Emerging Global Epidemic of Obesity: The Renal Perspective

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Obesity, as a core component of the metabolic syndrome, is among the top ten global health risks classified by the World Health Organization (WHO) as being strongly associated with the development and progression of chronic renal disease—a widely prevalent but often silent condition. Obesity carries elevated risks of cardiovascular morbidity and mortality besides having an array of metabolic complications. Maladaptive glomerular hemodynamics with increased intraglomerular pressure in association with vasoactive, fibrogenic substances released from adipocytes, in addition to cytokines and hormones, are the key factors in the causation of renal injury and the progression of nephron loss among obese subjects.

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Obesity is one of the most challenging public health problems ever envisioned by the contemporary world, being shared for the most part by wealthy societies and progressively more by the developing nations. More than one billion people worldwide are currently overweight (BMI [body mass index] >25 to 30) or obese (BMI > 30).[1] Over the last decade, the prevalence of obesity in Western and westernizing countries has more than doubled. The National Health and Nutrition Examination Survey (NHANES-II) revealed that more than half of the adult population in the USA is overweight and nearly one third of the population is obese.[2] Although the prevalence of obesity varies from region to region, people in the Middle East, Central and Eastern Europe and North America are reported to have peak prevalence rates.[3] However, the most disturbing global trend is the rapidly increasing prevalence of obesity among children who are bred and brought up in the 'fast-food' and 'small screen' culture.[2-5] As the obesity epidemic spreads, concerns about its considerable health and economic consequences have also grown. Owing to its strong association with a range of diseases, obesity has been linked to approximately 300 000 deaths each year and 117 billion dollars in direct and indirect annual costs in the United States alone.[5]

Recent research has revealed that obesity really plays a key role in the initiation and/or development of chronic renal disease among subjects with otherwise normal kidneys. It could also potentiate the progression of underlying renal disease even to the extent of causing end-stage renal disease (ESRD).[6,7]

Role of obesity in the development of renal disease in otherwise normal kidneys

Investigators have reported frequently on the strong association of obesity with systemic arterial hypertension and proteinuria (microal-

buminuria to the nephrotic range of proteinuria), including the commonest obesity-specific histopathological lesion, focal segmental glomerulosclerosis (Ob-FSGS).

Obesity-associated systemic arterial hypertension

Large epidemiological investigations have clearly demonstrated that obesity plays a central contributory role in the genesis and progression of systemic hypertension. Surplus body weight is one of the recognized predictors for subsequent development of hypertension.[8-12] A synergistic link may also exist among the various effects of obesity, including hyperlipidemia, glucose intolerance, and hypertension, in raising the risk for cardiovascular and kidney diseases. The risk estimates from the Framingham Heart Study signify that about 78% of hypertension in men and 65% in women is directly attributable to excess body weight.[13]

Although the exact mechanism of obesity-associated hypertension is not fully understood, it seems that leptin-induced increased sympathetic activity, abnormalities in renal sodium handling, activation of the renin-angiotensin-aldosterone system (RAAS) and direct mechanical effects of fat deposits in the perinephric space appear to play a principal role in the pathogenesis and progression of obesity-associated arterial hypertension (Figure 1).[13-20]

Leptin is a small peptide predominantly produced by adipocytes. It is involved in the maintenance of steady body mass and is vital in the regulation of appetite, food intake and energy expenditure. Obese individuals have high plasma leptin levels. Leptin receptors are found in many tissues including the kidneys.[14] These receptors modulate functions such as increasing diuresis and natriuresis, in the absence of changes in blood pressure and potassium excretion. Leptin stimulates activity of the sympathetic nervous system which, in turn, increases tubular sodium reabsorption.[14-17]

