© Med Sci Monit, 2010; 16(8): RA163-170
PMID: 20671624

www.MedSciMonit.com
Review Article

Received: 2010.03.06
Accepted: 2010.05.25
Published: 2010.08.01

Renal consequences of obesity

Beata Naumnik, Michał Myśliwiec

Department of Nephrology and Transplantation with Dialysis Unit, Medical University, Bialystok, Poland

Source of support: Self financing

Summary

The worldwide prevalence of obesity and its associated metabolic and cardiovascular disorders has risen dramatically within the past 2 decades. Our objective is to review the mechanisms that link obesity with altered kidney function.

Current evidence suggests that excess weight gain may be responsible for 65–75% of the risk for arterial hypertension. Impaired renal pressure natriuresis, initially due to increased renal tubular sodium reabsorption, is a key factor linking obesity with hypertension. Obesity increases renal sodium reabsorption by activating the renin-angiotensin and sympathetic nervous systems, and by altering intrarenal physical forces. Adipose tissue functions as an endocrine organ, secreting hormones/cytokines (e.g., leptin) which may trigger sodium retention and hypertension. Additionally, excess visceral adipose tissue may physically compress the kidneys, increasing intrarenal pressures and tubular reabsorption. Eventually, sustained obesity via hyperinsulinemia, due to resistance to insulin, causes hyperfiltration, resulting in structural changes in the kidneys – glomerular hypertrophy and occasionally focal segmental glomerulosclerosis. The consequences of kidney injury are continuous loss of glomerular filtration rate, further increase of arterial pressure and escalation of cardiovascular morbidity and mortality.

There is a growing awareness of the renal consequences of obesity, and considerable progress is being made in understanding its pathophysiology. Weight reduction results in lowered proteinuria. Aside from low sodium diet and exercises, more widespread use of renoprotective therapy (e.g., ACE inhibitors and statins) in treatment of hypertension in obese subjects should be advocated. Renal protection should result in reducing the cardiovascular complications of obesity.

key words: **secondary FSGS • obesity • obesity-related glomerulopathy • obesity-related hypertension**

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/881092

Word count: 3540
Tables: 2
Figures: 2
References: 63

Author's address: Beata Naumnik, Department of Nephrology and Transplantation with Dialysis Unit, Medical University, 14 Żurawia Str., 15-540 Bialystok, Poland, e-mail: bnaumnik@poczta.onet.pl

MAGNITUDE OF THE PROBLEM

Overweight and obesity have become mass phenomena with a pronounced upward trend in prevalence in most countries throughout the world. Obesity presents as one of the most important public health problem in the United States [1,2]. As the prevalence of obesity increases, so does the prevalence of its associated comorbidities [3].

"Overweight" technically refers to an excess of body weight (including increased muscle), whereas "obesity" refers to an excess of fat. Body mass index (BMI) is the accepted standard measure of overweight and obesity for adults and children 2 years of age and older [4,5]. Body mass index provides a guideline for weight in relation to height, and is equal to the body weight divided by the height in meters squared. Other measures include weight-for-height and measures of regional fat distribution (e.g., waist circumference, and waist-to-hip ratio) [4].

Adults with a BMI between 25 and 30 kg/m^2 are considered overweight; those with a BMI ≥30 kg/m^2 are considered to be obese (Table 1). A BMI threshold of ≥40 kg/m^2 distinguishes individuals with severe obesity and the highest risks for comorbidities. This category is sometimes termed "class III obesity" or "extreme obesity". The term "morbid obesity" is usually used to identify individuals with severe extreme obesity-related complications.

Epidemiology

Obesity is now considered to be a global epidemic. In most populations the prevalence of overweight and obesity has steadily increased over the past 20 years. In 2001, 55% of population was overweight in the United States. From 1980 to present the number of obese people tripled in Europe [4]. There are about 4 million additional obese Europeans every year [4]. Thus, across a wide range of developed and developing countries, studies show increasing prevalence of obesity in children. Currently, almost one-third of children and adolescents in the United States are either overweight or obese [7]. Childhood obesity is more common among American Indian, non-Hispanic blacks, and Mexican Americans than in non-Hispanic whites [3,7–9]. Only one small study, examining children in Scotland, showed a reversal of the trend between 2001 and 2004 [10]. As a general rule, girls are more prone than boys to develop persistent obesity during adolescence [6,11]. Approximately 80% of obese adolescent girls and 30% of obese adolescent males remain obese [11].

Etiology

Etiology of obesity includes different factors (Table 2); the role of genetic factors is minor. The most important are environmental factors caused by either a sedentary lifestyle or a caloric intake that is greater than the body's needs. Increasing trends in glycemic index of foods, sugar-containing beverages, larger portion sizes for prepared foods, fast food service, and decreasing structured physical activity have all been considered as causal influences on the rise in obesity. In particular, a number of well-designed studies have shown associations between intake of sugar-containing beverages or low physical activity and obesity and/or metabolic abnormalities [12–14]. Television viewing and the use of electronic or video games are perhaps the best-established environmental influence on the development of obesity during childhood [17–19]. There are several proposed mechanisms for this association [16,17]: displacement of physical activity, depression of metabolic rate and poor information on diet quality.

