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Obesity Nephropathy: A Current Overview

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Abstract **Review Article**

The obesity pandemic is a public health problem that is evolving at high speed with both functional and vital outcomes. Recently, many studies have shown that obesity is a driver of chronic kidney disease onset and progression. The mechanisms underlying this fact are multiple including inflammation, oxidative stress, insuline resistance and hemodynamic change with inappropriate RAAS and SNS activation; occuring on a particularly genetic basis of individual predisposition. In this field, Obesity-related glomerulopathy is characterized by glomerulomegaly with localized and segmental glomerulosclerosis lesions. Main symptoms are non specific, dominated by microproteinuria, rarely nephrotic syndrome and a slowed decline in glomerular filtration rate. As for treatment, it starts essentially with lifestyle interventions targeting a meaningful and sustainable weight loss, accompanied by antiobesity medications (AOMS) including RAAS blockers, SGLT2inhibitors and since very recently, long-acting glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1 RA) which were shown to be effective in managing weight loss in non-chronic kidney disease (CKD) patients. Preliminary results of more definitive studies in CKD patients are currently being finalized. Bariatric surgery could reduce the risk of mortality in obese CKD patients; it is recommended for patients with severe morbid obesity, poor tolerance to AOMS, particularly GLP RA, or those whose long-term medication costs represent a barrier to sustainable results. In this review, we summarize epidemiological data on obesity nephropathy, its pathophysiological mechanisms, clinical features and perspectives on its treatment.

Keywords: Obesity-related glomerulopathy, Chronic kidney disease, RAAS blockers, GLP-1 receptor agonists, Bariatric surgery.

INTRODUCTION

Obesity and overweight are a major health problem. Its prevalence has dramatically rised and accounted for over 5.0 million deaths globally in 2019, with more than half of these deaths occurring among people under 70 years old [1]. This increase in obesity prevalence has economic, societal and health consequences with a profound impact on morbidity and mortality. In last decades, many studies find obesity as a driver of chronic kidney disease (CKD) progression, with complex mechanisms including hemodynamic changes, inflammation, oxidative stress, and activation of the renin-angiotensin-aldosterone system (RAAS). Nevertheless, there is also a widening therapeutic options that positively affect metabolic risk factors, kidney function, or both that also have cardioprotective effects.

In this review, we summarize epidemiological data on obesity nephropathy, its pathophysiological mechanisms, clinical features and perspectives on its treatment.

Epidemiological data on Obesity Nephropathy

Obesity is characterized by an excessive accumulation of body fat and an expansion of adipose tissue resulting from adipocyte hypertrophy, which causes weight gain [2]. Recently, many studies were reported showing that obesity or body mass index (BMI) is related to the risk of CKD. In the cohort of Framingham Offspring Study which includes participants without pre-existing kidney disease, higher BMI was associated with higher risk of developing CKD [3]. In the Hypertension Detection and Follow-Up Program (HDFP) study, authors found that in patients without baseline CKD, obesity was associated with incident CKD [4]. In the Swedish National Population Register, it was documented that overweight at age 20 was associated with risk for CKD compared to

participants with BMI <25 kg/m^2. Moreover, obesity among men and morbid obesity among women, anytime during lifetime, were linked to increased risk for CKD [5]. The highest risk was found for diabetic nephropathy, but a high risk was also found for nephrosclerosis, glomerulonephritis, and other causes of CKD [5]. Wang *et al*., found that obesity is associated with 24%–33% of all renal disease cases in the United States [6]. According to Kambham *et al.*, the incidence of obesity related glomerulopathy biopsies gradually rised from 0.2% in 1986–1990 to 2.0% in 1996–2000, a 10-fold increase in 15 years [7]. Hu *et al*., reported recently an analysis of 34,630 primary kidney biopsy cases at Zhengzhou University in China and showed that the annual incidence of obesity related glomerulopathy increased from 0.86% in 2009 to 1.65% in 2018 [8]. Furthermore, Obesity is associated with progression of CKD of the underlying pathology. Indeed, It was shown that obesity is associated with progression of IgA nephropathy and autosomal dominant polycystic kidney disease [9].