Adipose tissue almost entirely encapsulates the kidneys and penetrates into the medullary sinuses of obese subjects, causing compression and increased intrarenal pressures. Intra-abdominal pressure in obese subjects is also increased in proportion to the sagittal abdominal diameter, reaching levels as high as 35 to 40 mm Hg in some subjects with central obesity. Increased intra-abdominal pressure has been reported to be associated with raised renal venous pressure, plasma renin and aldosterone levels and increased peripheral vascular resistance. The mechanical compression of renal medullary tissue due to accumulation of adipose tissue around the kidneys and increased extracellular matrix within the kidneys are also closely linked to the activation of the sympathetic and RAA systems and likely changes in the intrarenal hemodynamic forces.[18] Renal compression cannot explain the initial rise in blood pressure associated with rapid weight gain, but it could contribute to more sustained increases in tubular reabsorption, volume expansion, and hypertension associated with chronic obesity. Renal compression could also explain why there is a much better correlation between abdominal obesity and hypertension than observed with lower body obesity and hypertension.

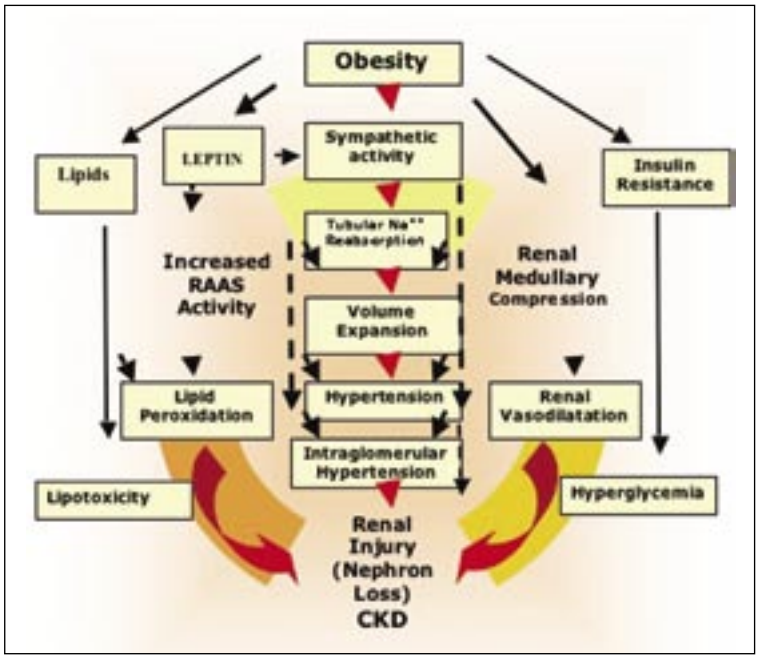

Figure 1. Mechanism of obesity-associated hypertension and chronic kidney disease (CKD)

Although excess weight gain is associated with marked sodium retention and expansion of extracellular fluid volume, obese subjects usually have increases in plasma renin activity, plasma angiotensinogen, angiotensin converting enzyme (ACE) activity, and plasma angiotensin II (ANG II) levels. A significant role for ANG II in stimulating sodium reabsorption, impairing renal-pressure natriuresis, and causing hypertension in obesity is supported by the finding that treatment of obese dogs with an ANG II antagonist or an ACE inhibitor blunts sodium retention and volume expansion, as well as increasing arterial pressure.[12,13,19-21] Also, ACE inhibitors are effective in reducing blood pressure in obese humans, particularly in young patients.[21]

However, hemodynamic forces and oxidative

stress are both implicated in compromising the integrity of vascular endothelium in human obesity, resulting in abnormalities of the basal vascular tone and endothelial dysfunction.[20] Further supportive evidence comes from substantial data indicating that appropriate body weight reduction and the use of antioxidants such as ascorbic acid, alpha-tocopherol and β-carotenes improves impaired endothelium-dependent vasodilatation, and enhances insulin sensitivity and blood pressure control among obese subjects.[21-25]

Microalbuminuria, nephrotic syndrome and obesity-associated focal segmental glomerulosclerosis (Ob-FSGS)

