Obesity and chronic kidney disease: therapeutic implications

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Obesity has now reached epidemic proportions, with far-reaching healthcare and economic implications. Obesity has been associated with end-organ damage in several tissues including the kidney and is one of the most important modifiable and preventable causes of death. Insulin resistance and the compensatory hyperinsulinemia, oxidative stress and adipocytokines, among others, have been implicated in the causation of obesity-related kidney damage. Obesity-related focal glomerulosclerosis is now a well recognized distinct histopathological entity and its pathophysiology has been related to the 'hyperfiltration' mechanism associated with increased renal plasma flow and glomerular filtration rate. This review will discuss the epidemiology and pathophysiology of obesity-related kidney damage with special focus on the central role of insulin resistance/hyperinsulinemia, adipocytokines and oxidative stress, as well as summarize the current evidence and recommendations in the management of this condition.

Keywords: chronic kidney disease, metabolic syndrome, microalbuminuria, obesity

Obesity is one of the most important healthcare challenges of the present era. Its cause is complex and multifactorial, involving both genetic and environmental factors. The NIH and the WHO define overweight as a BMI of 25–29.9 kg/m² or greater, and obesity as a BMI of 30 kg/m² or greater [1,2]. Approximately two-thirds of US adults are above ideal body weight (BMI >25 kg/m²) [3] and the trend is increasing, as evidenced by the doubling in the prevalence of obesity between 1960 and 2002 [201]. Unfortunately, this negative trend is also seen among children and adolescents, further contributing to the obesity epidemic [3]. This increasing prevalence of obesity has far-reaching economic (annual medical spending of US$92.6 billion in 2002 due to obesity and overweight [202]) and survival implications with higher all-cause mortality [4], including higher death rates from cancer with increasing BMI [5]. Furthermore, obesity is a phenotypic marker for the metabolic syndrome, also known as the cardiometabolic syndrome (CMS), and is strongly associated with other components of CMS, which are each associated with increased all-cause mortality.

Recently there has been a lot of attention on obesity-related kidney damage and it is now increasingly recognized as an independent risk factor for chronic kidney disease (CKD). This risk increases further in the presence of other CKD risk factors such as Type 2 diabetes mellitus (T2DM) and hypertension, also common causes of CKD. Obesity, with its associated cardiovascular disease (CVD) risk and effects on the kidneys, is emerging as an important healthcare issue and understanding its pathophysiology has never been more important. In this review, we will discuss the role of obesity in the pathophysiology of CKD/end-stage renal disease (ESRD), the hemodynamic and structural abnormalities associated with obesity-related kidney injury and also discuss potential interventions to prevent the progression of CKD in obese individuals.

Epidemiology of obesity & CKD/ESRD

Obesity has now reached epidemic proportions throughout the world. Data from the WHO suggest over a billion adults are overweight, and of them over 300 million are obese. The WHO further projected that by 2015 there would be approximately 2.3 billion overweight adults, more than 700 million of whom will be obese [203]. Obesity-related mortality is now the second largest environmental cause of death after smoking, accounting for more than 300,000 deaths per year [6]. It is the single most important contributor to chronic diseases and is also one of the most important preventable risk factors for renal disease. Congruent with obesity epidemic, there is an exponential increase in the ESRD patient population. This trend is supported by the 2006 US Renal Data System (USRDS) annual data report, which showed an increase in the mean weight and mean BMI of incident ESRD patients with and without diabetes from 66.3 kg/25.2 kg/m² to 78.2 kg/27.7 kg/m², respectively [7]. Recent studies have demonstrated a close association between increasing