Genetic factors – Genetic factors play a permissive role and interact with environmental factors to produce obesity. Studies suggest that heritable factors are responsible for 30 to 50% of the variation in adiposity [1], but most of the genetic polymorphisms responsible have not yet been established. Thus, genetic contributions to common obesity likely exist, but the molecular mechanisms for these factors have yet to be determined. A variety of specific syndromes

Table 1. Classification of overweight and obesity by BMI, waist circumference, and associated disease risk.

	BMI kg/m^2	Obesity class	Disease risk* relative to weight and waist circumference	
			Men ≤102 cm	>102 cm
			Women ≤88 cm	>88 cm
Underweight	<18.5		–	–
Normal**	18.5–24.9		–	–
Overweight	25.0–29.9		Increased	High
Obesity	30.0–34.9	I	High	Very high
	35.0–39.9	II	Very high	Very high
Extreme obesity	≥40	III	Extremely high	Extremely high

* Disease risk for type 2 diabetes, hypertension, and CVD. ** Increased waist circumference can also be a marker for increased risk even in persons of normal weight.
Reproduced from: Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. Obes Res 1998; 6: 515.
The recommended classifications for BMI adopted by the National Institute of Health (NIH) and World Health Organization (WHO) and endorsed by most expert groups.

Table 2. Etiologic classification of obesity.

Iatrogenic causes
Drugs and hormones
Hypothalamic surgery
Tube feeding
Dietary obesity
Infant feeding practices
Progressive hyperplastic obesity
Frequency of eating
High fat diets
Overeating
Neuroendocrine obesities
Hypothalamic obesity
Seasonal affective disorder
Cushing's syndrome
Polycystic ovary syndrome
Hypogonadism
Growth hormone deficiency
Pseudohypoparathyroidism
Social and behavioral factors
Socioeconomic status
Ethnicity
Psychological factors
Restrained eaters
Night eating syndrome
Binge-eating
Sedentary lifestyle
Enforced inactivity (post-operative)
Aging
Genetic (dysmorphic) obesities
Autosomal recessive traits
Autosomal dominant traits
X-linked traits
Chromosomal abnormalities
Other
Low birth weight

and single-gene defects, including Prader-Willi syndrome, account for less than 1% of childhood obesity [1,22,23].

Endocrine disease – Endocrine causes of obesity are identified in less than 1% of children and adolescents with obesity [23]. The disorders include hypothyroidism, cortisol excess (i.e., the use of corticosteroid medication, Cushing syndrome), growth hormone deficiency, and acquired hypothalamic lesions (i.e., infection, vascular malformation, neoplasm, trauma) [22].

Metabolic programming and maternal nutrition during gestation – There is increasing evidence that environmental and nutritional influences during critical periods in development (infancy and early childhood) can have permanent effects on an individual's predisposition to obesity and metabolic disease. The precise mediators and mechanisms for these effects have not been established, but are the subjects of ongoing investigations [24,25].

Additional maternal endocrine factors – Other markers of the maternal endocrine milieu, such as younger mother's age at menarche, are also associated with childhood obesity, although the mechanisms for that association still are unknown [26].

Sleep – Cross-sectional studies suggest an association between shortened sleep duration and obesity or insulin resistance, after adjustment for a number of potential environmental confounders [20,21]. The mechanism for the association has not been established, but may include alterations in serum leptin and ghrelin levels, both of which have been implicated in the regulation of appetite, or perhaps less sleep creates greater opportunity to ingest food.

Clinical Implications

Measurement of BMI does not take into account the body fat distribution, which may be an important agent in further risk factors assessment [27,28]. It is well known that central (visceral, abdominal) obesity is associated with an increased risk for atherosclerosis, stroke, and coronary heart disease (CHD). A recent meta-analysis showed a 29% increase in CHD for each 5-unit increase in BMI [29]. This risk is confounded by the common coexistence of other risk factors such as hypertension, dyslipidemia, and abnormal glucose metabolism. Visceral obesity in men correlates positively with higher prevalence of prostate and bowel cancers. Lower body obesity ("women" type) presents as an independent risk factor for arrhythmias, abnormalities in sympathetic nervous system control, osteoarthrosis, varicose veins and sleep apnea, and is associated with higher risk of breast and uterus cancers. Despite sex and obesity type, excess body weight correlates positively with increased risk of neoplasmatic diseases of the anus, liver, pancreas and kidney [27,28].

