CKJ REVIEW

Consequences of morbid obesity on the kidney. Where are we going?

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Abstract

Obesity and morbid obesity are modifiable risk factors for the development and progression of kidney disease. Obesity has reached epidemic proportions and is currently an important health problem in Europe, so it is necessary to develop therapeutic and preventive strategies. The obesity-related glomerulopathy has been defined as a secondary form of focal segmental glomerulosclerosis, and its most characteristic feature is glomerulomegaly. The renal evolution of patients with obesity-related glomerulopathy (ORG) who have not been treated is unfavourable. However, morbidly obese patients with ORG that underwent bariatric surgery and drastic weight loss had a better outcome. Many inflammatory factors have been implicated in the pathogenic mechanism of renal disease in obesity. Hypoadiponectinaemia, hyperleptinaemia and hyperaldosteronism have been associated with glomerular injury in obese patients. The application of modern techniques has provided important insights that increase the current understanding of ORG. However, further investigation is needed.

Key words: adiponectin, chronic inflammation, CKD, leptin, obesity

The morbid obesity epidemic and its renal consequences

Obesity has become a worldwide epidemic in the twenty-first century due to its increasing prevalence in recent decades, as well as its impacts on morbidity, mortality and quality of life, and its economic burden. Morbid obesity [body mass index (BMI) ≥ 40 kg/m^2] is a type of obesity that does not respond to medical treatment; it requires a surgical approach and its prevalence has continued to rise at an alarming rate [1–3]. The distribution of obesity (BMI ≥ 30 kg/m^2) is not consistent across geographic regions, and its prevalence in Europe ranges from 4 to 28% in men and from 6.2 to 36.5% in women [1]. The obesity epidemic, which is the result of combined effects of genetic predisposition, increased accessibility to high-calorie foods and decreased physical activity, has led to an increase in the risk of developing cardiovascular disease, diabetes, dyslipidaemia, hypertension and/or renal disease. Consequently, in obese patients, overall cardiovascular morbidity and mortality are increased [2, 3].

A retrospective cohort study of >320 000 American adults with 15 and 35 years of follow-up [4] described a strong relationship between the risk of developing advanced chronic kidney disease (CKD) and an increased BMI, especially for subjects with a BMI of >25 kg/m^2, regardless of age, sex and race, and the presence of underlying renal disease, diabetes or hypertension. Similar results were published 3 years earlier [5] in an epidemiological study of >9000 American adults who participated in the National Health and Nutrition Examination Survey (NHANES II). In that study physical inactivity, smoking and morbid obesity were

found to be risk factors for CKD. Additional studies have shown that obesity can exacerbate the progression of pre-existing renal disease [6, 7]. Although the absolute individual risk of developing CKD is very low for obese individuals [8], there has been increasing interest in obesity as a risk factor for the development and progression of CKD [9], considering the prevalence of obesity in this patient population. Because obesity is a preventable risk factor for CKD and because obesity, particularly morbid obesity, is currently an important health problem in Europe, it is necessary to develop therapeutic and preventive strategies [10].

Renal involvement in morbid obesity: a glomerulopathy with its own entity

Studies of patients with differing degrees of obesity have recognized obesity-related glomerulopathy (ORG) as its own entity and have defined it as a secondary form of focal segmental glomerulosclerosis (FSGS) [11–22]. The most characteristic feature of ORG is the presence of glomerulomegaly [11–13]. Our working group first described the presence of early stages of ORG in morbidly obese (MO) patients without overt clinical renal manifestations who were undergoing open bariatric surgery [11]. The findings indicated that structural changes primarily involving the glomerular compartment may be observed in MO patients before they begin to exhibit significant proteinuria and/or renal failure. The most characteristic feature identified was glomerulomegaly in >38% of the patients. In most patients, glomerulomegaly was accompanied by other glomerular lesions. However, in six patients, glomerulomegaly was the only lesion observed. In addition, there were high prevalences of increased mesangial matrix, podocyte hypertrophy, glomerular sclerosis and mesangial cell proliferation. Despite the lack of clinical manifestations, five of the study patients had already developed FSGS [11]. The presence of these renal lesions was only associated with the BMI, and no association with hypertension or hyperglycaemia was detected, further demonstrating the correlation between morbid obesity and kidney disease. These findings clarify that glomerular hypertrophy in patients with morbid obesity is likely the initial lesion that stimulates podocyte effacement and triggers the inflammatory response eventually resulting in focal segmental glomerulosclerosis. This histological injury leads to the development of CKD in obese patients. It is therefore important to identify at-risk patients to prevent or precociously treat obesity-related nephropathy at an early stage and thereby prevent the development of irreversible CKD. The 'hyperfiltration theory' is also thought to be involved in the progression to end-stage renal disease, although in the presence of normal renal mass this mechanism is not completely understood [23]. However, not all MO patients develop ORG, implicating the importance of genetic susceptibility and environmental conditions in its development. Apparently, it seems to be a subgroup of obese patients with a unique phenotype, the metabolically healthy obesity, that does not associate higher risk of incident CKD [24, 25]. Although the incidence of ORG is unknown due to a lack of data in the literature, D'Agathi and co-workers [13, 26] observed an alarming increase in its incidence in a retrospective study of patients with proteinuria or proteinuria and renal failure performed between 1986 and 2000. Recent data from the same group showed further rise in the incidence of ORG between 2001 and 2015 (from 2 to 2.7%) [26]. These findings are consistent with the increasing prevalence of obesity in the general population during this period.