Obesity is an independent risk factor for the development of proteinuria.[26-33] Microalbuminuria is a renal marker of general vascular endothelial damage and early atherosclerosis with adverse prognostic implications. It is also associated with insulin resistance, central adiposity, hypertension and increased cardiovascular mortality.[19] While a graded, positive increase in prevalence of microalbuminuria across quintiles of waist-to-hip ratio was observed in non-hypertensive subjects in the MONICA Augsburg survey (1994-1995), microalbuminuria was consistently high among the subjects with hypertension and central obesity. Signs of early endothelial dysfunction manifested as microalbuminuria were strongly and independently associated with central obesity.[28]

Obesity-associated nephropathy occurs in the form of FSGS which differs from idiopathic FSGS in several ways.[30] A study of 6818 native renal biopsies reviewed from 1986 to 2000 revealed a progressive and significant increase in biopsy incidence of Ob-FSGS from 0.2% in 1986-1990 to 2.0% in 1996-2000.[30] This tenfold increase in the incidence of histologically demonstrated Ob-FSGS, which aptly overlaps with the "epidemic" of obesity witnessed during the last two decades, is also supportive of a significant epidemiological link between obesity and renal disease.[3,7,30]

Distinct clinico-pathological features, such as FSGS lesions with glomerulomegaly (with dilatation of the glomerular diameter due to glomerular loop elongation), less severe foot process effacement, an absence of features of nephrotic syndrome despite nephrotic-range of proteinuria, are helpful in differentiating this entity from idiopathic FSGS.[31] Ob-FSGS is an indicator of poor prognosis with nearly 50% of patients developing advanced renal failure.[32]

Experimental evidence suggests a role of obesity and hyperlipidemia in the creation and progression of some glomerular lesions, principally through proliferation of mesangial cells and extracellular matrix expansion induced by low-density lipoprotein cholesterol.[29,33] The obese Zucker rat, an excellent experimental model of obesity, hyperinsulinemia and hyperlipidemia, has been shown to develop nephrotic range of proteinuria, glomerulosclerosis and progressive renal failure.[29,34] The treatment of hyperlipidemia reduces glomerular injury in obese Zucker rats, signifying that statins and other hypolipidemic agents may be beneficial in the management of Ob-FSGS.[34] In addition, Morales et al, have recently reported the beneficial effects of weight reduction among overweight individuals with chronic proteinuric nephropathies.[35]

Obesity and renal cell carcinoma

A substantially elevated risk of development of renal cell carcinoma (RCC) among obese and overweight subjects has been reported by several studies.[36-38] The incidence of RCC has gradually but certainly risen over the past decade. Therefore, it is probable that the rise in the incidence of RCC could also be due to a lifestyle that has predisposed to development of obesity, worldwide, during the past few decades.[36] Lipid peroxidation, which is increased in obese and hypertensive subjects, has been proposed as the probable mechanism responsible for the increased incidence of RCC.[38] The majority of epidemiologic investigations have demonstrated an association that tends to affect women more than men. In general, past studies suggested that with increasing weight, a threshold point exists whereby a certain range of BMI dramatically worsens the risk.[39] However, elevated estrogen and insulin levels, a greater concentration of growth factors in adipose tissue, lipid metabolism abnormalities, and immune malfunction are other proposed potential mechanisms that could add to risk for the development of RCC among obese people.[39] Consequently, appropriate adjustments in lifestyle, leading to significant weight reductions among the people with higher BMI, are likely to be effective in reducing the risk of development of RCC.