Renal Involvement

Excess body weight may be associated with various functional and structural lesions of the kidney. In 1974, an association between massive obesity and nephritic-range proteinuria was first reported [29]. The spectrum of renal injury ranges from glomerulomegaly with or without focal segmental glomerulosclerosis (FSGS), to diabetic nephropathy, carcinoma of the kidney and nephrolithiasis. The first sign of renal injury is microalbuminuria or frank proteinuria, particular in the presence of hypertension. The occurrence of microalbuminuria is related to the increasing number of components of the metabolic syndrome (e.g., central obesity, elevated fasting glucose level, hypertriglyceridemia, low high-density

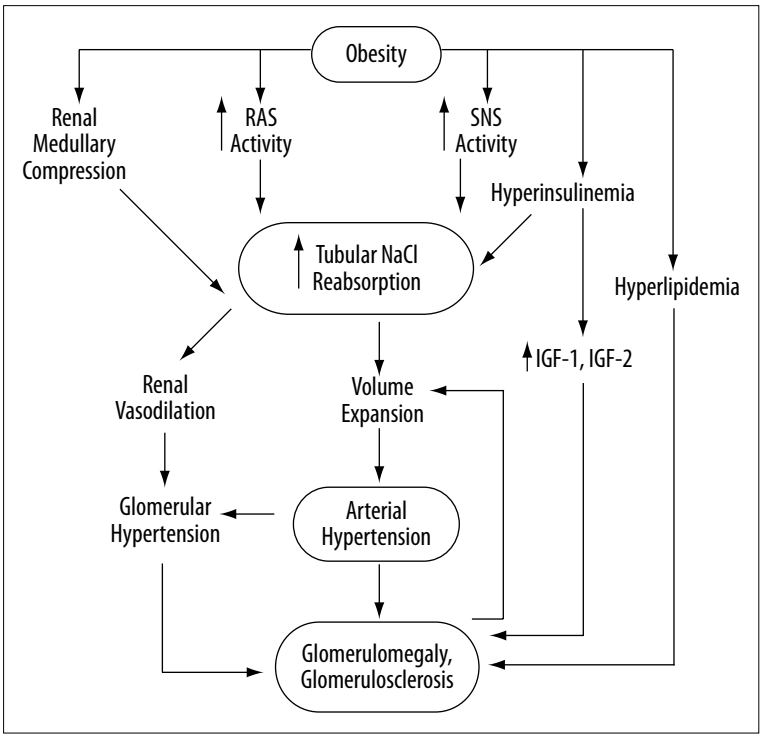

Figure 1. Mechanism of hypertension and kidney disease development due to obesity.

lipoprotein cholesterol, and hypertension) [30]. The benefit of weight reduction includes decreased proteinuria [31,32].

The BMI is also one of the predictors of chronic kidney disease (CKD) that has been observed in the Framingham Study and supported by others [32,33]. BMI not only predicts CKD, but also end-stage renal disease (ESRD). The risk of ESRD is elevated when BMI exceeds 25 kg/m^2 in Caucasians, and the threshold is still lower in Asians [34]. The true hazard of ESRD in adults may be underestimated by such observational studies, because many of the obese elderly die from cardiovascular events before they have a chance to develop ESRD. The link between obesity and ESRD is not fully explained by the known sequelae of exceed body weight, such as diabetes and hypertension. The relation between BMI and ESRD persists even when adjusted for diabetes and hypertension. Waist circumference and waist-to-hip ratio as indices of visceral obesity are even more sensitive predictors of renal injury than is BMI [35].

Mechanisms responsible for abnormal kidney function in obesity include (Figure 1) [36,37]:
1. Activation of sympathetic nervous system;
2. Activation of Renin-Angiotensin System (RAS);
3. Adipocyte-derived cytokines, e.g., leptin;
4. Physical compression of the kidney due to accumulation of intrarenal fat and extracellular matrix;
5. Hemodynamic changes – hyperfiltration, due to increased intraglomerular pressure;
6. Impaired renal-pressure natriuresis (higher pressure is needed for excretion of sodium load).

Hemodynamic changes associated with excess weight gain

Obesity is associated with increases in regional blood flows, cardiac output, and arterial pressure [36–41]. Cardiac index (cardiac output/body weight) does not change during weight gain, but absolute cardiac output increases markedly. Although part of the increased cardiac output is due to the additional blood flow required for the extra adipose tissue, blood flow in nonadipose tissue, including the heart, kidneys, gastrointestinal tract, and skeletal muscle also increases with weight gain [36–41]. The vasodilatation in these tissues appears to be due to 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. It should be noted that similar mechanisms occur in individuals with weight gain connected with increases of muscle mass.