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BMI and increased incidence of CKD and ESRD. A large national population-based case–control study from Sweden estimating the relative risk for CKD in relation to BMI found a threefold increased risk for CKD in overweight patients with a BMI of 25 kg/m^2 or over in comparison with those with a BMI less than 25 kg/m^2. Obese males with a BMI of 30 kg/m^2 or more and morbid obesity in females with BMI of 35 kg/m^2 or greater anytime during their lifetime were associated with a three- to four-fold increased risk for CKD. After adjusting for T2DM and hypertension, a similar association between BMI at age 20 years and incidence of advanced stages of CKD, even in those without these comorbidities, held [8]. Investigators used data from community-based screening registries to examine the relationship between BMI and risk for CKD or ESRD and concluded that the incidence of ESRD increased with an increasing BMI, particularly in men [9]. Another Japanese study investigating the risk factors for CKD in a community-based population demonstrated an increased incidence of stage I and II in men compared with women. Also, obesity was associated with an increased hazard ratio of developing proteinuria; however, this trend was reversed in the incidence of stage III or higher [10].

In addition, a large historic cohort further demonstrated obesity as a risk factor for ESRD. Similarly, in this study higher BMI was an independent risk factor for ESRD, even in multivariate models that adjusted for hypertension and T2DM [11].

Renal effects of obesity in normal & pre-existing kidney disease

It is now increasingly recognized that obesity may hasten the progression of CKD, in addition to deleterious renal effects in otherwise healthy subjects. One study including 73 patients (of whom 14 were obese) with unilateral nephrectomy were followed for 20 years to investigate the effects of obesity. Only 30–40% of the obese patients had normal renal function, while the majority of nonobese patients retained normal kidney function [12]. Similar findings were demonstrated in patients with IgA nephropathy [13].

The renal effects of obesity in the general population are best evident from the results of a subanalysis of the Prevention of Renal and Vascular End stage Disease (PREVEND) study, that was designed to study the effect of microalbuminuria on renal and cardiovascular risk in the general population. Interestingly, this analysis found that 75% of all cases of microalbuminuria occurred in patients without T2DM or hypertension [14]. Data supported BMI as an independent risk factor for urinary albumin excretion (UAE) with an association between male gender, increasing BMI and UAE [15]. This suggests that obesity may lead to progressive loss of renal function, not only in patients with pre-existing renal disease, but also in healthy subjects [16].

The link between obesity, CMS & microalbuminuria

Obesity is a phenotypic marker of the CMS. The development of obesity is also thought to be integral in the exponential increase of the CMS patient population (one in four people in the US has CMS [17]) worldwide. Obesity contributes to progressive deterioration of renal function and can manifest initially with microalbuminuria, an easily measurable marker for both renal damage and also generalized endothelial dysfunction [16]. Microalbuminuria is defined as UAE of 30–300 mg/day on a 24 h urine collection, or 30–300 mg/g when spot albumin:creatinine ratio is used. The progression of albuminuria to levels above the limit for microalbuminuria has been associated with faster decline in renal function and is considered a sign of overt nephropathy [18,19]. Microalbuminuria also clusters with other components of the CMS, such that it has been integrated in the WHO definition for the CMS. The risk of CKD and microalbuminuria increases further with the presence of increasing number of components of the CMS [20]. In addition, microalbuminuria has also been considered a marker of increased vascular permeability, systemic low-grade inflammation and also an independent predictor for CVD-associated morbidity and mortality [21].

Obesity-related glomerulopathy

Obesity-related glomerulopathy is now recognized as a distinct histological entity characterized by obesity-associated focal segmental glomerulosclerosis (FGS) with glomerulomegaly or obesity associated glomerulomegaly alone [22,204]. A biopsy study demonstrated that the increasing incidence of FGS associated with the increase in the incidence of obesity [22]. Indeed, even patients with submorbid obesity developed obesity-related FGS that was indistinguishable [22] from the entity associated with morbid obesity reported in previous studies [23,24]. Obesity-related FGS typically presents with subnephrotic range proteinuria, but can present in the

nephrotic range. It can be distinguished from idiopathic FGS by the lower incidence of nephrotic syndrome and a more indolent course with slower progression to ESRD. Histologically, obesity-related FGS can be distinguished by the consistent presence of glomerulomegaly (100% compared with 10% in the idiopathic variety), presence of predominantly perihilar sclerotic lesions and milder podocyte effacement [22]. The consistent presence of glomerulomegaly in obesity-related FGS highlights the role of hyperfiltration mechanisms in its pathogenesis [22]. Indeed, 45% of the obesity-related FGS biopsies demonstrated focal glomerular basement membrane thickening or focal mesangial sclerosis similar to the changes seen in early diabetic kidney disease [22].

