Renin-angiotensin-aldosterone system, FFAs—free fatty acids, TNF—tumor necrosis factor, IL—interleukin, CRP—C reactive protein, MCP—monocyte chemo attractive protein, TGF—transforming growth factor, PAI—plasminogen activator inhibitor

a 51% increase in renal perperfusion and 31% increase in filtration in severe obesity [33]. The reduced renal resistance with increased FF is compatible with glomerular capillary hypertension [33], a perfect setting for future glomerulosclerosis. Obesity induces single-nephron adaptations typical of the reduced nephron number accompanying CKD.

Adverse Adaptations to Excess Retention of Sodium

Hall et al. proposed that in obesity, there is reduced capacity for sodium excretion, acting at sites proximal to the macula densa through Ang II and sympathetic activation. The reduced sodium chloride delivery to the macula densa site induces afferent vasodilation and renin release to produce compensatory glomerular hyperfiltration, thus restoring normal distal delivery [46]. Thomson et al. considers a mechanism similar for the increase in proximal tubular sodium reabsorption induced by hyperglycemia seen in diabetes [42]. The result is intraglomerular hypertension and proteinuria which form the final common pathway for chronic glomerular and tubular injury, as with excess excretory load induced hyperfiltration.

Hypertension

Hypertension is common in obesity and may be due to a range of factors including sympathetic nervous system activation and angiotensinogen release from adipose tissue [36].

The rise in blood pressure may damage microvasculature within the kidney through intensified RAAS activity. Ang II excess in the kidney can enhance renal injury through proinflammatory mechanisms and can also promote proteinuria-related renal damage [49].

The Role of Adipose Tissue

Adipose tissue is a highly active endocrine organ involved in the clearance and storage of fatty acids, regulation of energy homeostasis and metabolism, insulin function and inflammatory processes. Adipose tissue is involved in progression of diseases associated with metabolic dysfunction [51–56]. Increased fat deposition in obesity also correlates with renal injury [29].

Obesity is a chronic low-grade inflammatory condition, in which adipose tissue serves as the source of inflammatory cytokines [57]. Visceral adipose tissue produces less adiponectin and more of pro-inflammatory cytokines, including tumor necrosis factora (TNF-α) and interleukin-6 (IL-6), which can induce IR and promote endothelial dysfunction [58].

There is in obesity, lipid accumulation in the kidney suggesting a role for fat accumulation in the organ for the development of CKD [59–62]. Visceral fat elaborates bioactive substances which contribute to the abnormal hemodynamic and structural changes leading to obesity-related nephropathy. Visceral adipose tissue mediates obesity-related disease through production of pro-inflammatory cytokines (adipokines) and causing IR [63]. Adipocytes secretes angiogenic factors as well and thus can facilitate vasculogenesis locally and in distal organs [64]. In a study using obese Zucker rats, in parallel with intrarenal inflammation, significant increases in the density of cortical and medullary microvascular was found [65].

Adipocytes contain adipocyte-specific metabolites such as free fatty acids, leptin, and adiponectin and all the components of the RAAS, plasminogen activator inhibitor (PAI), all of which affect renal structure and function. In addition, fat is infiltrated by macrophages that can alter their phenotype and foster a proinflammatory environment which in the kidney, advances pathophysiologic changes associated with obesity. Adipose tissue of patients with ESRD has elevated levels of the pro-inflammatory cytokines TNF-α and monocyte chemoattractant protein-1 (MCP-1) and more infiltration of macrophages [66]. Elevated levels of pro-inflammatory cytokines or chemokines (TNF-α, IL-6, IL-1β, MCP-1) and infiltrated macrophages in the adipose tissue correlate with renal inflammation in obese rodents [67].

Metabolic Factors

Altered fatty acid and cholesterol metabolism is responsible for ipid accumulation, inflammation, oxidative stress and fibrosis in the kidney [68]. BMI seems to determine the degree of accumulation of triglycerides in the human renal cortex [69]. Triglyceride accumulation is seen in both glomerular and tubular cells, more in proximal tubular cells [69].