Impaired renal pressure-natriuresis in obesity-related hypertension

As is true with other forms of hypertension, the increased blood pressure associated with obesity is accompanied by impaired pressure-natiuresis [36,42]. In obese subjects, impaired pressure-natriuresis is initially due to increased renal sodium reabsorption because glomerular filtration rate (GFR) and renal plasma flow are actually increased. Three mechanisms appear to be especially important in mediating increased sodium reabsorption associated with weight gain: (1) increased renal sympathetic activity, (2) activation of the RAS system, and (3) altered intrarenal physical forces. Another mechanism, hyperinsulinemia, has also been suggested to raise arterial pressure in obese subjects through increased renal tubular sodium reabsorption [43]. The majority of the available evidence suggests that elevated insulin levels do not raise blood pressure in dogs or humans [43]. With prolonged obesity, increases in arterial pressure, renal vasodilatation and glomerular hyperfiltration, neurohormonal activation, as well as metabolic changes may cause glomerular injury and further impairment of renal

pressure-natriuresis, resulting in more severe hypertension and a gradual loss of kidney function [38,42].

Sympathetic activation

Multiple observations in animals and humans indicate that excess weight gain is associated with increased sympathetic activity, especially in the kidney [40,44]. Increased sympathetic activity appears to raise blood pressure, mainly though the renal sympathetic nerves, because renal denervation blunts the sodium retention and markedly attenuates the rise in blood pressure associated with dietary obesity in dogs [45]. It is likely that the renal nerves also play a key role in human obesity-related hypertension. One of the most probable mechanisms by which obesity may increase sympathetic activity is hyperleptinemia [40]. Leptin is produced by adipocytes, and its fasting plasma levels rise in proportion to adiposity. Leptin regulates energy balance by decreasing appetite and also by stimulating thermogenesis *via* sympathetic activation. Although acute infusion of leptin raises sympathetic activity, the question of whether this effect would cause chronic hypertension was unclear until leptin infusion was demonstrated to cause sustained increase in blood pressure in rats despite marked hypophagia and weight loss [46].

Another observation that points toward leptin as a potential mediator of obesity-related hypertension is the finding that obese leptin-deficient mice and obese rats with leptin receptor mutation usually have little or no hypertension compared with lean controls [47]. Therefore, increased leptin synthesis and functional receptors appear to be necessary for obesity to cause significant increases in blood pressure in rodents. Another mechanism of leptin-induced sympathetic activation is its interaction with other neurohormones in the hypothalamus. For example, leptin stimulates the hypothalamic melanocortin pathway, and antagonism of the melanocortin 3/4-receptor (MC3/4-R) completely abolished the acute effects of leptin to stimulate renal sympathetic activity [48]. Moreover, chronic blockade of the MC3/4-R in rats caused rapid and marked weight gain, but little or no increase in arterial pressure [48].

The renin-angiotensin system in obesity

Although excess weight gain is associated with marked sodium retention and expansion of extracellular fluid volume, obese subjects usually have increases in plasma levels of: angiotensinogen, angiotensin-converting enzyme (ACE) activity, and angiotensin II (ANG II). They result in increased sodium reabsorption in the proximal tubular cells, decreased sodium levels in distal tubules sensed by macula densa, and through the tubulo-glomerular feedback-caused dilatation of the afferent arteriole. This is probably the main cause of glomerular hyperfiltration, apart from efferent artery constriction. A significant role of 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 ACE inhibitor blunts sodium retention and volume expansion, as well as increasing arterial pressure [49]. In addition, ACE inhibitors are effective in reducing blood pressure in obese humans, particularly in young patients [36].

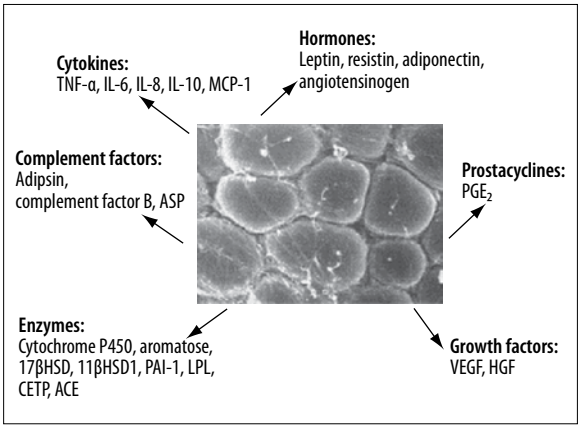

Figure 2. Cytokines produced by adipose tissue (according to Medscape: *www.medscape.com*).

In addition to hypertension, activation of the RAS also contributes to glomerular injury and nephron loss associated with obesity because ANG II formation constricts the efferent arterioles and exacerbates the rise in glomerular hydrostatic pressure caused by systemic arterial hypertension. Studies in patients with type II diabetes, who are usually overweight, clearly indicate that ACE inhibitors and ANG II receptor antagonists slow progression of renal disease [50].

Interestingly, recent evidence indicates that visceral fat cells apparently secrete a factor, different from ACTH, which stimulates aldosterone secretion by adrenocortical cells [51]. This factor may be an epoxy-keto derivative of linoleic acid, one of the oxidized products of fatty acids [51]. These findings potentially open a new perspective for the treatment of renal sequelae of the metabolic syndrome, e.g., aldosteron blockade [52].

