



Obesity related Glomerulopathy

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ABSTRACT

Obesity is a major risk factor for renal disease and can cause de novo glomerulopathy. The characteristic finding of obesity-induced renal injury includes glomerular hypertrophy, glomerular basement membrane thickening, mesangial matrix expansion, and increased renal inflammation. These changes may lead to albuminuria, a progressive impairment of renal function, glomerulosclerosis and tubulointerstitial fibrosis. The mechanisms of obesity-related glomerulopathy (ORG) are not well understood however, several mechanisms acting singly or in combination have been suggested as excess excretory load, excess renal sodium retention and insulin resistance (IR) and hyperinsulinemia, increased monocyte chemoattractant protein 1 (MCP-1) expression, Lipotoxicity in proximal tubular cells, increased inflammatory cytokine production such as Interleukin (IL) IL-6, IL-1, and tumor necrosis factor (TNF- α). Activation of NF κ B transcription, increase Leptin levels, reduction in plasma adiponectin expression with its anti-inflammatory effects, decrease nitric oxide (NO) level, increase reactive oxygen species (ROS) generation, Hypertlipidemia, and increases in plasma renin activity, angiotensinogen, angiotensin-converting enzyme activity, and circulating AngII. Many lines of treatment are suggested for ORG as Peroxisome proliferator-activated receptors (PPAR) Agonistic, Statins, anti-inflammatory therapy, and antioxidants are under trial. Weight loss decreases of proinflammatory factors, increase of anti-inflammatory molecules and reduces oxidative stress state in obesity, which may protect renal function. This review discusses recent data about ORG, the characteristics of pathogens and possible interventions to prevent kidney injury in obesity.

Keywords: obesity, insulin resistance, inflammation, cytokines

INTRODUCTION

Obesity is considered a major risk factor for the development of chronic diseases and mortality (1). Overweight and obesity are the fifth leading risk for global deaths. Overall, more than one in ten of the world's adult population was obese (2). Metabolic syndrome identifies the common cluster of metabolic abnormalities, defined as three or more of five criteria: 1) abdominal obesity (waist circumference, >102 cm in men and >88 cm in women), 2) hypertriglyceridemia ≥ 150 mg/dl, 3) low HDL <40 mg/dl in men and 50 mg/dl in women], 4) hypertension $\geq 130/85$ mm Hg, and 5) elevated fasting glucose ≥ 110 mg/dl (3, 4). Obesity is an important risk factor for chronic kidney diseases (CKDs). Obesity increases the risk for chronic kidney disease (CKD) 4-fold and considered as the second highest predictive factor to predict end stage renal diseases (ESRD) now even independent of diabetes and hypertension. Subsequent studies confirmed that obesity could induce renal injury, namely obesity-related glomerulopathy (ORG). The clinical characteristics of ORG manifest with nephrotic or subnephrotic proteinuria, accompanied by renal insufficiency. Experimental and clinical studies have revealed that the characteristic features of obesity-induced kidney injury include glomerular hypertrophy, glomerular basement membrane thickening, expansion of mesangial matrix, and increased renal inflammation (5, 6). These alterations may lead to albuminuria, a progressive decrease in renal function, glomerulosclerosis and tubulointerstitial fibrosis (7).

Weisinger et al. 1974, (8) first reported massive proteinuria associated with obesity; which can be strikingly reduced by weight loss. Subsequent reports have consistently confirmed the presence of glomerulomegaly and proteinuria in obesity, often with focal segmental glomerulosclerosis (FSGS) (9). An autopsy study of 22 kidneys of obese subjects: glomerulomegaly was a consistent feature and FSGS was present in seven (10). Seventy-one renal biopsies from obese patients (BMI 30 kg/m²) were compiled from 6818 consecutive biopsies over 10 years;

all were associated with glomerulomegaly, and proteinuria (48% nephrotic range). The histological types identified were FSGS and glomerulomegaly. The obese FSGS group differed from classic idiopathic FSGS (50 in a comparison group) via the concomitant presence of glomerulomegaly, less severe proteinuria, less podocyte injury, less hypercholesterolemia, and more progression that is indolent. The 14 proteinuric obese patients who exhibited only glomerulomegaly on biopsy, suggesting the possibility that glomerular hypertrophy alone in hyperinsulinemic obesity may be associated with macroproteinuria (11). It is unknown whether glomerulomegaly is a cause or simply an associated feature of proteinuria in ORG. However, the actual mechanisms underlying the association between obesity and progressive renal disease are not well understood.