Lipid disturbances in obesity appears to directly involve in renal damage. Young C57BL/6 mice fed a high fat diet (HFD) have increased body weight, and elevated blood levels of glucose, insulin, triglycerides and cholesterol and lower circulating adiponectin. Proteinuria, glomerulomegaly, expanded mesangial matrix, thickened glomerular basement membrane and podocyte effacement have been observed in these mice [59]. There is evidence that lipid moieties can injure mesangial cells. Low density lipoprotein (LDL), oxidized LDL, and glycated LDL, at levels observed in blood significantly increase synthesis of mesangial matrix components, fibronectin and laminin [70]. Lipid moieties also stimulate production of macrophage migration inhibitory factor in mesangial cells and expression as well as release of inflammatory activators, CD40 and IL-6 [70]. Renal toxicity and proteinuria in mice with hyperlipidemia can be attenuated by treatment with anti-IL-6 monoclonal antibody [71].

Lipids also damage podocytes [28]. Oxidized LDL decreases phosphorylation of AKT, involved in cell survival and can thus contribute to nephrin loss and podocyte apoptosis [72, 73]. In podocytes cultured with palmitate, there is increase in the synthesis of ceramide resulting in reduced insulin-stimulated glucose uptake [74]. Thus, lipid abnormalities may interact with changes in glucose metabolism to actuate nephropathy.

Normal insulin/phosphatidylinositol 3-kinase/AKT and mTOR signalling are critical for podocyte hypertrophy and adaptation. Adipokines and lipid stores in the kidney result in IR in podocytes and maladaptive responses, to cope with the mechanical forces of hyperfiltration [68].

Sterol regulatory element binding protein-1 (SREBP-1) also seem to play a role in the damage to the kidney from lipid accumulation and ensuing inflammatory and fibrotic responses [75, 76]. The effects of HFD on the kidney were not seen in SREBP-1c −/− mutant mice, while SREBP-1a transgenic mice had lipid deposition in the glomeruli, glomerulosclerosis and albuminuria. In patients with ORG, expression of SREBP-1 in the glomeruli is up-regulated [27].

Adipokines

Visceral fat releases into the circulation a large number of adipocytokines with autocrine, paracrine and endocrine activities, which contribute to the pathogenesis of renal injury [77].

The secreted peptides include leptin, adiponectin, resistin, TNF-α, IL-6 and components of the RAAS such as angiotensinogen, ACE and ATII-1R as well as

VEGF, MCP-1, RBP-4 and TIMP-1. There is a positive correlation between increase in adipose tissue and elevated inflammatory markers [78]. Axelsson et al. 2004 observed a positive relationship between truncal fat mass and inflammation in patients with ESRD [79]. Adipose tissue also has macrophages and immune cells which secrete pro-inflammatory cytokines. The link between dysfunctional adipose tissue in obesity and raised proinflammatory adipocytokine patterns, systemic inflammation, IR and cellular dysfunction, is well recognized [49]. Be that as it may, role of this link in the pathogenesis of CKD is not well elucidated.

Leptin

Leptin levels rise in response to increase in fat mass. Elevated leptin levels in obese individuals correspond to the fat stores. Central hypothalamic resistance to leptin may also be present in the obese. Leptin has immuno-regulatory and proinflammatory actions in the obese [80].

In patients with obesity, leptin levels rise and there is leptin resistance during the initial stages of development of CKD [81]. When CKD progresses, reduced renal clearance of leptin contributes to hyperleptinemia and is associated with concomitant inflammation [82, 83].

Mice overexpressing leptin have more renal disease than leptin deficient mice [84]. Long-term infusion of recombinant leptin in rats is associated with proteinuria, increased expression of extracellular matrix proteins (collagen type IV), TGF-β and other pro-inflammatory cytokines, macrophage infiltration and glomerulosclerosis [85]. These observations indicate that leptin promotes renal injury in obese subjects. Despite severe obesity, renal dysfunction is not seen in the absence of leptin or mutation in the leptin receptor gene [13].

Adiponectin

Adiponectin (also called Acrp30), one of the most abundant adipokines produced by the adipocytes is down-regulated in obesity and type 2 diabetes [86]. Low adiponectin levels is linked to inflammation, atherosclerosis, IR, and raised blood pressure [87]. Endothelial cell dysfunction, impaired endothelium-dependent vasodilation, enhanced leukocyte-endothelium adhesion and activation of RAAS have been found in both humans and experimental animals with decreased levels of adiponectin.