Obesity alters glomerular hemodynamics by increasing renal plasma flow (RPF) and thereby glomerular filtration rate (GFR) with resultant albuminuria [25–28]. It is thought that the increased GFR associated with a high RPF noted in obesity is due to an increased transcapillary pressure gradient, which is most likely due to transmission of the elevated arteriolar pressure (obesity-related hypertension) through a dilated glomerular afferent arteriole [29]. The mechanism of increased RPF and GFR is due to increased tubular reabsorption of sodium, resulting in decreased salt delivery to the macula densa, resulting in glomerular arteriolar vasodilatation and subsequent increased plasma flow [30].

Pathophysiology of obesity-related kidney injury

Obesity is closely associated with a state of insulin resistance and a compensatory hyperinsulinemia. Pro-inflammatory adipokines and hormones released from adipose tissue such as tumor necrosis factor (TNF)-α, IL-6 and leptin, by various mechanisms, have been incriminated in the development of insulin resistance/hyperinsulinemia as well as vascular and renal injury observed in obese individuals (**Figure 1**) [31,32]. Studies have shown the association between the release of adipokines and early renal abnormalities seen in patients with obesity [32]. The following sections will discuss the central role of insulin resistance/hyperinsulinemia and related factors to adipose tissue and adipocytokines in obesity-related kidney damage.

Insulin resistance/hyperinsulinemia

Several studies have examined the structural and functional effects of insulin on the kidney (**Figure 2**). Direct effects of insulin on the kidneys include increased proliferation of mesangial cells and extracellular matrix protein production. Furthermore, in conjunction with hypertension, insulin is shown to cause glomerular mesangial expansion, basement membrane thickening and loss of slit pore diaphragm integrity, which could all lead to glomerulosclerosis, tubulointerstitial injury and fibrosis [33]. Other actions of insulin include antinatriuresis [34], increased salt sensitivity [35], increased glomerular pressure and increased UAE [36].