Clinical manifestations and evolution of obesity-related glomerulopathy

The degree of kidney function in obesity nephropathy depends on the time of its determination. It is not uncommon to detect glomerular hyperfiltration at the time of onset of renal injury as occurs in patients with diabetes mellitus [27–29]. This hyperfiltration decreases when patients undergo drastic weight loss [29–31]. Once renal injury occurs, glomerular hyperfiltration can be observed in addition to apparently normal renal function or renal function deterioration. The initial clinical feature of renal injury is the presence of albuminuria or proteinuria [4, 28–30]. Both of these conditions may precede a decrease in renal function by several years, as occurs in diabetes. Proteinuria and albuminuria develop in 10–41% [4, 28, 32] and in 12–43% [28–34] of obese patients, respectively. In addition, some studies have described the presence of microhaematuria in 5–26% of patients with differing degrees of obesity [4, 29]. In contrast, proteinuria in obese patients can be of low grade or have levels of nephrotic range and it is not usually accompanied by oedema, hypoalbuminaemia or severe hyperlipidaemia [13]. The renal evolution of patients with ORG and clinical proteinuria or renal failure who have not been treated is unfavourable in those with FSGS and in those with glomerulomegaly alone [13, 35]. Different studies have reported variable renal survival rates, a rate of 60% at 8 years of follow-up has been reported in a study by Kambham *et al.* [13] and rates of 77 and 51% at 5 and 10 years, respectively, have been described in a study by Praga *et al.* [35]. Nevertheless, a comparison of the survival curves between idiopathic FSGS and FSGS secondary to obesity revealed that the latter was associated with better prognosis [13]. In our experience, the long-term renal outcome of patients with ORG with normal renal function or with or without proteinuria is very good (10 years) if they undergo bariatric surgery and drastic weight loss [36].

Obesity as a state of chronic inflammation

Adipose tissue is not inert; rather, it is considered a true endocrine organ that produces bioactive substances that directly influence insulin resistance and vascular injury. The dysregulation of these factors mediates the pathogenesis of obesity comorbidities [37, 38]. In addition, the identification of some genes responsible for obesity has increased the understanding of how the body deals with disturbances in the energy balance [39, 40]. Leptin is a product of the *ob* gene, and it is synthesized mainly in adipose tissue of obese patients in whom the plasma level is elevated so that these increased leptin levels are proportional to the amount of adipose tissue. Thus, when there is an increase in intake accompanied by a decrease in energy expenditure, adipocyte size increases, resulting in increases in both the synthesis and release of leptin. Despite these increased levels, obese patients typically exhibit resistance to leptin; however, the mechanisms through which this occurs are unknown [39]. Furthermore, the kidneys contain a leptin receptor that is present mainly in the renal medulla. Because this receptor belongs to the family of class I cytokine receptors, it is thought that leptin may have an important role in inflammatory kidney disorders such as obesity [37]. Although the functions of leptin receptor in the kidneys are unknown, experimental studies have demonstrated that leptin exerts a fibrogenic effect by increasing the expression of glomerular transforming growth factor-β1, and that this effect is associated with the appearance of proteinuria [41]. In addition, leptin acts on the renal tubules by increasing the tubular reabsorption of sodium, which promotes an increase in glomerular

