

# Obesity, proteinuria and progression of renal failure

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## Purpose of review

Recent studies have reported an alarming increase in the incidence of obesity-related glomerulopathy, in a context of a worldwide spread of obesity.

## Recent findings

Several epidemiological investigations have confirmed that obesity is a significant risk factor for the appearance of proteinuria and end-stage renal disease in a normal population. Obesity-induced hemodynamic changes and glomerular deposition of lipids (partly mediated by sterol regulatory element-binding proteins) play an important role in the pathogenesis of obesity-related renal disease. In addition, the renin-angiotensin-aldosterone system is markedly activated in obesity, adipocytes being an important source of these hormones. Weight loss induces a marked reduction in all renin-angiotensin-aldosterone system components.

Patients with reduced renal mass of any origin appeared to be particularly susceptible to the detrimental influence of obesity: body mass index was the most important risk factor for the development of proteinuria and renal insufficiency in patients with unilateral renal agenesis, unilateral nephrectomy and remnant kidneys. Weight loss induces a very important reduction in proteinuria in chronic proteinuric nephropathies of different etiologies.

## Summary

Prevention and treatment of obesity should be a first-line objective in the therapeutic approach of patients with diabetic and nondiabetic chronic renal diseases.

## Keywords

focal glomerulosclerosis, glomerulopathy, hyperfiltration nephropathy, obesity, proteinuria, renin-angiotensin-aldosterone system

## Introduction

The relationship between obesity and proteinuria was known more than 20 years ago, when several papers reported a minority of obese patients who developed proteinuria [1]. Subsequent studies confirmed these findings, and renal biopsies showed focal and segmental glomerulosclerosis (FSGS) as the most common histologic lesion [2,3]. More recent studies have shown obesity-related glomerulopathy as an epidemic disease [4], whereas other epidemiologic investigations have concluded that obesity represents a significant risk factor for the appearance of renal insufficiency in a normal population [5,6]. The alarming worldwide spread of obesity has reinforced the interest in these obesity-related renal diseases, however.

## Obesity as a risk factor for end-stage renal disease

In spite of the well known implication of obesity as a cause of proteinuria and FSGS, it was not until a few years ago that information was available on the possible role of obesity as a risk factor for the appearance of renal insufficiency. Fox *et al.* [5] reported a community-based, longitudinal cohort study of 2585 participants, which performed a baseline examination in 1978–1982 and a follow-up examination in 1998–2001. All participants had normal renal function at the baseline. After a mean follow-up of 18 years, 9.4% of the participants had developed kidney disease, defined as a glomerular filtration rate (GFR) lower than 59.2 ml/min/1.73 m<sup>2</sup> in women and 64.2 ml/min/1.73 m<sup>2</sup> in men. Body mass index (BMI) was found as a significant risk factor for the appearance of renal insufficiency, together with age and GFR at baseline, and other classic cardiovascular-disease risk factors (diabetes, hypertension, low HDL-cholesterol levels and smoking). In another study performed in Japan [6], BMI was associated with an increased risk of the development of end-stage renal disease (ESRD) in the general population.

More recent publications have confirmed this detrimental influence of BMI on the evolution of renal function in the general population. Hsu *et al.* [7\*\*] performed a historical cohort study of 320 252 adults who volunteered for health checkups between 1964 and 1985. A total of 1471 cases of ESRD appeared, and higher BMI was a risk factor for ESRD after adjusting for other variables. Compared with people who had normal weight (BMI lower than 25 kg/m<sup>2</sup>), the relative risk for ESRD was 1.87 for those who were overweight (BMI 25–29.9 kg/m<sup>2</sup>), 3.57

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## Abbreviations

<b>BMI</b>	body mass index
<b>CKD</b>	chronic kidney disease
<b>ESRD</b>	end-stage renal disease
<b>FSGS</b>	focal and segmental glomerulosclerosis
<b>GFR</b>	glomerular filtration rate
<b>OR</b>	odds ratio
<b>OZR</b>	obese Zucker rat
<b>RAAS</b>	renin-angiotensin-aldosterone system
<b>SREBP</b>	sterol regulatory element-binding protein

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for those with class I obesity (BMI 30–34.9 kg/m<sup>2</sup>), 6.12 for those with class II obesity (BMI 35–39.9 kg/m<sup>2</sup>) and 7.07 for those with a BMI higher than 40 kg/m<sup>2</sup>.