Adipocytes derived cytokines

Recent studies suggest a paracrine role of adipose tissue in the regulation of vascular tone and function, as well as the development of renal injury [54,55]. It has been demonstrated that adipocytes release several substances, named adipocytokines (Figure 2). Both their local and systemic actions influence body mass homeostasis and many metabolic processes. Adipokines play a crucial role in inflammation, insulin resistance, diabetes, atherogenesis, and satiety-hunger balance. The precise mechanisms linking obesity and hypertension are not fully understood, however, adipocyte-derived mediators may significantly contribute to the development of the above diseases. Several active proteins generated in the central adipose tissue, including leptin, proinflammatory cytokines, plasminogen activator inhibitor-1, angiotensin, and growth factors (mainly transforming growth factor-beta 1; TGF-β_1), as well as low levels of the protective adiponectin, may contribute to renal injury [55].

Structural and functional renal changes directly connected with fat deposition

Adipose tissue almost completely encapsulates the kidneys and penetrates into medullary sinuses of obese subjects, causing compression and increased intrarenal pressure [38,42]. Intra-abdominal pressure of obese subjects is also

increased in proportion to the sagittal abdominal diameter, reaching levels as high as 35 to 40 mmHg in patients with central obesity [36].

Obesity also causes marked changes in renal medullary histology that could compress the medulla and impair pressure natriuresis. Total glycosaminoglycans containing hyaluronan, a major component of the renal medullary extracellular matrix, are markedly elevated in the inner medulla of obese dogs and rabbits, compared with controls [38,53]. Because the kidney is surrounded by a capsule with low compliance, increased extracellular matrix would raise renal interstitial pressure and solid tissue pressure, finally causing compression of the thin loops of Henle, reducing vasa recta blood flow, and increasing tubular reabsorption. In support of this, markedly elevated renal interstitial fluid pressure has been found in obese dogs [38].

Obviously, 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 between lower body obesity and hypertension [39].

Obesity-related glomerulopathy (ORG)

The clinical manifestation of renal involvement in obesity is proteinuria, and the histological features are glomerular capillary loop enlargement (glomerulomegaly), occasionally with focal segmental glomerulosclerosis (FSGS). Glomerulomegaly, as well as histological lesions resembling those of early diabetic nephropathy (e.g., increased mesangial matrix, mesangial cell proliferation, glomerular basement membrane thickening and podocyte hypertrophy) are observed in kidney biopsies of patients with morbid obesity, even before the appearance of microalbuminuria [56,57]. Obesity-related glomerulopathy, clinically and morphologically indistinguishable from that seen in morbid obesity, has recently been found even in patients with submorbid (class I and II) excess weight gain [56]. Non-obese patients with increased BMI due to elevated muscle mass are also at risk of developing a secondary FSGS that resembles obesity-related glomerulopathy [58].

The pathophysiology of ORG and glomerular sclerosis is incompletely understood at present. It is postulated that afferent arteriolar dilatation has a role in the mediation of the increased transcapillary hydraulic pressure gradient. Because insulin directly reduces norepinephrine-induced efferent arteriolar constriction, insulin resistance could have the effect of increasing the transcapillary pressure gradient by increasing efferent arteriolar resistance. Hyperinsulinemia has been shown to stimulate the synthesis of growth factors such as insulin-like growth factor (IGF)-1 and IGF-2, which may promote glomerular hypertrophy [59]. Elevated plasma levels of leptin in obesity may predispose to glomerulosclerosis through up-regulation of TGF-β_1 [60]. Hyperlipidemia itself also may promote glomerulosclerosis through mechanisms that involve engagement of low-density lipoprotein receptors on mesangial cells, oxidative cellular injury, macrophage chemotaxis, and increased production of fibrogenic cytokines [61]. Recent evidence suggests that hyperlipidemia may also mediate FSGS by direct podocyte toxicity [61].

The combination of focal segmental glomerulosclerosis and glomerulomegaly in ORG resembles the secondary forms of FSGS arising in conditions of chronic hypoxia and altered glomerular capillary hemodynamics, such as cyanotic congenital heart disease, sickle cell nephropathy, polycythemia and idiopathic pulmonary hypertension [56]. In all these conditions, FSGS develops despite an initially normal nephron number. Finally, data from experimental models suggest that obesity promotes increased matrix deposition in the medullary interstitium and that the secondary effects on tubular sodium handling may stimulate the RAS [62]. To this point, it is of interest that 20% of ORG patients had histological evidence of juxtaglomerular apparatus hyperplasia, half of whom had no history of systemic hypertension [56].