Mechanisms of Renal Injury in obesity: Several mechanisms acting singly or in combination has been suggested (12).

Excess Excretory Load

Obesity is associated with an excess excretory load due to increased body mass, increased energy intake and tissue turnover (10). Chagnac *et al.* (13) confirmed renal hyperperfusion and hyperfiltration in severe obesity, averaging 51 and 31% increases, respectively. The decreased renal resistance with increased filtration fraction was compatible with afferent dilation and glomerular capillary hypertension (13). Obese individuals have been shown to have an increase in glomerular filtration rate (GFR) by about 50% above lean subjects. Elevated GFR lead to an increase in filtration fraction, indicating afferent arteriole vasodilatation that can result in renal hyperfiltration, increased glomerular capillary pressure, and glomerular injury. A high filtration fraction results in an increase in NaCl reabsorption because of increased post-glomerular pressure. Increased NaCl reabsorption and decreased NaCl delivery to the macular densa causes

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tubuloglomerular feedback to further propagate glomerular hyperfiltration (10).

Excess Renal Sodium Retention

Hall *et al.* (12) proposed that, reduced NaCl delivery to the macula densa site induces afferent vasodilation and renin release to produce compensatory glomerular hyperfiltration and restoring normal distal delivery. As with hyperfiltration driven by excess excretory load, the following intraglomerular hypertension and proteinuria represent the final common pathway leading to chronic glomerular and tubular injury. The kidney in obesity has the hemodynamic equivalent of CKD (12).

Hyperinsulinemia

Insulin plays a homeostatic role in normal kidney function and has direct dose-dependent dilator effects on the renal microvasculature. Obesity has been linked directly with the development of insulin resistance (IR) due to increased free fatty acid release, which inhibits glucose transport directly and lead to the phosphorylation of serine/threonine sites on insulin receptor substrates, leading to reduction in glucose transport as well as increased adipokine production (13). IR lead to increased production of insulin and hyperinsulinemia, hyperglycemia, and ultimately type 2 diabetes (T2DM). Obesity and IR are associated with endothelial dysfunction, inflammation, and microalbuminuria which contribute to the pathogenesis of renal injury via a number of mechanisms (7). In the rhesus monkey with spontaneous obesity, glomerular hypertrophy appears in the hyperinsulinemic phase in the absence of hyperglycemia, hypertension, renal dysfunction, or increase in mesangial matrix deposition (6). Insulin augments endothelial dependent vasodilation thus, hyperinsulinemia could contribute to preglomerular vasodilation and glomerular hypertension (12). In addition, hyperinsulinemia may induce glomerular hypertrophy by stimulating the insulin-like growth factor 1 (IGF-1) receptor which induce vasodilation and increase glomerular capillary permeability (14).

Hyperinsulinemia could interact with elevated intrarenal angiotensin II (Ang II) levels to augment Ang II contraction of glomerular mesangial cells (15). Abrass *et al.* (16) showed that high dose insulin on renal mesangial cell culture, stimulating expression of inflammatory collagens typical of the diabetic phenotype and treatment of normal rats with insulin was associated with glomerular hypertrophy, new expression of interstitial collagens, and glomerulosclerosis. Hyperinsulinemia can cause cell proliferation and renal injury by promoting the expression of transforming growth factor (TGF) β in proximal tubular cells, which promote renal fibrosis and the down regulation of matrix metalloproteinase (MMP)-2, an enzyme responsible for matrix degradation (11).

Lipotoxicity

Advanced stages of intracellular lipid overload are marked with the intracellular synthesis of excess fatty acids (FA) that can induce cell damage: e.g., diacylglycerol, and ceramide. Diacylglyceride enhances protein kinase C (PKC) activities; while, ceramide is a major candidate mediator of apoptosis (17). Lipotoxicity can impair function of liver, skeletal muscle, cardiomyocytes, pancreatic cells and endothelial cells and reduces cell mass via apoptosis (18). Lipotoxicity in proximal tubular cells with its associated tubulointerstitial inflammation is now a recognized consequence of heavy proteinuria because of accumulation of excess albumin-bound free FA (19). Therapeutic lowering of free FA could improve proteinuria-associated proximal tubular lipotoxicity and tubulointerstitial nephritis. Oxidative stress is another mechanism of free FA toxicity, where reactive oxygen scavengers block free FA-induced apoptosis in vitro (17).