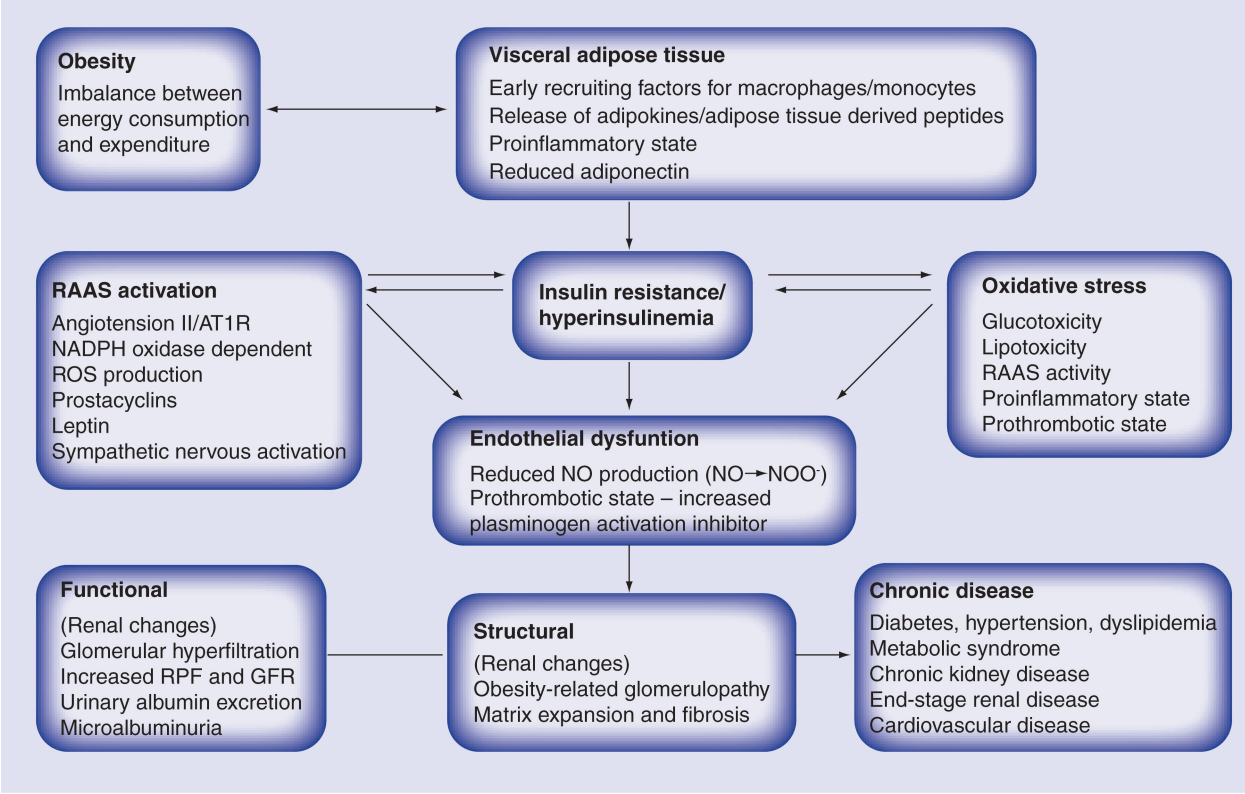
In normal conditions, insulin promotes endothelial nitric oxide (NO) release, resulting in vasodilatation [37]. However, in the insulin resistant state, this action is severely impaired, resulting in a blunted endothelial vasodilatatory response [38]. Decreased NO production due to a variety of factors has been shown to be associated with advanced nephropathy [39], raising the possibility of renal endothelial dysfunction due to insulin resistance/hyperinsulinemia as one of the potential causes for the progression of CKD.

Indirect effects of insulin include an insulin-dependent expression of other growth factors such as IGF-1 [40,41] and transforming growth factor (TGF)-β [42]. IGF-1 is produced by both the mesangial and vascular smooth muscle cells under the influence of insulin. Studies have shown that IGF-1 induces growth and inhibits apoptosis of the mesangial cells [43]. It also facilitates excess formation of extracellular matrix by inhibiting the matrix metalloproteinase [44]. TGF-β is the other cytokine largely produced, by the mesangial and proximal tubular cells, in the presence of insulin. Its action results in the extracellular matrix expansion and fibrosis [45]. Furthermore, a close interplay exists between IGF-1 and TGF-β, resulting in further stimulation of other cytokins such as connective tissue growth factor and other profibrotic factors, thus potentiating extracellular remodeling [46]. Other indirect effects of insulin include activation of renin–angiotensin–aldosterone system (RAAS) [47,48], endothelin-1 production by the endothelial cell (causes vasoconstriction and mesangial cell proliferation) [48], increased production of plasminogen activation inhibitor (PAI) [49] and oxidative stress.

Adipose tissue

Adipose tissue was long thought to be a storage organ, but emerging evidence suggests that it is a metabolically active endocrine organ. Adipose tissue consists of multiple cell lines, including

Figure 1. Pathophysiology of obesity-related renal/other end-organ injury.



Insulin resistance and compensatory hyperinsulinemia are central to the development of end-organ damage in obesity and cardiometabolic syndrome. Insulin resistance and hyperinsulinemia lead to increased oxidative stress and markedly increased activation of the renin–angiotensin–aldosterone system, leading to endothelial dysfunction and eventually causing end-organ injury.
AT1R: Angiotensin type 1 receptor; GFR: Glomerular filtration rate; NO: Nitric oxide; ROS: Reactive oxygen species; RPF: Renal plasma flow.