It has been suggested that the difference between ORG and idiopathic FSGS (I-FSGS) is that ORG has a lower percentage of glomeruli affected by segmental sclerosis, meaning only some nephrons leak proteins in ORG, while all nephrons leak proteins in I-FSGS. Since it is the leakage of protein that leads to abnormal nephron handling of sodium and renal retention of salt and water, ORG is not associated with edema, while I-FSGS typically manifests with nephrotic syndrome [56]. Clinically, it is distinguished from I-FSGS by its lower incidence of nephrotic syndrome, more benign course, and slower progression to renal failure. Morphologic features include the consistent presence of glomerulomegaly, predominance of classic perihilar lesion of sclerosis, and relatively mild foot process fusion [56–58]. However, because there is significant overlap in clinical and pathologic features with idiopathic FSGS, heightened physician awareness of this entity is required to ensure accurate diagnosis and appropriate therapy.

Benefits of Weight Loss

Weight loss can improve or prevent many of the obesity-related risk factors. Benefits include: decreased blood pressure in hypertensive patients, decreased incidence of diabetes mellitus, improved lipid profile, decreased insulin resistance, reduced C-reactive protein concentration, and improved endothelial function. Behavioral modification is a cornerstone in the treatment of obesity. Exercise programs combined with moderate to severe caloric restriction have additional effect upon weight loss. For individuals older than 75 years, excess body weight does not appear to be an important risk factor for kidney disease. For persons free of disease, prevention of obesity beginning in early life is crucial.

Drug therapy may be a helpful component of treatment for overweight subjects; however, among patients with cardiovascular diseases, certain drugs (such as sibutramine) are contraindicated. Anti-obesity drugs have been used as an adjunct to diet and exercise for obese patients with a BMI greater than 30 kg/m^2. The role of drug therapy has been questioned, because due to concerns about efficacy, the potential for abuse, and side effects.

Surgery (gastric bypass or banding) is another option for patients at high risk of complications from obesity. Like dietary weight loss, bariatric surgery can reduce obesity-related

risk factors, including blood pressure, diabetes incidence, and lipid profile. However, this does not appear to occur with liposuction, suggesting that the negative energy balance associated with decreased nutritional intake may be necessary for achieving the metabolic benefits of weight loss. In extremely obese subjects, gradually decreasing (meaning – normalization) GFR and daily proteinuria were observed 12 and 24 months after drastic weight loss due to bariatric surgery [31]. Recently, meta-analysis of 13 studies conducted to assess the benefits of intentional weight loss in patients with non-dialysis CKD and glomerular hyperfiltration was done [63]. In smaller, short-duration studies in patients with CKD, nonsurgical weight loss interventions reduced proteinuria (weighted mean difference [WMD] –1.31 g/24 h) and systolic blood pressure, and seem to prevent further decline in renal function. In morbidly obese individuals with glomerular hyperfiltration (GFR >125 ml/min), surgical interventions normalize GFR (WMD –25.56 ml/min) and reduce blood pressure as well as microalbuminuria [63]. Nevertheless, larger, long-term studies are still needed to analyze renal outcomes such as development of end-stage renal disease.

Therapy in Obesity-Related Glomerulopathy

The first line of therapy in ORG should be correction of underlining conditions. Although difficult to achieve, weight loss alone can reduce proteinuria, as demonstrated above. Lipid lowering agents, especially HMG-CoA reductase inhibitors, are effective in reducing mesangial sclerosis and proteinuria in obese Zuker rats; however, their role in humans remains to be defined [56]. ACE-inhibitors have been shown to be effective in reducing proteinuria in obese patients [36,49,56]. Longer follow-up will be required to determine the potential benefits of prolonged ACE inhibition in allaying progression to end-stage renal disease and preventing the possible evolution of obesity-related glomerulomegaly to obesity-related FSGS [56].

References:

1. Ogden CL, Flegal KM, Carroll MD, Johnson CL: Prevalence and trends in overweight among US children and adolescents, 1999–2000. JAMA, 2002; 288: 1728–32
2. Strauss RS, Pollack HA: Epidemic Increase in Childhood Overweight, 1986–1998. JAMA, 2001; 286: 2845–48
3. Dietz WH, Robinson TN: Clinical practice. Overweight children and adolescents. N Engl J Med, 2005; 352: 2100–9
4. Flodmark CE, Lissau I, Moreno LA et al: New insights into the field of children and adolescents' obesity: the European perspective. Int J Obes Relat Metab Disord, 2004; 28: 1189–96
5. Deurenberg P, Weststrate JA, Seidell JC: Body mass index as a measure of body fatness: age- and sex-specific prediction formulas. Br J Nutr, 1991; 65: 105–14
6. Baker S, Barlow SS, Cochran W et al: Overweight children and adolescents: a clinical report of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr, 2005; 40: 533–43
7. Ogden CL, Carroll MD, Flegal KM: High body mass index for age among US children and adolescents, 2003-2006. JAMA, 2008; 299: 2401–5
8. Anderson SE, Whitaker RC: Prevalence of obesity among US preschool children in different racial and ethnic groups. Arch Pediatr Adolesc Med, 2009; 163: 344–48
9. Obesity prevalence among low-income, preschool-aged children – United States, 1998–2008. MMWR Morb Mortal Wkly Rep, 2009; 58: 769
10. Mitchell RT, McDougall CM, Crum JE: Decreasing prevalence of obesity in primary schoolchildren. Arch Dis Child, 2007; 92: 153–54
11. Garn SM, Cole PE: Do the obese remain obese and the lean remain lean? Am J Public Health, 1980; 70: 351–53
12. Bremer AA, Auinger P, Byrd S: Relationship between insulin resistance-associated metabolic parameters and anthropometric measurements with sugar-sweetened beverage intake and physical activity levels in US adolescents: findings from the 1999–2004 National Health and Nutrition Examination Survey. Arch Pediatr Adolesc Med, 2009; 163: 328–35
13. Malik VS, Schulze MB, Hu FB: Intake of sugar-sweetened beverages and weight gain: a systematic review. Am J Clin Nutr, 2006; 84: 274–88
14. Ebbeling CB, Feldman HA, Osganian SK et al: Effects of decreasing sugar-sweetened beverage consumption on body weight in adolescents: a randomized, controlled pilot study. Pediatrics, 2006; 117: 673–80
15. Menschik D, Ahmed S, Alexander MH, Blum RW: Adolescent physical activities as predictors of young adult weight. Arch Pediatr Adolesc Med, 2008; 162: 29–33
16. Ludwig DS, Gortmaker SL: Programming obesity in childhood. Lancet, 2004; 364: 226–27
17. Epstein LH, Roemmich JN, Robinson JL et al: A randomized trial of the effects of reducing television viewing and computer use on body mass index in young children. Arch Pediatr Adolesc Med, 2008; 162: 239–45
18. Epstein LH, Roemmich JN, Paluch RA, Raynor HA: Influence of changes in sedentary behavior on energy and macronutrient intake in youth. Am J Clin Nutr, 2005; 81: 361–66
19. Stettler N, Signer TM, Suter PM: Electronic games and environmental factors associated with childhood obesity in Switzerland. Obes Res, 2004; 12: 896–903
20. Jiang F, Zhu S, Yan C et al: Sleep and obesity in preschool children. J Pediatr, 2009; 154: 814–18
21. Cappuccio FP, Taggart FM, Kandala NB et al: Meta-analysis of short sleep duration and obesity in children and adults. Sleep, 2008; 31: 619–26
22. Speiser PW, Rudolf MC, Anhalt H et al: Childhood obesity. J Clin Endocrinol Metab, 2005; 90: 1871–87
23. Reinehr T, Hinney A, de Sousa G et al: Definable somatic disorders in overweight children and adolescents. J Pediatr, 2007; 150: 618–22
24. Leunissen RW, Kerkhof GF, Stijnen T, Hokken-Koelega A: Timing and tempo of first-year rapid growth in relation to cardiovascular and metabolic risk profile in early adulthood. JAMA, 2009; 301: 2234–42
25. Gardner DS, Hosking J, Metcalf BS et al: Contribution of early weight gain to childhood overweight and metabolic health: a longitudinal study (EarlyBird 36). Pediatrics, 2009; 123: e67
26. Ong KK, Northstone K, Wells JC et al: Earlier Mother's Age at Menarche Predicts Rapid Infancy Growth and Childhood Obesity. PLoS Med, 2007; 4: e132
27. Kissebah AH, Krakowem GR: Regional adiposity and morbidity. Physiol Rev, 1994; 74: 761–811
28. Bjorntorp P: Metabolic implication of body fat distribution. Diabetic Care, 1991; 14: 1132–43
29. Weisinger JR, Kempson RL, Eldridge L, Swenson RS: The nephritic syndrome: A complication of massive obesity. Ann Intern Med, 1974; 81: 440–47
30. Chen J Gu D, Chen CS et al: Association between the metabolic syndrome and chronic kidney disease in Chinese adults. Nephrol Dial Transplant, 2007; 22: 1100–6
31. Navarro-Diaz M, Serra A, Romero R et al: Effects of drastic weight loss after bariatric surgery on renal parameters in extremely obese patients: long-term follow-up. J Am Soc Nephrol, 2006; 17 (12 Suppl.3): S213–17
32. Ishizaka Y, Ishizaka N, Tani M et al: Association between changes In obesity parameters and incidence of chronic kidney disease in Japanese individuals. Kidney Blood Press Res, 2009; 32: 141–49
33. Fox CS, Larson MG, Leip EP et al: Predictors of new-onset kidney disease in a community-based population. JAMA, 2004; 291: 844–50
34. Iseki K, Ikemiya Y, Kinjo K et al: Body mass index and the risk of development of end-stage renal disease in a screened cohort. Kidney Int, 2004; 65: 1870–76
35. Pinto-Sietsma SJ, Navis G, Janssen WM et al: A central body fat distribution is related to renal function impairment, even in lean subjects. Am J Kidney Dis, 2003; 41: 733–41
36. Hall JE: The kidney, hypertension, and obesity. Hypertension, 2003; 4: 625–33
37. Hall JE, Brands MW, Henegar JR: Mechanisms of hypertension and kidney disease in obesity. Ann N Y Acad Sci, 1999; 892: 91–107
38. Hall JE, Cook ED, Jones DW et al: Mechanisms of obesity-associated cardiovascular and renal disease. Am J Med Sci, 2002; 324: 127–37