Adiponectin is also known to aid the normal function of the podocyte [88]. In hypoadiponectinemia, function of podocytes in maintaining glomerular filtration breaks down causing glomerular damage and sclerosis. Glomerulomegaly, collagen deposition in glomeruli, loss of podocyte foot processes, increased TGF-β, and albuminuria have all been observed in adiponectin null mutant mice [89]. Adiponectin restitution reverts podocyte effacement and albuminuria. This benefit is attributed to reduction in oxidant stress [88, 90]. Adiponectin deficiency can also

lead to increased NADPH oxidase activity and a rise in the levels of reactive oxygen species.

Adiponectin is an insulin-sensitizing factor as well and has also anti-inflammatory effects. Reduced plasma adiponectin level is inversely correlated with IR in obese patients [88, 89]. Though obese subjects have consistently low circulating adiponectin levels, in patients with CKD due to obesity, adiponectin levels are increased, possibly because of renal dysfunction [90, 91].

The role of adiponectin in obesity-related disease has been extensively investigated using transgenic mice or pharmacological globular Acrp30 compound [92–96]. Adiponectin is an important regulator of lipid and glucose metabolism and a key link among TNF-α, MCP-1, and IR.

Effects of adiponectin are tightly linked to the activation of AMP-activated protein kinase (AMPK) [88, 97]. Obesity is known to modulate the activity of AMPK. Steinberg et al. demonstrated that TNF-α could suppress AMPK activation through the TNF receptor 1 (TNFR1), suppress fatty acid oxidation and promote IR in skeletal muscle [98]. How TNF-α inhibits AMPK activation is unclear. Steinberg et al. showed that this process might involve the upregulation of protein phosphatase 2C (PP2C) by TNF-α. Treatment with TNF-α increases PP2C activity and decreases AMPK activation in WT mice but not in the transgenic ob/ob TNFR$^{-/-}$ mice. This change is also accompanied with a reduction of fatty acid oxidation and an increase of diacylglycerol (DAG) and triacylglycerol (TAG) in skeletal muscle [103]. AMPK activation reduces TNF-α and increases adiponectin levels in human adipose tissue, improving insulin sensitivity [99]. A decrease of adiponectin and AMPK activation is also associated with increase in the levels of MCP-1 in human adipocytes [100].

Recently, a role for AMPK in regulating macrophage infiltration and activation has been proposed [101]. AMPK activation completely reverses HFD induced infiltration of macrophages in the kidney [62]. AMPK activation is also a key regulator of lipid accumulation in vacuolated proximal tubular cells, maintenance of integrity of the brush border, as well as nitrotyrosine and NOX4 levels. These findings suggest that AMPK activation may have a role in tubular dysfunction [62].

Macrophage Infiltration of Adipose Tissue and Phenotype Switch in Macrophages

There are evidences for macrophage influx in adipose tissue of obese humans and animal models of obesity [102–104]. Macrophage infiltration of adipose tissue results in inflammation and IR [102, 103]. Obesity induces a phenotype switch in macrophages [105–108]. In lean rodents, M2 phenotype, involved in the resolution of inflammation and tissue repair are predominant; proinflammatory M1 macrophage population is dominant in obese animals [106]. Macrophages that infiltrate the adipose tissue are a source of a large number of proinflammatory mediators such as TNF-α, IL-6, C-reactive protein (CRP), MCP-1 and macrophage migration inhibitory factor [109]. Inhibition of proinflammatory macrophages reduces kidney

injury [110–112]. There is indication from animal experiments that macrophage AT1 receptor may mediate macrophage polarization [113].

Adiposity-Driven Proinflammatory Cytokines

Inflammation markers are inversely associated with measures of kidney function and positively with albuminuria [114]. Thus, there is a strong evidence for the contribution of inflammation in obesity associated renal disease.

Rapid expansion of adipose tissue results in an altered synthesis of pro-inflammatory adipokines which leads to a state of low-grade inflammation [115]. Among the large number of pro-inflammatory adipokines, TNF-α is one of the most critical mediators of adipose tissue inflammation and development of IR [116, 117].