Relationship of obesity to renal stones

A recently published large prospective study with 46 years follow up involving thousands of overweight and obese people, after adjusting for age, dietary factors, fluid intake, and thiazide use, found that weight gain, BMI and waist circumference were as-

sociated with a significantly higher risk of clinically symptomatic kidney stone formation.[43] Men weighing >220 lbs (100.0 kg) had a 44% higher relative risk (RR) for stone formation (95%CI, 1.11-1.86; *P*=0.002 for trend) than those men who had a body weight <150 lbs (68.2 kg). Men who gained more than 35 lbs (15.9 kg) since age 21 years were shown to be at a 39% higher risk of renal stone formation (95%CI, 1.14-1.70; *P*=0.001 for trend) than men whose weight did not change. A BMI of 30 or greater for men was associated with a 33% greater risk of kidney stone formation (95%CI, 1.08-1.63; *P*<0.001 for trend) and waist circumference was also positively associated with risk in men (*P*=0.002 for trend) and in older and younger women (*P*<0.001). The authors concluded that obesity and weight gain increase the risk of kidney stone formation. The magnitude of the increased risk may be greater in women than in men.[40] Larger body size with secondary increased renal blood flow and hyperfiltration may result in increased urinary excretion of calcium, oxalate, and uric acid, thereby increasing the risk for calcium-containing kidney stones.

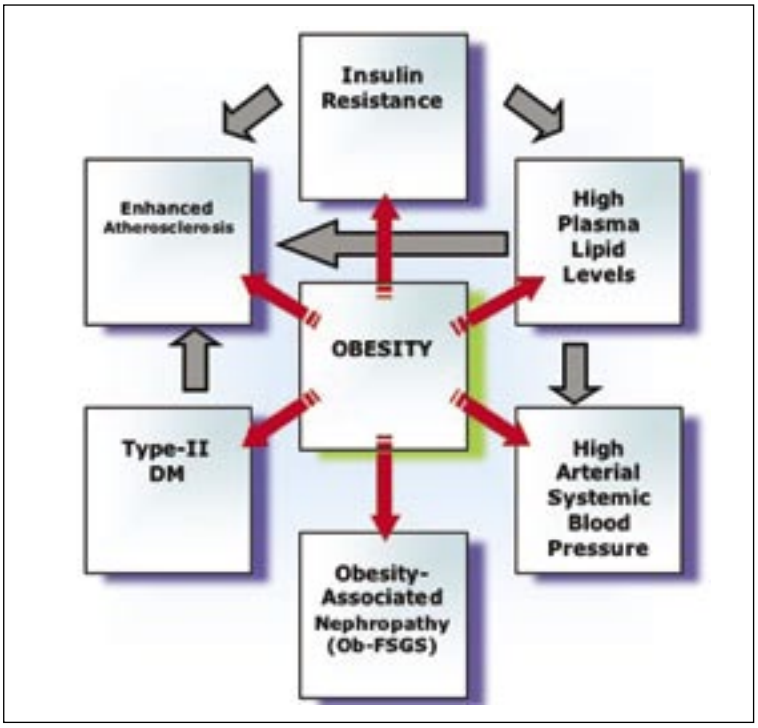

Figure 2. Renal outcome of metabolic syndrome.

Obesity and carcinoma of the prostate

Obesity may be more linked to the higher incidence and mortality of malignancies of the prostate than previously anticipated. Increased BMI possibly leads to enhancement of the progression of carcinoma of the prostate and also appears to have a consistent relationship with the mortality of prostate cancer.[41] However, some studies have suggested that excess body weight may be related to higher recurrence rates after radical prostatectomy. Since obesity is one of the few modifiable risk factors that may impact the clinical course of these cancers, lifestyle and dietary changes to limit obesity should be recommended.