filtration through tubuloglomerular feedback. This glomerular hyperfiltration mechanism has also been implicated for other molecules, such as insulin, angiotensin II and aldosterone [27, 42, 43]. Although leptin and adiponectin exert beneficial effects on energy balance by promoting sensitivity to insulin, increased leptin levels and decreased adiponectin levels may have deleterious effects on the kidneys. Obesity is associated with hypoadiponectinaemia, which has been linked to insulin resistance, cardiovascular disease and glomerular injury [44, 45]. Reduction in adiponectin levels appears to be regulated by fetuin-A, which is a glycoprotein synthesized in the liver that promotes insulin resistance, among other functions. Obese individuals have increased levels of fetuin-A, which promotes a down-regulation of adiponectin synthesis by the adipocytes. Both excess caloric intake and decreased adiponectin reduce the activation of an energy sensor that is present in liver cells and podocytes (5′-AMP activated protein kinase), thereby promoting podocyte effacement and albuminuria [44].

Experimental studies have demonstrated [45] that adiponectin deficiency in mice is associated with podocyte effacement and fusion, as has been observed in some patients with obesity and morbid obesity [12, 28]. These changes are accompanied by albuminuria and do not occur in mice with no such deficit. The administration of adiponectin to mice reduces podocyte damage and leads to the partial resolution of albuminuria [45].

In our previous study, we found that patients with morbid obesity and early stages of ORG had an increased leptin level and a decreased adiponectin level compared with normal-weight controls [28]. The drastic weight loss that occurred in patients who underwent bariatric surgery helped to reduce leptin levels and increase adiponectin levels, which were accompanied by a decreased albuminuria [28]. Therefore, all of the mechanisms, including weight loss, that contributed to decreasing leptin levels and increasing adiponectin levels helped to prevent or improve obesity-related renal injury. Another adipokine with an increased level in obesity is aldosterone. This increase can occur independently or as part of the renin–angiotensin axis and may contribute to the development of ORG through two mechanisms: by promoting glomerular hyperfiltration via tubuloglomerular feedback (similar to leptin) or by direct injury of podocytes due to the production of reactive oxygen species [46]. Spontaneously hypertensive rats with a spontaneous mutation in the gene encoding leptin receptor were compared with a group of rats without this mutation. In the spontaneous evolution of the mutated rats, they developed obesity, which did not occur in the rats without the mutation. Parallel to the development of obesity and proteinuria, podocyte alterations appeared. The aldosterone levels were measured, revealing increased levels in the obese rats. When an inhibitor of aldosterone (eplerenone) was administered, reduction in podocyte damage was observed, accompanied by decreased proteinuria [46]. In patients with obesity, central fat is associated with increased risks of morbidity and mortality [9, 47], especially in men. In fact, central obesity is the most important factor that predisposes individuals to insulin resistance and hyperinsulinaemia, thus favouring the development of type 2 diabetes mellitus [48–50]. Notably, Fontana et al. [50] published an interesting study on 25 MO patients. High levels of adipokines were observed in the portal vein, and these levels were compared with those in the peripheral blood. The findings suggested that visceral adipose tissue is the largest producer of interleukin-6 (IL-6), thus confirming the association between visceral fat and systemic inflammation in patients with morbid obesity [50]. In a study conducted by our group with MO patients with normal renal function and early stages of ORG, we found

that BMI was correlated with IL-6 plasma concentration. However, we did not observe any relationships between the plasma levels of inflammatory mediators and glomerular lesions [51].

Many other factors related to inflammation in obesity have been studied recently. Despite various attempts to elucidate the pathogenic mechanisms of renal disease in obesity, most of which have been experimental, there is still a lack of knowledge on this subject, and further investigation is needed. Only a few studies have reported associations among obesity, renal injury and inflammatory hormones [51–53]. Insulin-like growth hormone-1 (IGF-1) levels are decreased in obesity [54, 55]. We have recently identified a link between a low IGF-1 hormone level and the presence of renal injury in MO patients with early stages of ORG [53]. Additionally, *IGF-1* gene expression has been shown to be decreased in kidney biopsies from MO patients with early stages of ORG compared with those from a normal-weight control group (M. Navarro, unpublished data), whereas expression of the proinflammatory genes IL-6 and glucose transporter-1 was increased (M. Navarro, unpublished data). Wu et al. [52] have previously demonstrated the differential expression of genes related to inflammatory cytokines, lipid metabolism and insulin resistance in kidney biopsies from obese patients with proteinuria and ORG. This altered gene expression was not observed in biopsies from kidney donors. These findings indicate the existence of a cause–effect relationship of lipid dysmetabolism, insulin resistance and activation of an inflammatory process with the development of obesity-related glomerulopathy.

Thus, these results provide important insights that increase the current understanding of ORG. The application of modern techniques, such as genomic techniques, might be useful to open new avenues for further investigation.

