The Fatty Kidney: Obesity and Renal Disease

Manuel Praga · Enrique Morales

Nephrology Division, Instituto de Investigación Hospital 12 de Octubre, Universidad Complutense, Madrid, Spain

Key Words

Angiotensin-converting enzyme inhibitors ·
Hyperfiltration · Focal and segmental glomerulosclerosis

Abstract

Obesity-related glomerulopathy (ORG) is characterized by glomerulomegaly accompanied in many patients by lesions of focal and segmental glomerulosclerosis. Slowly increasing subnephrotic proteinuria is the commonest presentation of ORG. Occasionally, massive proteinuria (>5–10 g/day) is detected, but the typical findings of nephrotic syndrome are characteristically absent even in patients with massive proteinuria. Superimposed obesity can fuel the progression of other renal diseases, and a reduced number of functioning nephrons (of congenital or acquired causes) synergizes with obesity to induce end-stage renal disease. Weight loss, either induced by diet or bariatric surgery, and renin-angiotensin blockers are effective treatments to slow progression, but a significant proportion of cases will develop end-stage renal disease.

© 2016 S. Karger AG, Basel

Contribution from the CME course of the DIABESITY Working Group of the ERA-EDTA, Bergamo, December 4–5, 2015.

In the last 3 decades, the proportion of overweight and obese adults has increased from 28.8 to 36.9% among men, and from 29.8 to 38.0% among women. This worldwide epidemic of obesity has immense socioeconomic and medical consequences. Kidneys can also be affected by the detrimental effects of obesity. It has been estimated that in 14–30% of patients with chronic kidney disease (CKD), overweight/obesity likely plays an important pathogenic role [1].

Pathology

Of the ways through which obesity can affect the kidneys, the best known is the so-called obesity-related glomerulopathy (ORG). It is characterized by glomerulomegaly, which may or may not be accompanied by lesions of focal and segmental glomerulosclerosis (FSGS) [2]. FSGS lesions are predominantly perihilar and are observed mainly in hypertrophied glomeruli. Other typical features are the presence of an irregular, mild effacement of foot processes, in contrast with the diffuse effacement seen in other glomerular entities causing nephrotic syndrome (such as primary FSGS), and the presence of lipid deposits in mesangial and tubular cells. ‘Diabetoid’ changes (focal mesangial sclerosis, focal

thickening of glomerular and tubular basement membranes) are frequently seen in obese patients without diabetes [2].

Pathogenesis

The characteristic glomerular hyperfiltration that accompanies obesity has been implicated as one of the most important pathogenic mechanisms in ORG [3]. Several studies have shown a close linear correlation between different markers of obesity (BMI, waist circumference, waist-to-hip ratio) and the glomerular filtration rate [4]. Obesity is associated with reduced preglomerular vascular resistances and increased glomerular flow; these hemodynamic changes result in glomerular hypertension, glomerulomegaly and microvascular stretching leading eventually to podocyte loss and the appearance of FSGS lesions.

As in diabetic nephropathy, obesity-related hyperfiltration could have a tubular origin. Increased proximal tubular reabsorption of glucose and sodium via SGLT2 and SGLT1 would result in a decreased sodium load to macula densa and distal tubule, which in turn activates tubuloglomerular feedback inducing preglomerular vasodilation and increased glomerular filtration rate [5]. Recent studies show that SGLT2 inhibitors lower glomerular filtration rate and albuminuria in hyperfiltering diabetic patients and that these drugs could have an important nephroprotective role as well as substantial beneficial influence on cardiovascular risk [5, 6]. The potential benefits of SGLT2 inhibitors in non-diabetic obesity-related renal disease constitute an important issue that deserves further investigation.