Fatty acids released by adipocytes promote TNF-α release by macrophages which, in turn, increases IL-6 production in fat cells and thus an inflammatory milieu in both adipose tissue and kidney [82]. TNF-α is an important mediator of progressive renal fibrosis. Gene expressions of both TNF-α and its receptors, as well as IL-6, a signal transducer are seen increased in glomeruli of patients with ORG and indicates the importance of TNF-α and IL-6 in development of ORG [27].

A rise in TNF-α levels is generally associated with increased production of MCP-1 by both adipocytes and macrophages. MCP-1 is also a key mediator of both adipose tissue inflammation and development of IR [117–119]. The mediatory role of MCP-1 and its receptor CCR2 in chronic kidney disease has recently received much attention [120]. In human podocytes, MCP-1 regulates nephrin expression via CCR2 [121]. Studies in mesangial cells have revealed that palmitate stimulates marked secretion of MCP-1 indicating that in obesity, circulating saturated fatty acids, such as palmitate may trigger production of MCP-1 [61].

The major source of pro-inflammatory cytokines that directly contribute to renal injury in obese subjects are the infiltrated macrophages [84]. In addition, renal parenchyma also releases proinflammatory cytokines in response to hyperglycemia or locally active vasoactive peptides such as Ang II [122]. These mediators produce low grade chronic inflammation and participate in the pathogenesis of ORG. TNF-α has been shown to reduce the expression of key components of the slit diaphragm, nephrin and podocin, thus contributing to podocytopathy [78]. IL-6 promotes expression of adhesion molecules and oxidative stress [123].

Insulin Resistance

Insulin resistance (IR) is a common accompaniment of obesity and related metabolic syndrome [124, 125]. In obese rodents and humans, inflamed adipose tissue is known to contribute to development of IR [124, 126]. IR is a salient metabolic risk for CKD [127]. Many studies indicate the association between IR and CKD. This association is seen even before the onset of diabetes [128, 129].

The direct link between adipose tissue dysfunction and associated IR with obesity related kidney disease is presently more evident. The low adiponectin levels in obesity is associated with reduced insulin sensitivity, which leads to a pro-inflammatory state in the kidney [130].

In the captive rhesus monkey with spontaneous obesity, glomerular hypertrophy appears in the prediabetic hyperinsulinemic phase; hyperglycemia, hypertension, renal dysfunction, and increase in mesangial matrix deposition are absent at that stage [131].

Insulin, although a weak vasodilator, augments endothelial-dependent vasodilation. Hyperinsulinemia can contribute to preglomerular vasodilation, glomerular hypertension and increase in glomerular capillary permeability [132, 133]. Structural damage is not manifest during this period. Hyperinsulinemia may induce glomerular hypertrophy either directly or by stimulating the IGF-1 receptor [134]. Hyperinsulinemia can also augment Ang II contraction of glomerular mesangial cells [135]. Abrass et al. demonstrated that high-dose insulin stimulates expression of inflammatory collagens in renal mesangial cells in culture [136]. They also found that the altered gene expression after exposure to high insulin is not reversible by later withdrawal of insulin [137, 138].

Walsh et al. through a study in transgenic mice missing insulin receptors in their podocytes, have elucidated the critical role of insulin signaling in normal podocytes [139]. They showed that these mice have normal glomeruli when they are at their early age (three weeks old), but later starting at the age of 5 weeks, have loss of podocyte foot processes, increased glomerular matrix and albuminuria [139].

Free Fatty Acids (FFA) might also contribute to IR [74]. Increased FFA flux from excess adipose tissue to non-adipose organs results in lipid accumulation in ectopic organs including the kidney. Lipid stores later advances impairment of glucose metabolism and insulin sensitivity in these organs. This adverse effect is associated with an increase of ceramide, a highly lipotoxic molecule, that is related to IR [140]. In addition, a dysregulation of the insulin receptor and the impairment of recruitment of the glucose transporter GLUT4 to the cell surface have been noted with FFA increase [74].

Though there are evidences for considering IR as a driver of the renal disease in obesity, how critical is IR for progression of the disease is still unclear.

There are many similarities between the 'obese' and 'diabetic' kidney; there are also features unique to obesity sans diabetes. Kidneys of obese individuals frequently have lipid deposits (foam cells) in glomeruli and mesangium. This is an evidence for the concept that renal injury is caused by lipotoxicity. Lipid accumulation in the glomerulus may result in the upregulation of SREBP-1 and 2 and promote podocyte apoptosis, mesangial cell proliferation and cytokine synthesis [140].