Gelber *et al.* [8\*\*] studied a cohort of 11 104 initially healthy men. After an average 14-year follow-up, 1377 participants (12.4%) had developed chronic kidney disease (CKD), defined as a GFR less than 60 ml/min/1.73 m<sup>2</sup>. The study demonstrated that a higher baseline BMI was associated with increased risk for CKD. Compared with participants in the lowest BMI quintile (<22.7 kg/m<sup>2</sup>), those in the highest quintile (>26.6 kg/m<sup>2</sup>) had an odds ratio (OR) of 1.45. Those participants whose BMI increased more than 10% during follow-up also had a significant increase in the risk for CKD (OR 1.27). Data from the Hypertension Detection and Follow-Up Program (HDFP) have also confirmed this association between obesity and renal function derangement [9\*]. In 5897 hypertensive adults without CKD at baseline (defined as the presence of 1+ or greater proteinuria and/or a GFR lower than 60 ml/min/1.73 m<sup>2</sup>), the incidence of CKD at year 5 was 28% in people with normal BMI, 31% in the overweight group, and 34% in obese participants. Both overweight (OR 1.21) and obesity (OR 1.40) were risk factors for the appearance of CKD at year 5.

### Clinical features

The aforementioned epidemiological studies, while providing a strong evidence of the importance of obesity as a risk factor for CKD and ESRD, do not present detailed clinical aspects of the participants that developed these complications. Obesity can affect renal function through several pathogenic mechanisms: the most accurately described type of renal involvement is the so-called 'obesity-related glomerulopathy'. Typically, obese patients show a slowly progressive proteinuria, which can reach the nephrotic range [4,10–12]. The appearance of proteinuria usually precedes the onset of GFR decline by several years [4,10–12]. The histological counterpart of these clinical manifestations includes FSGS and glomerulomegaly as the most significant and frequent findings [4,10,12]. In comparison with 'primary' or 'idiopathic' FSGS, obesity-related FSGS usually exhibits a slower progression of proteinuria and renal failure, although renal prognosis is poor: in a series of 15 obese patients with biopsy-proven FSGS, Kaplan-Meier estimated probabilities of renal survival after 5 and 10 years were 77% and 51%, respectively [10].

Glomerular diseases other than obesity-related glomerulopathy can also affect obese people. Since prognosis and therapeutic attitudes are drastically different, the differential diagnosis between these entities is crucial. A distinctive clinical characteristic of patients with obesity-related FSGS and nephrotic proteinuria is that

they never develop edema, hypoalbuminemia or extreme hyperlipidemia, all typical findings of classical nephrotic syndrome, even in the presence of massive proteinuria levels (higher than 15–20 g/24 h in some cases) [4,10]. This peculiar characteristic is shared by other nephropathies related to hyperfiltration, such as reflux nephropathy or proteinuria associated with renal mass reduction [13]. Patients with proteinuria due to hyperfiltering disorders exhibit significantly lower urinary excretions of N-acetyl-B-glucosaminidase and  $\beta$ 2-microglobulin than patients with other types of nephrotic proteinuria and hypoalbuminemia, suggesting a different tubular handling of filtered proteins in hyperfiltering diseases [14].

### Hemodynamic changes

Several experimental studies have demonstrated that obesity induces renal hemodynamic changes consistent with glomerular hyperperfusion and hyperfiltration. An increase of GFR, renal plasma flow (RPF), glomerular pressure and filtration fraction through a dilated glomerular afferent arteriole, has been repeatedly found in experimental models of obesity [15] and in obese subjects [16]. In addition, it has been recently demonstrated that obesity-related hyperfiltration improves substantially after drastic weight loss induced by bariatric surgery [17]. The mechanisms through which overweight induces these hemodynamic changes are only partially known. An increased renal sodium reabsorption has been observed in obesity, and this impaired natriuresis is likely to play an important role in the vasodilation of afferent glomerular arteriole and the consequent transmission of increased arterial pressure to the glomerular capillary [18]. Increased renal sympathetic activity and activation of the renin-angiotensin system are other important stimulus for obesity-related increased renal sodium reabsorption [18].