An important pathogenic issue is the frequent concomitant presence of other clinical conditions also associated with hyperfiltration, such as diabetes or renal mass reduction in ORG patients. In this regard, several studies have shown that the risk of developing proteinuria and end-stage renal disease in patients undergoing unilateral nephrectomy or in patients with extreme renal mass reductions was significantly higher among overweight/obese patients, as compared to lean subjects [7]. Obesity, thus, fuels the typical hyperfiltration of patients with significant reductions of renal mass. The detrimental effect of obesity, when superimposed in other renal diseases, has been scarcely investigated, with the exception of IgA nephropathy [8]. Several studies have shown a significant worse renal outcome among obese patients with this disease.

Reduced nephron mass may also have a congenital origin, owing to inadequate intrauterine development. Epidemiological studies have shown that the risk of CKD is significantly higher in subjects with birth weight in the <10th percentile [9]. Notably, it has been shown that glomerular density (a surrogate marker of the total number of nephrons) is significantly lower in patients with biopsy-proven ORG as compared to control patients [10]. These findings are also in accordance to the synergistic effect of obesity and a reduced renal mass, either of congenital or of acquired origin.

Recent studies have suggested that the combination of reduced nephron endowment associated with prematurity or low birth weight and the occurrence of obesity later in life is an increasing problem with serious medical consequences. On the other hand, this combination appears to be particularly frequent in underdeveloped countries, in which the epidemic of obesity is reaching alarming proportions.

Epidemiological investigations have provided important findings about the reasons why some obese subjects develop CKD, while others, with equal or greater degree of obesity, do not. The presence of each of the components of the so-called metabolic syndrome (hypertension, hypertriglyceridemia, low HDL-cholesterol, elevated fasting serum glucose levels) was significantly associated with the risk of developing CKD. In fact, the likelihood of developing CKD was higher in metabolically unhealthy non-obese subjects than in metabolically healthy obese ones [11]. These findings are remarkable and indispensable to identify obese patients who are really at risk to develop CKD and to implement preventive strategies.

Clinical Manifestations

The most common clinical presentation is the detection of proteinuria in an obese patient with normal urinary sediment [12, 13]. In most cases, proteinuria does not reach the nephrotic range. But even in those cases with nephrotic proteinuria (>3.5 g/day), which occurs in about 30% of cases, there is a characteristic absence of edema, hypoalbuminemia and the typical disproportionate hyperlipidemia of nephrotic syndrome [12, 13]. Proteinuria can be massive in some cases (>20 g/day), but the presence of full nephrotic syndrome is exceptional even in such cases. The reason why ORG patients do not develop nephrotic syndrome even in the presence of massive proteinuria is not known. On the one hand, the slow progression of proteinuria along many years might allow the development of compensating mechanisms that limit

Table 1. Differences between obesity-related FSGS and primary-FSGS

Obesity-related FSGS	Primary FSGS
Slowly increasing proteinuria	Sudden onset of proteinuria
Subnephrotic proteinuria in most of the patients	Nephrotic-range proteinuria in most of the patients
Absence of nephrotic syndrome (edema, hypoalbuminemia) even in patients with massive proteinuria	Full nephrotic syndrome frequently observed
Glomerulomegaly	Normal glomerular volume
Irregular effacement of foot processes in electron microscopy	Diffuse effacement of foot processes

its systemic and metabolic impact by increasing hepatic synthesis of albumin and other proteins. On the other hand, it has been suggested that tubular handling (degradation and reabsorption) of filtered proteins can be different in nephropathies caused by hyperfiltration, like ORG, as compared to glomerular diseases that cause full nephrotic syndrome.

The knowledge of this peculiarity of ORG is very important from a diagnostic point of view. For example, in an obese subject who presents with proteinuria accompanied by edema and all other components of nephrotic syndrome (hypoalbuminemia, hyperlipidemia), diagnostic suspicions must be focused on minimal change disease, primary FSGS, membranous nephropathy or other glomerular diseases that cause nephrotic syndrome. Since FSGS lesions are a characteristic finding in ORG, these clinical features, in conjunction with pathologic findings, are very important in order to establish a correct diagnosis. Table 1 summarizes the main distinctive clinical and histological data of obesity-associated FSGS and primary FSGS.