Therapeutic approach

It is justifiable to consider that if obesity is a modifiable risk factor for kidney disease, then developing the first therapeutic intervention to prevent obesity, given its high prevalence, should be a public health priority. By preventing obesity, a high percentage of all CKD cases in industrialized countries might be prevented [56, 57]. For patients who are already obese, an effective treatment should be established to promote weight loss and thus prevent or treat its comorbidities, such as CKD. There is increasing evidence that weight loss not only helps to reduce glomerular hyperfiltration and proteinuria [28–30, 34, 58–62] but also attenuates metabolic disorders associated with obesity, such as hypertension [28, 29, 58, 63], altered lipid metabolism [28, 29], insulin resistance and inflammation [28]. Few studies have investigated the fundamental pathophysiological effects that lead to improvement of renal disease in obese patients on low-calorie diets. Ix and Sharma [44] investigated the effect of a low-calorie diet on AMPK pathway activation and found that it reduced the fetuin-A level, which led to an increase in the adiponectin level and subsequently prevented the occurrence of podocyte injury. The effects of dietary modification on other adipokines and on the secretion of fatty acids are additional areas of interest in the study of obesity-related kidney disease [64].

Weight loss in patients with obesity and morbid obesity has renal benefits. However, what is the most effective method for maintaining weight loss over a long period of time? Many clinical trials have demonstrated that low-calorie diets aid in weight loss in obese patients, although these studies have failed to demonstrate the maintenance of this weight loss over time and have reported high dropout rates [65]. The use of anti-obesity agents such as orlistat and sibutramine, which have been recommended

in combination with low-calorie diets and exercise, has resulted in modest decreases in weight and may cause significant side effects, especially in patients with cardiovascular disease [42, 66]. The results of different studies examined in two meta-analyses [67, 68] that included 18 studies (assessing medical and surgical interventions) and 813 patients with differing degrees of obesity have demonstrated that medical interventions for obesity result in a reduction in proteinuria and glomerular filtration rate stabilization. In contrast, surgery normalizes glomerular hyperfiltration and albuminuria, and encouraging data have been reported indicating improved/stable renal function in some patients with renal insufficiency who have undergone surgery [67, 68]. Regarding morbid obesity, both medical treatments and lifestyle changes have limited effects. In these patients, bariatric surgery is the only treatment that has demonstrated efficacy in maintaining long-term weight loss. In a recent study with a median follow-up time of 4.4 years and 985 patients who underwent bariatric surgery the authors observed that bariatric surgery prevented the decline in renal function in MO patients [69]. In addition, drastic weight loss secondary to bariatric surgery in MO patients with ORG, normal preoperative renal function and mild proteinuria resulted in excellent outcomes, as normal renal function was maintained, blood pressure was improved and albuminuria was attenuated after 10 years of follow-up [36]. Although the surgical approach can reduce morbidity and improve renal parameters in patients with morbid obesity, bariatric surgery is associated with an increased risk of acute renal failure postoperatively. This complication is associated with the appearance of oxalate nephropathy but is rarely observed [70–72].

Drugs that inhibit the renin–angiotensin system have proved useful for improving glomerular hyperfiltration in obese or MO patients with renal disease by reducing the intracapillary glomerular pressure and, consequently, podocyte injury and by enhancing the attenuation of proteinuria [73]. Because hyperaldosteronism promotes hyperfiltration and podocyte injury and mediates inflammation, the use of aldosterone inhibitors may be indicated in patients with hyperaldosteronism, such as those with obesity and obesity glomerulopathy. These drugs have renoprotective effects by blocking the fibrosis process that produces aldosterone [46]. Notably, no studies have been performed on patients with ORG. Further, the addition of aldosterone inhibitors to angiotensin-converting enzyme inhibitors or angiotensin II receptor blocker treatments improves proteinuria but does not enhance renal function. Given the scientific evidence regarding aldosterone inhibitors, these drugs should be considered as second-line drugs, and more studies demonstrating their efficacy should be conducted [67]. In a comprehensive review of the role of ectopic lipid accumulation in obesity-related kidney disease, De Vries *et al.* [12] suggested that this accumulation could represent a novel pathway of this disease and that this information could facilitate the development of new strategies for its treatment. In experimental models, interventions targeting cellular lipid metabolism have been shown to decrease renal lipid accumulation and reduce glomerular injury [74, 75]; however, further investigation is needed to fully understand what occurs in humans.

Conflict of interest statement

None declared.

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