### Hyperlipidemia

The pathogenic role of hyperlipidemia in the unspecific progression of renal damage has been demonstrated in several experimental models. Since hyperlipidemia is very common among obese people, some experimental studies have tried to link lipid disorders with glomerular abnormalities induced by obesity. Jiang *et al.* [19\*\*] administered a high fat diet to C57BL/6J mice: these animals developed significant obesity, hyperglycemia, and hyperinsulinemia in comparison with the control group. Renal expression of sterol regulatory element-binding proteins (SREBP-1 and SREBP-2) increased significantly in the high-fat group, and this increase resulted in the renal accumulation of cholesterol and triglycerides, together with significant renal increase of plasminogen activator inhibitor-1 (PAI-1), vascular endothelial growth factor (VEGF), type IV collagen and fibronectin. Glomerulosclerosis and proteinuria showed a strong correlation with the renal

accumulation of these factors. Genetic manipulation of SREBP, using SREBP-1c(-/-) mice, largely prevented renal deposition of lipids.

### Renin-angiotensin-aldosterone system

Adipose tissue, especially the visceral type, is a recognized source of all the components of the renin-angiotensin-aldosterone system (RAAS). Obese patients usually have increases in plasma renin activity, angiotensinogen, angiotensin-converting enzyme activity and circulating angiotensin II [18]. This obesity-induced RAAS activation is likely to play a role in the aforementioned renal hemodynamic changes induced by obesity. In addition, activated RAAS is very likely to play a fundamental role in the hyperinsulinemia, oxidative stress and inflammation that typically accompany overweight and obesity [20,21].

In a recent study, Xu *et al.* [22\*\*] analysed the renal expression of several inflammatory mediators and the influence of the AT1-receptor blocker losartan on obese Zucker rats (OZR). In comparison with lean controls, OZR showed mesangial expansion and increased mRNA expression of fibronectin, interleukin-6, monocyte chemoattractant protein-1 and several enzymes of arachidonate metabolism. This was associated with significant increases in p38, extracellular signal-regulated kinase (ERK) and upregulation of angiotensin II type 1 receptor mRNA and protein expression. All these abnormalities, as well as the appearance of proteinuria and glomerulosclerosis, were prevented by losartan. Blanco *et al.* [23\*] also used the OZR model to study the influence of the ACE inhibitor quinapril and atorvastatin on early podocyte damage. Quinapril normalized proteinuria, cholesterol levels, glomerular abnormalities and podocyte morphology. Atorvastatin improved, but did not normalize, these lesions.

Engeli *et al.* [24\*\*] studied the influence of obesity and weight loss on the circulating and adipose tissue RAAS in menopausal women. Circulating angiotensinogen, renin, aldosterone and ACE activity were higher in obese than in lean women. A reduction in body weight of -5% induced by a low calorie diet was accompanied by a reduction in angiotensinogen levels (-27%), renin (-43%), aldosterone (-31%) and ACE activity (-12%), in parallel with a significant blood pressure reduction.

Recent studies have shown that plasma aldosterone levels are disproportionately elevated in obese hypertensive patients, particularly those with abdominal obesity [25]; this elevation is relatively independent of plasma renin activity. Human adipocytes secrete partially characterized factors that directly induce the synthesis of aldosterone adrenal glands [26]. A recent study [27]

showed that the prevalence of metabolic syndrome was significantly higher in primary aldosteronism than in essential hypertension (41% compared with 29%). These data suggest that obese subjects could be particularly sensitive to the recently emphasized antiproteinuric, renoprotective and cardioprotective effects of spironolactone and other antagonists of aldosterone [28].

### Inflammation, oxidative stress and nitric oxide

Inflammatory abnormalities and oxidative stress are characteristic findings of both obesity and metabolic syndrome. Central adipose tissue is a rich source of inflammatory cytokines (CRP, TNF, interleukin-6), and oxidative stress, partially mediated by increased production of angiotensin II, is commonly demonstrated in experimental studies [20,21]. Chander *et al.* [29] provided conclusive evidence of the role of oxidative and nitrosative stress in the obese Zucker rats. Importantly, treatment with a peroxynitrate scavenger, ebselen, ameliorated not only markers of oxidative damage but also histologic and functional abnormalities linked to the obesity in this experimental model. The implication of oxidative stress in the renal damage associated with obesity has also been suggested in another experimental model of obesity, the spontaneously hypertensive/NIH-corpulent rat, SHR/NDmcr-cp(cp/cp). A low-calorie diet in these animals improved proteinuria, glomerulosclerosis and the renal content of pentosidine and advanced glycation end products [30\*]. Trujillo *et al.* [31\*] showed a protective effect of a soy diet on obese Zucker rats, which was correlated with a reduction of caveolin-1 and a restoration of nitric oxide generation.