The absence of nephrotic syndrome even in the presence of massive proteinuria is a characteristic that ORG shares with other hyperfiltration-induced renal diseases, such as reflux nephropathy or FSGS associated with renal mass reduction [14]. Another important consequence of this peculiarity is that obese people who develop proteinuria can go unnoticed for years, owing to the absence of clinical manifestations, and be detected at a stage when the renal function is already severely impaired. Besides proteinuria, hypertension and dyslipidemia are found in a majority of ORG patients.

According to the findings of some studies in which a renal biopsy was obtained at the time of bariatric surgery in morbidly obese patients, ORG lesions (glomerulomegaly, FSGS, vascular and tubulointerstitial fibrosis) can be present in a significant number of obese subjects without proteinuria or renal function derangement [15].

Treatment

Both weight loss and renin-angiotensin system (RAS) blockade have shown efficacy in the treatment of ORG. Some observational studies and some small prospective randomized trials have shown that weight loss is associated with a significant reduction in proteinuria [16, 17]. Most studies have compared low-calorie diets with normal diets and some of them have included diabetic patients and obese patients with other kidney disease (IgA nephropathy, lupus). Overall, weight loss was accompanied by a significant reduction of proteinuria, the greater the weight loss the greater the reduction in proteinuria. The antiproteinuric effect of weight loss was also evident in obese patients with other nephropathies. Given the short follow-up period of these studies and the small sample size, it has not been possible to ascertain if this antiproteinuric effect translates into prevention of renal events. Weight loss is in general much more effective with bariatric surgery than with low-calorie diets. Some clinical reports have shown a dramatic reduction in proteinuria in ORG patients after bariatric surgery. Bariatric surgery has demonstrated a significant favorable effect in type 2 diabetic patients with morbid obesity in terms of survival, and recent guidelines recommend the consideration of this type of weight-loss surgery in these patients. However, from a renal point of view, patients included in these studies had normal renal function and no or minimal albuminuria. Other studies have shown that the rate of peri-surgical complications was significantly higher in morbidly obese patients with CKD. Therefore, prospective controlled studies to evaluate the efficacy and safety of bariatric surgery in ORG patients, diabetics and nondiabetic, with proteinuria and/or CKD are needed.

RAS blockade, either with angiotensin-converting enzyme inhibitors or with angiotensin receptor blockers, has

shown a significant antiproteinuric effect in observational studies [13]. Antialdosterone agents are also able to reduce proteinuria in obese patients. A subsequent analysis of the REIN study, that compared ramipril versus placebo in patients with chronic proteinuric nephropathies, showed that obese patients were more sensible to the antiproteinuric and renoprotective effects of ramipril than non-obese patients [18]. However, some studies with a longer follow-up suggest that the reduction in proteinuria induced by RAS blockers can be exhausted over time, particularly in the absence of any weight loss or further weight gain.

The progressive discovery of new metabolic pathways and activating factors that control ectopic lipid deposition and the identification of other pathogenic mecha-

nisms involved in ORG can provide new therapeutic avenues for the coming years. On the other hand, more clinical research is needed about predictive markers of the occurrence of CKD in obese, the progression of renal damage in the absence of proteinuria and the synergy of obesity with diabetic and non-diabetic kidney diseases. The efficacy of weight loss, induced either by low calorie diets or by bariatric surgery, should be confirmed by well-designed large prospective trials.

Disclosure Statement

The authors have no conflicts of interest to declare.