39. Hall JE: Pathophysiology of obesity hypertension. Curr Hypertens Rep, 2000; 2: 139–47
40. Hall JE, Hildebrandt DA, Kuo J: Obesity hypertension: role of leptin and sympathetic nervous system. Am J Hypertens, 2001; 14: 103S–15
41. Hall JE, Brands MW, Dixon WN, Smith MJ Jr: Obesity-induced hypertension: renal function and systemic hemodynamics. Hypertension, 1993; 22: 292–99
42. Hall JE: Mechanisms of abnormal renal sodium handling in obesity hepertension. Am J Hypertens, 1997; 10: S49–55
43. Hall JE: Hyperinsulinemia: a link between obesity ad hypertension? Kidney Int, 1993; 43: 1402–17
44. Esler M: The sympathetic system and hypertension. Am J Hypertens, 2000; 13: 99S–105S
45. Kassab S, Kato T Wilkins C et al: Renal denervation attenuates the sodium retension and hypertension associated with obesity. Hypertension, 1995; 25: 893–97
46. Shek EW, Brands MW, Hall JE: Chronic leptin infusion increases arterial pressure. Hypertension, 1998; 31: 409–14
47. Mark AL, Shaffer RA, Correia ML et al: Contrasting blood pressure effects of obesity in leptin-deficient ob/ob mice and agouti yellow mice. J Hypertens, 1999; 17: 1949–53
48. Haynes WG, Morgan DA, Djalal WL, Mark AL: Interaction between the melanocortin system and leptin in control of sympathetic nerve traffic. Hypertension, 1999; 33: 1243–52
49. Hall JE, Henegar JR, Shek EW, Brands MW: Role of rennin-angiotensin system in obesity hypertension. Circulation, 1997; 96: I-33
50. Mogensen CE: The reno-protective role of AT(1)-receptors blockers. J Hum Hypertens, 2002; 16: S52–58
51. Nagase M, Yoshida S, Shibata S et al: Enhanced aldosterone signaling in the early nephropathy of rats with metabolic syndrome: possible contribution of fat-derived factors. J Am Soc Nephrol, 2006; 17: 3438–46
52. Ritz E: Metabolic syndrome and kidney disease. Blood Purif, 2008; 26: 59–62
53. Dwyer TM, Banks SA, Alonso-Galicia M et al: Distribution of renal medullary hyaluronan in lean and obese rabbits. Kidney Int, 2000; 58: 721–29
54. Thalmann S, Meier CA: Local adipose tissue depots as cardiovascular risk factors. Cardiovasc Res, 2007; 75: 690–701
55. Ronti T, Lupattelli G, Mannarino E: The endocrine function of adipose tissue: an update. Clin Endocrinol (Oxf), 2006; 64: 355–65
56. Kambham N, Markowitz GS, Valeri AM et al: Obesity-related glomerulopathy: An emerging epidemic. Kidney Int, 2001; 59: 1498–509
57. Goumenos DS, Kawar B, El Nahas M et al: Early histological changes in the kidney of people with morbid obesity. Nephrol Dial Transplant, 2009: 24(12): 3732–38
58. Schwimmer JA, Markowitz GS, Valeri AM et al: Secondary focal segmental glomerulosclerosis in non-obese patients with increased muscle mass. Clin Nephrol, 2003; 60(4): 233–41
59. Frystyk J, Skjaerbaek C, Vesto E et al: Circulating levels of free insulin-like growth factors in obese subjects: The impact of type 2 diabetes. Diabetes Metab Res Rev, 1999; 15: 314–22
60. Wolf G, Hamman A, Han DC et al: Leptin stimulates proliferation and TGF-β expression in renal glomerular endothelial cells: potential role in gloemrulosclerosis. Kidney Int, 1999; 56: 860–72
61. Joles JA, Kunter U, Janssen U et al: Early mechanisms of renal injury in hypercholesterolemic or hypertriglyceridemic rats. J Am Soc Nephrol, 2000; 11: 669–83
62. Dwyer TM, Banks SA, Alonso-Galicia M et al: Distribution of renal medullary hyaluronan in lean and obese rabbits. Kidney Int, 2000; 58: 721–29
63. Navaneethan SD, Yehnert H, Moustarah F et al: Weight loss interventions in chronic kidney disease: a systematic review and meta-analysis. Clin J Am Soc Nephrol, 2009; 4(10): 1565–74