Inflammatory Cytokine

Obesity is associated with increased inflammatory cytokine production, which contribute to the endothelial dysfunction and microalbuminuria that is a characteristic of ORG (20). Macrophage infiltration into white adipose tissue and the kidney has been observed in animal models of obesity, which release cytokines into the circulation, initiating an inflammatory response causing organ injury. Increased oxidized low-density lipoprotein levels in obesity stimulate monocyte adhesion to the glomerular endothelial cells and increase glomerular injury (21). Adiposity has been associated with release of pro-inflammatory cytokines such as IL-6, IL-1, and TNF- α .

IL - 6

Adipocytes, monocytes, and endothelial cells produce IL-6, and its levels closely related to adiposity (22). IL-6 increase expression of adhesion molecules and Ang II type 1 receptors, which lead to inflammation, oxidative stress and renal vascular damage (23). In the kidney IL-6 has pro-inflammatory and procoagulant effects and exacerbates ischemic injury and may stimulate the expression of C-reactive protein (CRP), which inhibits endothelial nitric oxide synthase (eNOS) contributing to its coagulant and atherogenic properties (24).

TNF- α

There is increased TNF- α expression in obese patients. Increased TNF- α levels have been associated with IR and endothelial dysfunction. TNF- α has apoptotic and proinflammatory properties and patients with glomerulosclerosis and glomerular endothelial dysfunction have high urinary TNF- α levels (25). Infusion of TNF- α in rat exacerbates glomerular injury and albuminuria (26).

Nuclear factor kappa B (NF κ B)

There is increasing evidence that NF κ B is involved in the progression of nephropathy as a result of obesity. Activation of NF κ B transcription is a characteristic of obesity-induced renal injury. NF κ B increases the expression of proinflammatory cytokines and adhesion molecules in the kidney, resulting in the progression of renal injury (27).

MCP-1

Insulin stimulates the production of MCP-1 in the ob/ob mouse. So, in the hyperinsulinemic state, there is an increased MCP-1 expression which leads to recruitment of macrophages to both the adipose tissue and the kidney, resulting in increased levels of circulating proinflammatory cytokines such as IL-6, intracellular adhesion molecule (ICAM)-1, and PKC causes renal cell proliferation and obesity associated injury. ICAM-1 promotes cellular proliferation and increased ICAM-1 expression by tubular cells has been observed in tubulointerstitial inflammation and glomerulonephritis (28).

Leptin

Leptin is an adipokine released into the circulation by adipose tissue, so plasma leptin levels increased in obese patients. Leptin stimulates the renal sympathetic nervous system, leading to increased blood pressure and subsequent glomerular injury. In addition, leptin stimulates the proliferation of glomerular endothelial cells and increase collagen type IV production. Leptin can increase ROS production, which could contribute to the development of renal endothelial dysfunction (29).

Adiponectin

Adiponectin is a cytokine produced by adipocytes with anti-inflammatory effects. It promotes the production of the anti-

inflammatory cytokine IL-10 and down regulates TNF- α and IL-6. Studies in obesity have reported that an increase in adipose tissue mass is accompanied by a reduction in plasma adiponectin levels, which correlate with low-grade albuminuria. The reduction in adiponectin expression and its anti-inflammatory effects may have a role in the development of renal injury in obesity; however, the mechanisms involved in this process are not clear (30). Adiponectin has a protective effect on podocytes via stimulating the enzyme AMP-activated protein kinase (AMPK) which is considered the master energy sensor in all eukaryotic cells. AMPK has been reported to be reduced in various organs, including the kidney after exposure to a high fat diet. Mice fed a high-fat diet exhibited an increase in body weight, renal hypertrophy, an increase in urine H₂O₂ and urine MCP-1, and a decrease in circulating adiponectin levels and renal AMPK activity. Urine albumin/creatinine ratio (ACR) progressively increased after 4 weeks of a high fat diet (31).

Resistin

Released by the adipocytes in white adipose tissue and has pro-inflammatory properties. Plasma resistin levels increase in diet-induced and genetic models of obesity. Resistin levels appear to be strongly correlated with chronic kidney disease; however, its role in the pathogenesis of renal disease in obesity is still unknown (32).