Vasoactive Peptides

Several vasoactive peptides have been implicated in the pathogenesis of OGR. There is upregulation in the intrarenal RAAS in obesity [141, 142]. Activation of the RAAS leads to both hemodynamic and cellular effects. Ang II leads to increases in efferent arteriolar vasoconstriction and glomerular pressure, sodium retention and cell proliferation [143–145]. In cells, Ang II activates protein kinase C (PKC), MAP kinase (MAPK) and transcription factors such as nuclear factor-κB. Their activation leads to alteration in the expression of genes of a number of growth factors and cytokines. Increase in TGF-β promotes podocyte apoptosis, mesangial cell proliferation and extracellular matrix synthesis, cellular events that are important in the development of obesity- and diabetes-associated glomerulopathy [146].

Renin-Angiotensin-Aldosterone System (RAAS)

Adipose tissue has all the components of the RAAS system. RAAS is activated in the adipose tissue of the obese [147, 148]. In obese adipocytes, production of angiotensinogen, aldosterone, and aldosterone-stimulating factor is increased [149–151]. In obese individuals, the RAAS is activated in renal tissue as well, resulting in increase in sodium reabsorption through many mechanisms [152–154]. Activation of the RAAS in the kidney, especially of aldosterone and or its receptor, is likely to play a major role in the development of kidney injury and proteinuria associated with obesity. Hyperglycemia and angiotensin II are known to upregulate the expression of sodium glucose co-transporter (SGLT-2) [155, 156]. Thus, in obesity, in which both hyperglycemia and RAAS activation occur, renal tubular reabsorption of glucose may be increased via upregulation of the expression of SGLT-2.

RAAS is a major regulator of vasomotor tone and cellular proliferation and thus regulates renal function and structure. Adipocytes and adipose-infiltrating macrophages are important sources of RAAS [157]. Circulating levels of angiotensinogen (Aog) increase with increasing BMI [158]. Adipose-derived increase in circulating RAAS ligands together with adipose-driven increase in renal AT1 is a potent alliance for efferent arteriolar vasoconstriction, to increase glomerular pressure and FF, as well as cellular proliferation and thus culminate in renal damage [159, 160]. There are also evidences to suggest that AT2 may mediate the substantial adipose inflammatory response associated with increased Aog [161].

Aldosterone blockade reduces renal injury. This benefit is independent of its antihypertensive effects and possibly relates to the blocking effects of aldosterone on PAI-1 and TGF-β, reactive oxygen intermediates, inflammatory mediators, and podocyte function [162–164]. Adipose tissue produces aldosterone independent of AngII as well. At least one oxidized derivative of linoleic acid is known to stimulate aldosterone synthesis [165]. Complement-C1q TNF-related protein 1 (CTRP1), prominently expressed by adipose tissue may also mediate Ang II-independent aldosterone production [166]. Thus, elevated aldosterone in obesity could be

injurious to glomeruli through its indirect action which increases GFR and also through its direct effects on the podocyte.

Plasminogen Activator Inhibitor-1 (PAI-1)

Obesity induces PAI-1 in adipose tissue and glomerular cells. PAI-1 is an independent risk factor for renal damage. PAI-1 can decrease protease-dependent matrix degradation and cellular migration [167]. In a model of podocyte injury-associated glomerulosclerosis, renoprotection by PPAR-γ agonist is partially through reduced PAI-1 [168]. PAI-1 modulates podocyte injury as well. Ablation of the kidney in PAI-1 deficient mice caused less of proteinuria, podocyte damage and glomerular sclerosis [169].

Several mechanisms involved in obesity-related organ dysfunction are concomitant. IR is linked to increased levels of Ang II, which is associated with the progression of renal damage in obesity. Indeed, Angiotensin II is an important mediator in the progression of obesity related kidney disease [170–172]. Angiotensin II contributes to hyperfiltration and glomerulosclerosis through both hemodynamic and non-hemodynamic effects [18, 173–175]. ANG II produces vasoconstriction while insulin induces vascular relaxation by promoting NO production through the phosphatidylinositol 3-kinase (PIK3-Akt) signaling pathway [176]. The inhibitory effects of ANG II on the insulin action is mediated by production of reactive oxygen species (ROS) [177, 178]. In turn, ROS induces inflammatory cytokines such as MCP-1 or TNFα which can then impair the PI3K-Akt pathway of insulin signaling, resulting in IR [116, 179, 180].