The effect of obesity on the progression of underlying renal disease

Obesity has been recently reported to cause progressive deterioration of renal function in patients who had underlying renal disease, such as IgA nephropathy, or a single kidney, either as a result of nephrectomy or unilateral renal agenesis, especially when associated with hypertension and hyperlipidemia.[42-46]

Immunoglobulin-A (IgA) nephropathy

IgA nephropathy is the most common cause of glomerulonephritis in adults. In a recent study involving 162 patients with biopsy-proven primary IgA nephropathy, an elevated BMI (≥ 25 kg/m2) was found to be an independent risk factor for the development of systemic hypertension and clinical and pathological progression to ESRD.[42] Another study demonstrated noteworthy improvement in renal function subsequent to weight reduction and the employment of ACEI in IgA nephropathy-associated proteinuria and renal insufficiency.[43]

Unilateral nephrectomy/ unilateral renal agenesis

Recent reports reveal that obesity could be one of the major risk factors in the progressive loss of nephrons and consequent deterioration of renal function among patients with unilateral nephrectomy and also among those who were born with unilateral renal agenesis.[44,45]

Diabetic nephropathy

Obesity sets off a complex cascade of complications that comprise insulin resistance, glucose intolerance, dyslipidemia, atherosclerosis, and hypertension. Although surplus weight gain is the raison d'être in most patients, this group of disorders is frequently described as syndrome X or metabolic syndrome (Figure 2).[46-48] A remarkable resemblance is seen in renal effects in obese subjects and persons with diabetes. An increased glomerular blood flow and glomerular filtration rate (GFR) culminating in renal

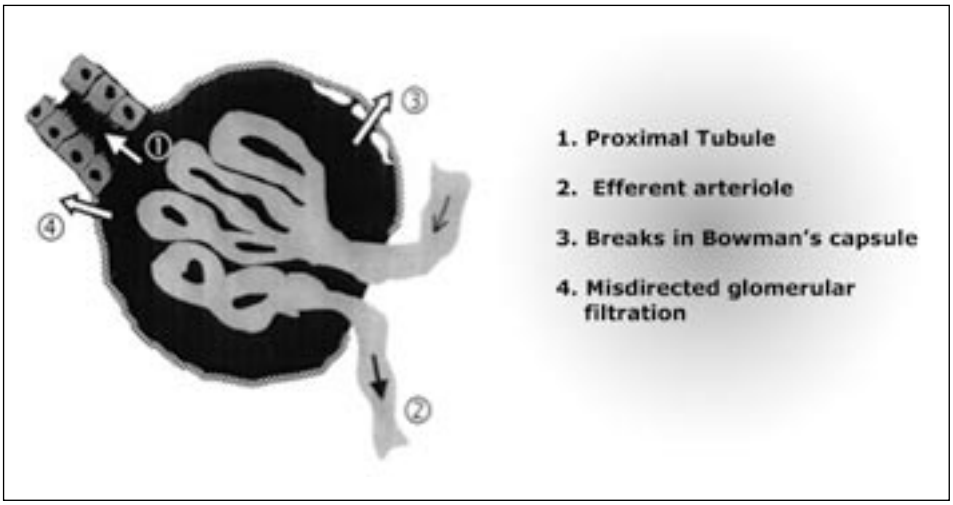

Figure 3. Altered renal hemodynamics in obesity (increased intraglomerular pressures, breaks in Bowman's capsule [arrow] with misdirected glomerular filtration [arrow] resulting in atubular glomeruli).

hypertrophy and hyperfiltration glomerular injury complicated subsequently by microalbuminuria, nephrotic range of proteinuria and eventually glomerulosclerosis, has been described individually, in both diabetes and obesity.[20]

Currently, data demonstrating a direct impact of BMI on the rate of progression of diabetic nephropathy is lacking; however, reasonable deductions regarding the rate of loss of renal function (which is likely to be considerably higher) could be made in view of the fact that nearly all components of metabolic syndrome, including the core component obesity, are capable of causing renal injury. Since patients with type II diabetes and hypertension, which collectively account for nearly 70% of patients with ESRD and proteinuric nephropathy, are both associated with excess weight gain, it is now being realized that obesity could be an underestimated potentiating and prognostic factor in the development of diabetic and non-diabetic proteinuric nephropathies.[7,47] Untreated diabetic nephropathy among overweight patients is considered to have a 2.5 times faster rate of progression, with a typical rate of loss of GFR being 10 mL/min/year than those with hypertensive nephrosclerosis.[48,49] Large prospective studies have demonstrated that weight reduction using a formula diet and use of angiotensin enzyme receptor (ACE/ARBs) blockers improves renal function and proteinuria or delays the progression of renal disease in obese patients with diabetic nephropathy.[50,51]