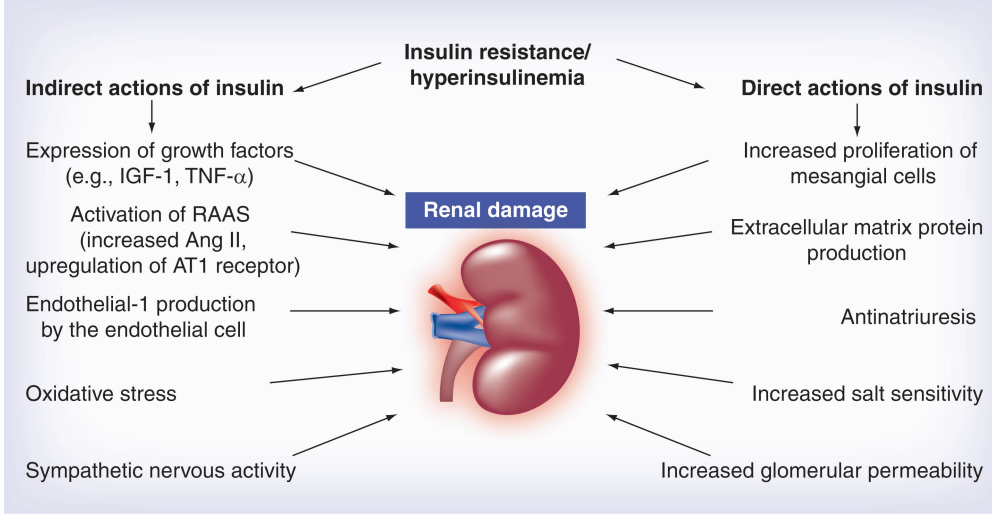
some immunological cells such as macrophages, which also seem to be contributing to its endocrine actions by secreting pro-inflammatory adipocytokines such as adiponectin, leptin, resistin, TNF-α and IL-6 [31]. Gene expression studies have shown that leptin is produced mainly by adipocytes whereas TNF-α and resistin are produced mainly by macrophages present in the adipose tissue. IL-6, on the other hand, is produced both by adipocytes and macrophages. This infiltration of fat cells with macrophages and subsequent development of pro-inflammatory state is thought to precede the development of insulin resistance/hyperinsulinemia and other features of the CMS [31]. Furthermore, adipocytokines such as leptin, resistin, TNF-α and IL-6 have been found to be elevated in ESRD patients, implicating an inflammatory role in obesity-related kidney disease [50–53]. In the following section the discussion will be limited to the role of adipokines in renal injury.

Leptin

Leptin is mainly produced by visceral adipose tissue and serum concentrations are directly related to BMI [54,55]. Under physiological conditions, leptin promotes weight loss by decreasing appetite and increasing energy expenditure through its action on the hypothalamus and also by activation of the sympathetic nervous system. However, obesity is associated with selective leptin resistance with an attendant loss of regulatory effects on the hypothalamus despite preserved sympathetic effects on vasculature and other organs such as the kidneys [56].

The kidneys are not only the main organ involved in clearance of leptin, but are also an important target organ for its action. This is supported by studies involving leptin infusion resulting in the development of renal damage including proteinuria and glomerulosclerosis. Multiple direct and indirect effects of leptin on the kidneys have been proposed based on data from animal

Figure 2. Mechanism by which insulin resistance and hyperinsulinemia (both of which are seen in obesity) lead to kidney damage.



This process is facilitated by the multitude of direct and indirect effects of insulin at several levels, eventually leading to renal injury.
Ang II: Angiotensin II; AT1: Angiotensin Type 1; RAAS: Renin–angiotensinogen–aldosterone system.

studies including natriuresis (anti-insulin effect), increased sympathetic activity [57], increased production of reactive oxygen species, early proliferation of endothelial cells and stimulation of TGF-β, all resulting in increased collagen deposition and endothelial injury, eventually leading to proteinuria and the development of glomerulosclerosis [58]. Also, activation of the RAAS with elevated levels of angiotensin II has been shown to have additive effects on the endocapillary proliferation and subsequent development of glomerulosclerosis, which could explain the much quicker renal damage in patients with CMS.