Wu *et al.* [32\*\*] studied gene expression profiles in renal biopsies of six patients with obesity-related glomerulopathy. Compared with normal controls, the expression of genes related to lipid metabolism, inflammation and insulin resistance was significantly increased. The list of these genes includes low-density lipoprotein receptor, fatty acid binding protein 3, sterol regulatory element binding protein 1, TNF-alpha, interleukin-6 signal transducer, interferon gamma, glucose-transporter 1, leptin receptor, peroxisome proliferator-activated receptor-gamma, and VEGF.

### Synergy of obesity and low nephron number

Postulated more than 20 years ago, the hyperfiltration theory tried to explain the progression of renal diseases by a series of unspecific maladaptive hemodynamic changes that would appear obligatorily in the remaining glomeruli when the total number of functioning nephrons is drastically reduced [33]. Renal diseases characterized by a reduction in renal mass (reflux nephropathy, unilateral renal agenesis, extensive surgical removal of renal parenchyma) are considered to be the clinical translation of the experimental models of hyperfiltration (3/4 or 5/6

nephrectomy). Whereas some patients with these renal diseases show progressively increasing proteinuria and renal insufficiency, others, however, maintain a normal renal function and negative proteinuria over prolonged follow-up. Some clinical studies suggest that obesity could be the key factor that determines these discrepant evolutions [34<sup>•</sup>]. Although the appearance of renal abnormalities (slowly progressive proteinuria and renal insufficiency) is relatively uncommon after unilateral nephrectomy, a clinical study showed that BMI at the time of nephrectomy and throughout follow-up was significantly higher among patients that developed these abnormalities in comparison with patients that did not [35]. González *et al.* [36<sup>••</sup>], in a series of studies of 54 patients with unilateral renal agenesis or remnant kidneys, found that BMI was the only clinical variable statistically associated with the risk of developing proteinuria and progression of renal failure. The long-term patients' follow-up allowed the detection of proteinuria and renal insufficiency in 45% of those showing no renal abnormalities at presentation. BMI was the most important difference between these patients and those who remained normal throughout follow-up:  $27 \pm 3.6 \text{ kg/m}^2$  compared with  $21.6 \pm 2.6 \text{ kg/m}^2$ , respectively.

The synergic interplay between obesity and reduction in nephron number has an apparently physiological basis. As already noted, obesity induces a series of renal hemodynamic changes that are almost identical to those induced by a significant reduction in the number of functioning nephrons.

The detrimental influence of obesity in patients with a reduced renal mass could also play an important role in renal transplant recipients. Ducloux *et al.* [37<sup>•</sup>] explored the impact of posttransplant weight gain on 292 patients. Those with an increase of more than 5% in BMI at 1 year posttransplant had an increased risk of graft loss.

## Conclusion

Weight loss induces an important reduction in obese patients with proteinuria [38–40]. Importantly, this anti-proteinuric effect of weight loss is observed in type-2 diabetic patients with obesity and in obesity-related glomerulopathy, but also in obese patients suffering from renal diseases whose pathogenesis is unrelated to hyperfiltration (e.g. primary glomerulonephritis) [40]. This generalized effect suggests that overweight/obesity could exert a detrimental influence on the evolution of chronic proteinuric nephropathies, as some authors have pointed out [41]. The mechanisms through which weight loss might reverse proteinuria are likely to be plural [42<sup>••</sup>, 43<sup>••</sup>]: a better control of blood pressure, improvement of serum lipid profile, improvement of insulin sensitivity, better glycemic control in diabetic patients, decrease of circulating leptin levels [44], reversal of

glomerular hyperfiltration [15–18] and decrease of RAAS activation [24<sup>••</sup>].

The reduction in proteinuria induced by weight loss is rapidly observed and shows a significant correlation with the percentage of weight reduction; however, rather modest weight losses, inferior to 5% of the baseline weight, can induce reductions in proteinuria higher than 30% of baseline values [40]. All these evidences strongly suggest that weight loss is a potent but poorly investigated and commonly forgotten antiproteinuric therapeutic measure which, in addition, offers a generalized improvement of patients' metabolic profile [40, 42<sup>••</sup>, 43<sup>••</sup>].

Some recent reports analysing the effects of bariatric surgery on patients with morbid obesity illustrate how dramatic the influence of weight loss on proteinuria can be [45, 46]. Palomar *et al.* [47<sup>•</sup>] studied the evolution of 35 morbidly obese patients that underwent bariatric surgery. Weight loss was 67% at 1 year after intervention. All cardiovascular risk factors (hypertension, diabetes, dyslipidemia) significantly improved during follow-up and microalbuminuria and proteinuria showed a drastic reduction.

## References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 538).

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