Mechanisms of renal injury in obesity

Maladaptive glomerular hemodynamics and subsequent changes in intraglomerular pressures bring about a cascade of events, which eventually lead to glomerular injury. Likewise, various vasoactive, fibrogenic substances synthesized and released from adipocytes, besides cytokines and hormones, synergize with the hostile renal hemodynamics in causing renal injury in obese subjects.[7,52-57]

Table 1. Cardiovascular, neurohumoral and renal changes caused by high fat diet in experimental obesity in animal models and in human obesity.

Animal/Human Model	BP	HR	COP	RSA	PRA	Sodium Balance	Renal Tubular Reabsorption of Na^+	GFR†
Obese rabbits on high fat diet	↑	↑	↑	↑	↑	↑	↑	↑
Obese dogs on high fat diet	↑	↑	↑	↑	↑	↑	↑	↑
Obese humans	↑	↑	↑	↑	↑	↑	↑	↑

Abbreviations: BP-blood pressure,HR-heart rate, COP-cardiac output, RSA-renal sympathetic activity, PRA-plasma renin activity; GFR-glomerular filtration rate.
†GFR changes refer to the early phases of obesity, before significant loss of function of nephrons has occurred.

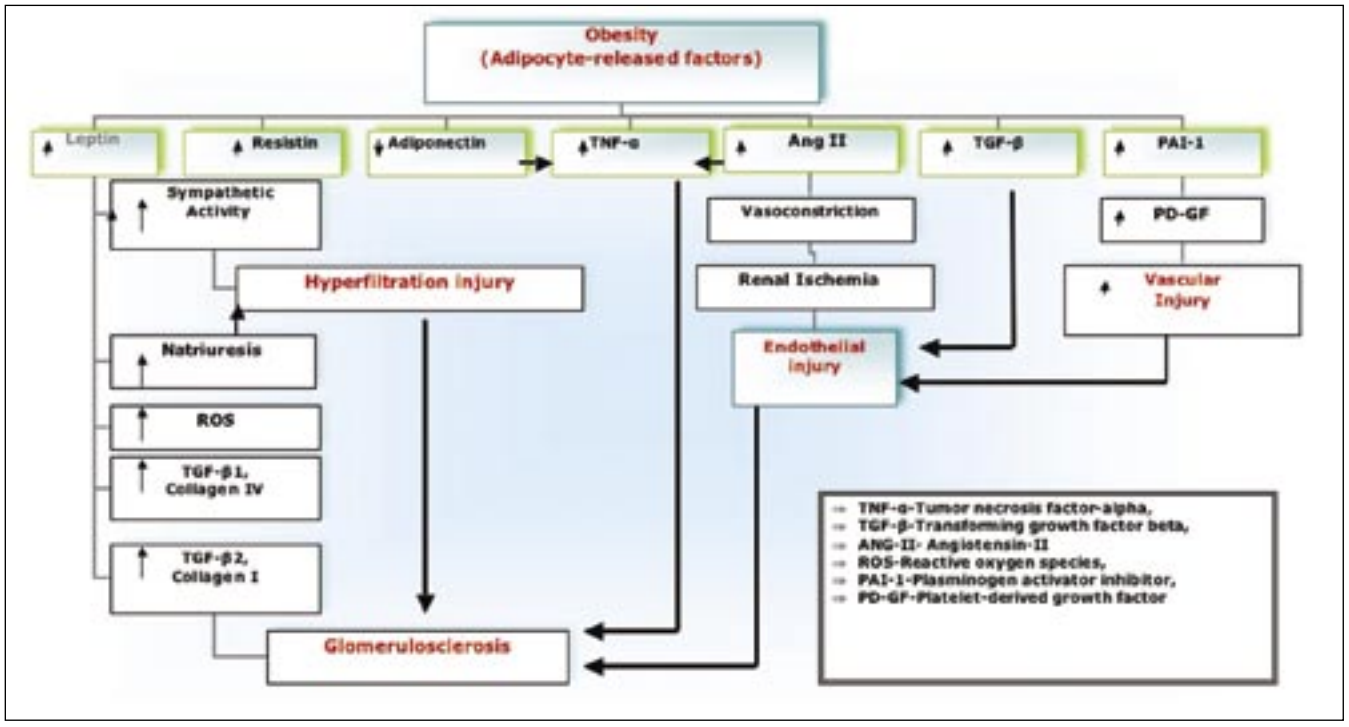

Figure 4. Adipocyte-derived and hemodynamic factors in the development of renal disease.

The role of altered renal hemodynamics

Studies on animal models (obese rabbit and dogs on high fat diet) and obese humans have clearly demonstrated that obesity is associated with increases in regional blood flows, heart rate, cardiac output, arterial pressure, renal sympathetic activity, plasma renin activity and increased GFR (Table 1).[7,55] Although cardiac index (cardiac output/body weight) does not change significantly during weight gain, absolute cardiac output increases markedly; blood flow in nonadipose tissues, including the heart, kidneys, gastrointestinal tract, and skeletal muscle increases with weight gain. The vasodilatation in these tissues is attributable in part to an increased metabolic rate and local accumulation of vasodilator metabolites, as well as growth of the organs and tissues in response to their increased metabolic demands.[7]