Resistin

Resistin is a compound produced mainly by macrophages in visceral adipose tissue. It is proposed to be a possible link between obesity and insulin resistance [59]. Human studies, however, did not show any association between serum resistin levels and insulin resistance, but certainly showed increased serum levels of resistin in obese individuals [60]. Interestingly, evidence from previous studies supports a role for resistin in subclinical inflammation associated with CKD and ESRD patients [61–63]. However, further studies are needed to establish the role of resistin in the pathophysiology of CKD/ESRD.

TNF-α

Adipose tissue has been shown to be a significant source of endogenous TNF-α production [64]. Positive correlation is seen not only between increased circulatory concentration of TNF-α and obesity, but also with insulin resistance [65]. An association has been suggested between excessive secretion of TNF-α with the development of the insulin resistant state and also significant improvement of insulin resistance/hyperinsulinemia with the blockade of TNF-α action [64]. TNF-α has also been shown to mediate inflammation in several models of renal injury, including glomerulonephritis [66] and tubulointerstitial injury [67] by causing macrophage infiltration and upregulation of inflammatory cytokines, which can be toxic to the kidney [68].

Adiponectin

Adiponectin is a multifunctional protein with a protective role, not only against insulin resistance, but also in conditions such as atherosclerosis [69]. As expected, adiponectin levels are decreased in obesity, but are noted to increase after weight loss and with the use of insulin-sensitizing drugs [70].

Similarly, other adipokines secreted by the adipose tissue include IL-6, acylation-stimulating protein, components of the RAAS and so on (**Box 1**). These adipose tissue-derived cytokines and peptides are considered to be involved in the development of a pro-inflammatory state and also in the regulation of the energy balance by its direct and indirect effects on insulin.

Box 1. Adipose tissue-derived cytokines and proteins.

Adipokines:

- Tumor necrosis factor-α
- IL-6
- IL-1 β
- Leptin

Adipose tissue-derived peptides:

- Adiponectin
- Resistin
- Angiotensinogen
- Plasminogen activator inhibitor type-1
- Acylation stimulating protein

Renin–angiotensin–aldosterone system

RAAS is the other important system, which is influenced by insulin at many levels in insulin resistance/hyperinsulinemia. In the insulin resistant state, the inhibitory role of insulin on angiotensinogen production is impaired, thus resulting in excessive production of components of the RAAS [47]. Several renal studies have shown the enhanced action of Ang II in the presence of insulin [42,71]. A study of cultured renal mesangial cells has shown a many-fold increase in Ang II-mediated production of TGF-β and collagen with the addition of insulin [42]. Studies on cultured vascular smooth muscle cells and renal mesangial cells have shown insulin increased Ang Type 1 receptor mRNA expression, which might further enhance the Ang action [71].

Several animal and human studies have shown increased adipocyte angiotensinogen production in adipose tissue, especially visceral adipose tissue depots [72–74]. Activation of visceral adipose tissue RAAS contributes to the pathophysiology of obesity by regulating multiple secretory products from adipocytes such as prostacyclins, leptin and PAI [75]. Other effects include sympathetic nervous system activation, oxidative stress and its direct effects on blood vessels.

Oxidative stress

Oxidative stress is the result of loss of homeostasis between free radical/reactive oxygen species (ROS) formation and antioxidative enzymes. Insulin resistance/hyperinsulinemia is closely associated with not only the enhanced production of free radicals, but also the downregulation of the antioxidant enzymes [76]. Multiple metabolic toxicities upregulate the RAAS and pro-inflammatory adipokines, further contributing to the already enhanced oxidative stress in obese individuals. Oxidative stress has also been shown to interfere with insulin signaling, further leading to the development of insulin resistance [77], thus facilitating a vicious cycle. Investigators have recently demonstrated a role for the activation of the RAAS and Ang II stimulation of NADPH oxidase activity and resultant oxidative stress, which is associated with insulin resistance and renal injury [78].