References

- Wang Y, Chen X, Song Y, Caballero B, Che-skin LJ: Association between obesity and kidney disease: a systematic review and meta-analysis. *Kidney Int* 2008;73:19–33.
- D'Agati VD, Kaskel FJ, Falk RJ: Focal segmental glomerulosclerosis. *N Engl J Med* 2011; 365:2398–2411.
- Chagnac A, Herman M, Zingerman B, Erman A, Rozen-Zvi B, Hirsh J, Gafter U: Obesity-induced glomerular hyperfiltration: its involvement in the pathogenesis of tubular sodium reabsorption. *Nephrol Dial Transplant* 2008;23:3946–3952.
- Bosma RJ, van der Heide JJ, Oosterop EJ, de Jong PE, Navis G: Body mass index is associated with altered renal hemodynamics in non-obese healthy subjects. *Kidney Int* 2004; 65:259–265.
- Novikov A, Vallon V: Sodium glucose cotransporter 2 inhibition in the diabetic kidney: an update. *Curr Opin Nephrol Hypertens* 2016;25:50–58.
- Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE, EMPA-REG OUTCOME Investigators: Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;373:2117–2128.
- Praga M, Hernández E, Herrero JC, Morales E, Revilla Y, Díaz-González R, Rodicio JL: Influence of obesity on the appearance of proteinuria and renal insufficiency after unilateral nephrectomy. *Kidney Int* 2000;58:2111–2118.
- Tanaka M, Yamada S, Iwasaki Y, Sugishita T, Yonemoto S, Tsukamoto T, Fukui S, Takasu K, Muso E: Impact of obesity on IgA nephropathy: comparative ultrastructural study between obese and non-obese patients. *Nephron Clin Pract* 2009;112:c71–c78.
- Vikse BE, Irgens LM, Leivestad T, Hallan S, Iversen BM: Low birth weight increases risk for end-stage renal disease. *J Am Soc Nephrol* 2008;19:151–157.
- Tsuboi N, Utsunomiya Y, Kanzaki G, Koike K, Ikegami M, Kawamura T, Hosoya T: Low glomerular density with glomerulomegaly in obesity-related glomerulopathy. *Clin J Am Soc Nephrol* 2012;7:735–741.
- Hashimoto Y, Tanaka M, Okada H, Senmaru T, Hamaguchi M, Asano M, Yamazaki M, Oda Y, Hasegawa G, Toda H, Nakamura N, Fukui M: Metabolically healthy obesity and risk of incident CKD. *Clin J Am Soc Nephrol* 2015;10:578–583.
- Kambham N, Markowitz GS, Valeri AM, Lin J, D'Agati VD: Obesity-related glomerulopathy: an emerging epidemic. *Kidney Int* 2001; 59:1498–1509.
- Praga M, Hernández E, Morales E, Campos AP, Valero MA, Martínez MA, León M: Clinical features and long-term outcome of obesity-associated focal segmental glomerulosclerosis. *Nephrol Dial Transplant* 2001;16:1790–1798.
- Praga M, Morales E, Herrero JC, Pérez Campos A, Domínguez-Gil B, Alegre R, Vara J, Martínez MA: Absence of hypoalbuminemia despite massive proteinuria in focal segmental glomerulosclerosis secondary to hyperfiltration. *Am J Kidney Dis* 1999;33:52–58.
- Serra A, Romero R, Lopez D, Navarro M, Esteve A, Perez N, Alastrue A, Ariza A: Renal injury in the extremely obese patients with normal renal function. *Kidney Int* 2008;73: 947–955.
- Morales E, Valero MA, León M, Hernández E, Praga M: Beneficial effects of weight loss in overweight patients with chronic proteinuric nephropathies. *Am J Kidney Dis* 2003;41: 319–327.
- Navaneethan SD, Yehnert H, Moustarah F, Schreiber MJ, Schauer PR, Beddhu S: Weight loss interventions in chronic kidney disease: a systematic review and meta-analysis. *Clin J Am Soc Nephrol* 2009;4:1565–1574.
- Mallamaci F, Ruggenti P, Perna A, Leonardi D, Tripepi R, Tripepi G, Remuzzi G, Zoccali C, REIN Study Group: ACE inhibition is renoprotective among obese patients with proteinuria. *J Am Soc Nephrol* 2011;22:1122–1128.