Altered renal hemodynamics in obesity in the form of increased regional blood flow attributed to enhanced cardiac output and renal vasodilatation leads to increased intraglomerular pressures. Hydrostatic forces thus generated cause injury to the glomerular endothelium, leading to a sequence of events including glomerular hypertrophy, macrophage accumulation in the mesangium, mesangial cell proliferation/dedifferentiation, stretching of podocytes, podocyte dysfunction and loss, and apoptosis of mesangial and endothelial cells. The end result is the loss of cellular elements of the glomerulus, matrix deposition and expansion, formation of tuft adhesions, misdirected infiltrate (leading to atubular glomeruli) and proteinuria, eventually leading to glomerulosclerosis (Figure 3).[52-54] Glomerulosclerosis is defined as the extracellular accumulation of amorphous material and matrix with obliteration of structural elements of the glomerulus.[52]

Adipocyte derived cytokines/hormones

Adipose tissue is not just a passive energy store, but also an active endocrine organ, the secretions of which influence various other organ systems, including the kidneys. In addition to the other factors associated with obesity as a part of metabolic syndrome—hypertension, atherosclerosis, hyperlipidemia, hyperglycemia due to associated insulin resistance—vasoactive (ANG II, angiotensinogen, prostaglandin I-2α), fibrogenic substances (TNF-α and TGF-1β) and hormones (leptin, ADPN, resistin) released from the adipocytes play a vital role in initiation and progression of nephrosclerosis (Figure 4).

Conclusion

Obesity essentially plays a central role in the development of systemic hypertension, nephrotic range of proteinuria with FSGS and RCC. Obesity also appears to potentiate the rate of progression of underlying renal diseases such as IgA nephropathy and possibly diabetic nephropathy. Prudently planned precise strategies to prevent obesity through comprehensive community and government-led programs, with realization that substantial modifications in lifestyle (healthy food habits and increased physical activity) and the judicious use of lipid-lowering agents (statins), ACE inhibitors/ARBs and agents that increase endogenous insulin sensitivity (glitazones), among high risk individuals, may hopefully ease the burden of obesity and improve the outcome of associated renal disease in the future.

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