Factors Which Increase Susceptibility for Renal Injury in the Obese

Severity of renal impairment does not always correlate with the severity of obesity. Considerable differences in susceptibility to renal injury have been noted among obese individuals and are possibly related to other predisposing factors (Table 2).

Obesity is a risk factor for type 2 diabetes, hypertension and other components of the metabolic syndrome as well as cardiovascular disease. All of them add to the risk for CKD in obese individuals. Each component of MetS (impaired glucose tolerance, hypertension, and dyslipidemia) can induce kidney injury and may also exacerbate pre-existing kidney disease [181]. Combinations of components synergistically increase the risk for CKD, and the risk of progression of pre-existing CKD [182]. The odds ratio for kidney disease is 1.89 when only one component of MetS is present, leaping to 5.85 when all five components of MetS are present together in an individual [183, 184]. A meta-analysis of eleven studies [185] involving 30,146 subjects revealed that MetS is associated with development of

Table 2 Predisposing factors for renal injury in obesity

1. Type of obesity type: Visceral fat obesity
2. Components of metabolic syndrome: impaired glucose tolerance, hypertension, dyslipidemia
3. Associated conditions: sleep apnea syndrome, pulmonary hypertension and right ventricular overload, nonalcoholic fatty liver disease
4. Decrease in nephron number: low birth weight, intra-uterine growth retardation, preterm birth
5. Reduced nephron mass: congenital anomalies of the kidney and urinary tract, nephrectomy
6. Progressive loss of functioning nephron: chronic kidney disease of any cause, aging

Adapted from Tsuboi N, Okabayashi Y, Shimizu A and Yokoo T. The renal pathology of obesity. *Kidney International Reports* 2:251–260, 2017

Stage III CKD with an odds ratio (OR) of 1.55 (95% CI: 1.34–1.80) [185]. Global as well as segmental glomerulosclerosis are seen in those with MetS. There is also a higher prevalence of tubular atrophy, interstitial fibrosis, and arterial sclerosis [186].

Interestingly, in comparison to normal subjects, patients with obesity related kidney disease have a significantly lower glomerular density as seen in kidney biopsies [26]. Aging related decreases in the number of glomerular podocytes can also greatly influence susceptibility to renal injury in obese individuals [187].

In obesity, nephron overwork and risk of intraglomerular hypertension would be exaggerated in those with intra uterine growth retardation and those who have had unilateral nephrectomy, as they have already a lower nephron number [188, 189].

Pulmonary hypertension secondary to sleep apnea and non-alcoholic fatty liver disease which commonly accompany obesity may also catalyze renal injury associated with obesity [190, 191].

Conclusions

Obesity is a major cause for the initiation and progression of renal injury resulting in CKD and ESRD. Many factors together cause renal vasodilation, glomerular hyperfiltration and albuminuria, leading to glomerulopathy. In obese individuals, excess excretory load induces hyperperfusion and hyperfiltration by the kidneys leading to glomerulomegaly. Obesity associated metabolic abnormalities such as increased FFA, hyperinsulinemia, IR, pro inflammatory conditions, reduced adiponectin, and leptin resistance mediate injury to glomerular and tubular cells and lead to CKD.

To a large extent, both obesity and related CKD can be prevented by following a healthy lifestyle. Renin-angiotensin-aldosterone blockade is effective in the

short-term. SREBP antagonists, PPARα agonists, FXR and TGR5 agonists and LXR agonists directly target lipid metabolism and hence are considered to have therapeutic value. Delineation of obesity linked factors, which lead to adaptive and maladaptive changes in the kidney and predispose patients to renal disease could lead to identification of molecular targets and reno protective and therapeutic strategies to improve outcomes for obese patients with CKD.

Several questions about the pathogenesis of nephropathy associated with obesity remain to be answered. Whether glomerulomegaly is a cause or only an associated feature of proteinuria in ORG is unclear. Whether glomerulomegaly is a precursor of obesity-related FSGS lesion is also obscure. Whether genetic factors have any role in determining the time of onset and the rate of progression of kidney disease in obese subjects is also unknown.

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