Management of obesity-related FGS

Treatment of obesity-related FGS should be directed at correcting the underlying condition and achieving weight loss. Weight loss has been shown to decrease proteinuria [22,79], stabilize the progression of CKD [80] and prevent the development of overt obesity-related FGS [29], besides achieving better control of hypertension and T2DM, and decreasing CVD risk. Furthermore, the elevated RPF and GFR along with albuminuria have been shown to decrease significantly with weight loss [29]. This suggests that weight loss decreases vasodilation of the afferent arteriole, leading to a lower transcapillary pressure gradient, which in effect is due to a combination of decreased systemic arterial pressure and increased afferent arteriolar resistance [29]. The above mechanism is supported by data from overweight, hypertensive individuals who showed a decrease in blood pressure with weight loss (independent of salt restriction) [81]. The decrease in filtration pressure increases the intraluminal concentration of macromolecules as blood flows along the glomerular capillaries, eventually leading to an increase in the glomerular capillary oncotic pressure. This ultimately results in a decrease in the fractional albumin excretion [82–88].

Apart from weight reduction, there has been a demonstrable effect of angiotensin-converting enzyme (ACE) inhibition and Ang Type 1 receptor blockade in the reduction of protienuria. The Ramipril Efficacy In Nephropathy (REIN) study was a randomized, double-blinded, placebo-controlled trial involving 352 patients with diabetic kidney disease. It showed a protective effect of ramipril on GFR decline and risk of ESRD in patients with proteinuria, independent of their baseline or follow-up blood pressure [89,90]. Similarly, the COOPERATE trial demonstrated the long-term renoprotective action of dual RAAS blockade [91]. As discussed in the pathophysiology, obesity

is associated with a higher quantity of circulating adipocytokines and a marked activation of RAAS, which explains the protective effect of the RAAS blockade as demonstrated in the aforementioned studies. As highlighted previously, there are a higher amount of circulating adipokines and a markedly activated RAAS in obese individuals, which explains the possible protective effects of the RAAS blockade. In addition to the the RAAS-blocking agents and lipid-lowering drugs, the 3-hydroxy-3-methylglutaryl-CoA reductase reductase inhibitors, in particular, have been shown to abrogate mesangial sclerosis and proteinuria in the Zucker obese rat [92], but their role in humans needs to be studied further. Furthermore, peroxisome proliferator-activated receptors (PPAR-α/γ) are being implicated in the pathogenesis of obesity [93] and treatment with PPAR-α agonists has been shown to reduce weight in animal studies [94,95]. A recent animal study (involving the Zucker obese rats) comparing the long-term beneficial effects of ACE inhibitors with a PPAR-γ agonist (thiazolidinediones [TZDs]) showed a reduction in proteinuria with the PPAR-γ agonists that was similar to the ACE inhibitors. However, PPAR-γ agonists were shown to confer superior renal protection compared with ACE inhibitors in this animal model of obese, diabetic CKD. This suggests a renoprotective effect by PPAR-γ agonists beyond the glycemic and lipemic control [96]. Similar protective renal effects were noted in other animal studies [97,98]. The above findings are encouraging, but need to be studied further and confirmed in large-scale human studies.

Based on current evidence, weight reduction and RAAS blockade should be utilized in the management of patients with obesity and renal disease. Thus, practical ways to achieve weight loss involving lifestyle modification that includes exercise and dietary restriction (low calorie, low salt intake) should be actively sought, to reduce progression of obesity-related kidney damage. A recent Finnish study linked obesity to increased salt intake by suggesting that increasing salt intake causes increase in thirst, resulting in an increase in the intake of beverages which, in turn, increase the net calorie consumption [99]. Therefore, salt restriction along with caloric restriction should be attempted as part of lifestyle modifications.