Renal Epoxyeicosatrienoic Acids

Cytochrome P450 enzymes, such as the epoxyeicosatrienoic acids (EETs), are expressed in the renal cortex primarily in the proximal tubules, ascending limb of the loop of Henle and the renal vasculature. The EETs maintain renal vascular function through induction of vasodilatation of the renal vasculature and regulate renal sodium tubular reabsorption. The protein expression of the cytochrome P450 enzymes is reduced in the renal microvessels of the obese Zucker rat. Also, the renal microvessel cytochrome expression is reduced in rats fed a high-fat diet compared with a normal diet, which is thought to contribute to the development of hypertension observed in this model. Decreased EET levels contribute to the microalbuminuria and endothelial dysfunction observed in an animal model of obesity. EET-induced vasorelaxation is impaired in vascular smooth muscle cells from insulin-resistant animals (33).

Renal Nitric Oxide

NO plays a role in endothelial and renal function. The albuminuria and glomerulosclerosis in the obese Zucker rat has been shown to be accompanied by a significant reduction in both eNOS and neuronal (n)NOS expression in the renal cortex as well as a fall in urinary excretion of NO metabolites. Fall in NO activity could be due to increase in plasma asymmetric dimethylarginine (ADMA) concentrations that are found in insulin-resistant subjects and those with dyslipidemia. ADMA acts as a competitive inhibitor in the conversion of L-arginine to nitric oxide, therefore reducing NO. In addition, reduction in NO availability can be due to increased circulating free FA, which can down regulate NO production by the endothelial cells via IKKB activation in obesity (34).

Oxidative Stress

Obesity related oxidative stress include increased oxygen consumption and subsequent production of free radicals derived from the increase in mitochondrial respiration, diminished antioxidant capacity, fatty acid oxidation, lipid oxidizability and cell injury causing increased free radical formation (35). In genetic and diet-induced obesity, there is an increase in ROS generation which has been identified as a cause

for eliciting endothelial dysfunction and renal injury. ROS are highly reactive molecules that oxidize lipids and proteins, cause cellular injury, and promote glomerular and renal tubule injury and associated proteinuria. Nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase has been reported to be elevated in animal models of obesity and can lead to the increased generation of ROS. Upregulation of NADPH has also been linked with the development of glomerulosclerosis (36). Increased ROS in obesity could be due to increased Leptin observed in obese patients, which also, correlate with an increase in the levels of thiobarbituric acid reactive substances (TBARS), indicating elevated oxidative stress. Also, endogenous production of antioxidants is impaired in obesity (37).

Hyperlipidemia

Hyperlipidemia may promote glomerulosclerosis through engagement of low-density lipoprotein receptors on mesangial cells, direct podocyte toxicity, oxidative cellular injury, macrophage chemotaxis, and increase renal expression of sterol regulatory element binding proteins (SREBP-1 and SREBP-2), resulting in the renal accumulation of cholesterol and triglycerides with significant renal increase of fibrogenic cytokines (38).

Activation of Renin-Angiotensin-Aldosterone System (RAAS)

Adipose tissue is the major source of the components of RAAS. Obese subjects usually have increases in plasma renin activity, angiotensinogen, angiotensin-converting enzyme activity, and circulating AngII, which promote renal damage by renal hemodynamic changes and non-hemodynamic pathways such as hyperinsulinemia, oxidative stress, and inflammation (39).

TREATMENT OF OBESITY ASSOCIATED RENAL INJURY

Peroxisome Proliferator-Activated Receptors (PPAR) Agonistic

PPARs play important roles in regulation of cellular cholesterol and triglyceride metabolism with direct effects on insulin sensitivity. PPARs agonists are an insulin sensitizing drugs can play a role in insulin sensitivity, lipid metabolism, and blood pressure control (40). PPARs agonists by modifying cellular lipid metabolism and direct effects on mesangial matrix synthesis can prevent or reverse diabetic glomerulosclerosis (41). There is recent evidence that PPARs have actions beyond those of metabolic control, such as cell growth, inflammation, and interaction with other endogenous molecules such as the eicosanoids. These actions contribute to the therapeutic actions of PPAR agonists in the treatment of renal disease associated with obesity and insulin resistance (42).

Statins

Statins are currently under study in prospective trials to assess their contribution to renal protection and are clearly indicated in the presence of hypercholesterolemia. Evidence revealed that statins have anti-inflammatory benefit independent of the lipid lowering effect (43).

Anti-Inflammatory Therapy

Anti-inflammatory therapy might be a potential treatment for renal damage. IL-6 is a key inflammatory molecule in renal diseases. Treatment with anti-IL-6 receptor antibody MR16-1 prevents progression of proteinuria, renal lipid deposit, and the mesangial cell proliferation in hypercholesterolemia-induced renal injury (44). Inhibition of TNF- α by a TNF- α antagonist, decreased blood pressure and protect the kidney through reduction of renal NF- κ B, oxidative stress, and inflammation

(45). Treatment of adiponectin-knockout mice with adenovirus-mediated adiponectin results in amelioration of albuminuria, glomerular hypertrophy, tubulointerstitial fibrosis and reduces the elevated levels of MCP-1, TNF- α , TGF- β 1, collagen type I/III, and NADPH oxidase components (46).

Weight Loss

Excessive fat accumulation contributes to macrophage infiltration in adipose tissue and increased production of proinflammatory cytokines (47). Consequently, it is possible that weight loss may be a potential method to reduce inflammation. Weight loss globally improves the inflammatory profile of obese subjects through a decrease of proinflammatory factors and an increase of anti-inflammatory molecules in white adipose tissue. Also reduces oxidative stress state in obesity, which may protect renal function in ORG. Weight loss improves renal function as shown by reduced levels of serum creatinine and improved creatinine clearance (48).

Antioxidant Intervention

Antioxidant supplementation may have renoprotective effects. Garcinia protects against obesity-induced nephropathy by attenuating oxidative stress through reduced lipid peroxidation and levels of oxidized LDL (49). Supplementation with an antioxidant ebselen improved kidney damage by ameliorating proteinuria and renal focal and segmental sclerosis in obese Zucker rat. Chronic ebselen therapy also improved vasculopathy with lipid deposits, tubulointerstitial scarring, and inflammation (50).

CONCLUSION

Obesity is a major risk factor for renal disease progression and can cause de novo glomerulopathy. The characteristic features of obesity-induced renal injury include glomerular hypertrophy, thickening of the glomerular basement membrane, mesangial matrix expansion, and increased renal inflammation. These alterations may contribute to albuminuria, a progressive decline in renal function and ultimately

glomerulosclerosis and tubulointerstitial fibrosis. The mechanisms of ORG are not well understood, however, several mechanisms acting singly or in combination has been suggested as excess excretory load, excess renal sodium retention and IR and hyperinsulinemia which are associated with endothelial dysfunction, inflammation, and microalbuminuria. Hyperinsulinemia induce glomerular hypertrophy by stimulating the IGF-1 receptor and promote the expression of TGF- β in proximal tubular cells. Hyperinsulinemia increased MCP-1 expression leads increased levels of circulating proinflammatory cytokines such as IL-6, ICAM-1, and PKC. Lipotoxicity in proximal tubular cells with its associated tubulointerstitial inflammation. Obesity is associated with the increased inflammatory cytokine production such as IL-6, IL-1, and TNF- α , which contribute to the endothelial dysfunction and microalbuminuria. Activation of NF κ B transcription increases the expression of proinflammatory cytokines and adhesion molecules in the kidney. Leptin stimulates the renal sympathetic nervous system, leading to increased blood pressure and subsequent glomerular injury. Obesity has been reported that it is accompanied by a reduction in plasma adiponectin expression with its anti-inflammatory effects. Decrease NO level is associated with albuminuria and glomerulosclerosis in the obese Zucker rat. The ROS generation increase in obesity has been identified as a cause of endothelial dysfunction and renal injury. Hyperlipidemia may promote glomerulosclerosis. Obese subjects usually have increases in plasma renin activity, angiotensinogen, angiotensin-converting enzyme activity, and circulating AngII, which promote renal damage by renal hemodynamic changes. Many suggestive lines for treatment of ORG as Peroxisome proliferator-activated receptors (PPAR) Agonistic, Statins, anti-inflammatory therapy, and antioxidant are under trial. Weight loss decreases of proinflammatory factors, increase of anti-inflammatory molecules in white adipose tissue and reduces oxidative stress state in obesity, which may protect renal function.

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