In obese subjects who fail to lose weight with ensuing health consequences, bariatric surgery may be considered. A study examining the effect of weight loss after bariatric surgery on renal parameters and renal function in 61 extremely obese patients, concluded that the 24-h albuminuria, 24-h proteinuria and GFR improved at 12-month follow-up and the 24 h albuminuria continued to decrease during the second year of follow-up [100]. Similarly, another study showed a significant improvement of cardiovascular risk factors including adiponection, creatinine clearance and albuminuria with weight loss after bariatric surgery [101].

Obesity paradox in ESRD

While weight loss improves glomerular hemodynamics and decreases proteinuria, a reverse epidemiology has been noted in obese dialysis patients who progress to ESRD. Higher degrees of obesity have been associated with improved survival in the dialysis population [102]. The exact mechanism is unclear, but the postulated hypothesis is that the circulating uremic toxins are sequestered by the adipose tissue and that the adipose tissue may produce factors that neutralize the adverse effects of TNF-α [103]. Although this has been shown only in hemodialysis patients, studies have not shown a decreased survival with higher BMI in patients on peritoneal dialysis [104]. Further studies are needed to clarify the survival advantage associated with higher BMI in the ESRD population, as this would alter the course of management in these patients.

Expert commentary

Obesity is now reaching epidemic proportions with a concurrent increase in the incidence of obesity-related FGS. Insulin resistance, the compensatory hyperinsulinemia and adipocytokines are thought to play a central role in the pathogenesis of obesity-related kidney damage. Obesity related FGS is now recognized as a distinct histopathological entity, characterized by glomerulomegaly and FGS with nephrotic/subnephrotic range proteinuria. Treatment should be aimed primarily at achieving weight loss and include pharmacologic RAAS blockade as both of them have been shown to have a renoprotective effect. While weight loss confers a protective effect in CKD patients, higher BMI has been shown to have a survival benefit in ESRD patients on dialysis. It is, however, clear that weight loss confers a protective effect in obesity-related kidney disease prior to its progression to ESRD and effective ways to achieve this should be actively sought.

Executive summary

- Obesity is now reaching epidemic proportions worldwide, and is one of the most important healthcare challenges of the present era.
- Obesity is a phenotypic marker for the cardiometabolic syndrome and has been noted as an independent risk factor for chronic kidney disease. In addition, obesity-related glomerulopathy is a newly recognized distinct histological entity.
- Adipose tissue is now increasingly recognized as a metabolically active endocrine organ and adipocytokines have been implicated in the pathogenesis of obesity-related kidney damage.
- Obesity is associated with a state of insulin resistance and a compensatory hyperinsulinemia, which by various mechanisms leads to vascular and renal injury.
- The use of angiotensin-converting enzyme inhibitors, angiotensin II-receptor blockers and 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors, along with weight reduction, are useful in the reduction of proteinuria and preventing the progression of obesity-related chronic kidney disease.
- In contrast to the increased risk of chronic kidney disease seen with obesity, an obesity paradox (survival benefit due to higher BMI) of unclear mechanism is seen in end-stage renal disease patients on dialysis.

Future perspective

The association of CKD and obesity is increasingly evident and is a public healthcare dilemma reaching epidemic proportions, especially with the increasing incidence of obesity in childhood and adolescence. Insulin resistance/hyperinsulinemia and adipocytokines have been implicated in the pathogenesis of obesity-related kidney damage, but the exact mechanisms are yet to be elucidated. This is an active area of research and adipose tissue is increasingly recognized as an active endocrine organ, with leptin being a major player in the pathogenesis of obesity as well as obesity-related CKD. Further research is needed to elucidate new interventions that can improve insulin resistance, proteinuria, oxidative stress and potentially target adipocytokines. Furthermore, increasing awareness among the general population regarding the morbidity and mortality associated with obesity and related CKD and the significance of adopting a healthy lifestyle is of paramount importance.

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