Pathophysiological mechanisms of obesity nephropathy

The mechanisms by which obesity instigates and/or is implicated in the progression of CKD are not clearly understood. Obesity may predispose to CKD directly, through several mechanisms (glomerular hyperfiltration, inflammation, oxidative stress, hormones, expansion of peri-renal and renal sinus fat, etc.), or indirectly through increased risk of metabolic syndrome, diabetes, and hypertension [10].

- **Directs mechanisms**

Obesity can directly lead to renal damage through hemodynamic processes due to vasodilation of the afferent arteriole and consequently increased salt reabsorption in the proximal tubule, with ultimately glomerular hyperfiltration and proteinuria [11]. All these changes are grouped together in an entity called obesity related glomerulopathy (ORG). Its diagnosis is made after ruling out any other obvious histhopathological renal cause in individuals with a BMI greater than 30 [12]. The common lesion in ORG is glomerulomegaly either alone or with secondary focal segmental glomerulosclerosis [13]. Decreased podocyte density, increased width of podocyte foot processes [13, 14], increased mesangial matrix and mesangial sclerosis and glomerular basement membrane thickening are all lesions found in most biopsies studies of ORG [15]. In fact, the hyperfiltration secondary to the greater renal hemodynamic and metabolic demand in obesity lead to an increase in filtration fraction with as result an hemoconcentration in the postglomerular circulation and increased oncotic pressure, inducing thus an enhancement of proximal tubular sodium reabsorption [16].

Moreover, persistant kidney inflammation is an essential feature in initiating the development and progression of obesity-related kidney disease. Many studies have found that white adipose tissue particularly visceral one, is a primary source of cytokine release in metabolic syndrom such as leptin, adiponectin, tumor necrosis factor (TNF), monocyte chemoattractant protein-1, transforming growth factor, and angiotensin II [17]. In addition to this, perirenal fat (PF), the adipose tissue that surrounds the kidneys plays endocrine roles in glucose and lipid homeostasis by generating and secreting adipokines [18]. On one hand, its accumulation exerts directly a renal compression, leading to increased interstitial hydrostatic pressure, stimulation of renin release, glomerular filtration, and sodium tubular reabsorption, which accelerate the progression of renal disease and ultimately the decreased of GFR [19]. On the other hand, excess PF may initiate kidney injury via the paracrine or systemic secretion of inflammatory factors and activation of the sympathetic nervous system (SNS) and RAAS [20].

- **Indirects mechanisms**

Obesity may indirectly damage kidneys contributing to glomerular hypertension and hyperfiltration previously cited, such as SNS over-activity, upregulation of the RAAS and insulin resistance (IR**)** [21]. In this regard, several studies have found a correlation between IR and decreased renal function [22-24]. Indeed, the presence of both obesity and IR contributes to oxidative stress, inflammatory pathways, and the unsuitable activation of the RAAS and the SNS, all of which are implicated in kidney dysfunction [25]. Cardiovascular-kidney-metabolic (CKM) syndrome, a health disorder recently defined is attributable to connections among obesity, diabetes, chronic kidney disease (CKD), and cardiovascular disease (CVD), including heart failure, atrial fibrillation, coronary heart disease, stroke, and peripheral artery disease ; all leading to poor health outcomes. CKM syndrome is classified into stages : *stage 0, no CKM risk factors present (absence of excess/dysfunctional adiposity, metabolic risk factors, CKD); *stage 1, excess adiposity, dysfunctional adiposity, or both, with dysfunctional adiposity defined as hyperglycemia or prediabetes; *stage 2, metabolic risk factors, moderate- to high-risk CKD, or both; stage 3, subclinical CVD overlapping with CKM risk factors, very high-risk CKD, or high predicted CVD risk; and *stage 4, clinical CVD overlappping with CKM risk factors. Stage 4 is further divided into stages 4a (without kidney failure) and 4b (with kidney failure) [26]. Besides the progression in pathophysiology and risk represented by the CKM staging construct, diverse factors augment the prabability of progression along CKM stages, with associated increased risk for kidney failure. These include belonging to high-risk demographic groups (individuals with low socioeconomic and those from South Asia) and having a family history of diabetes or kidney failure, sleep disorders, mental health disorders and chronic inflammatory conditions [26].

- **Predisposing factors**

Over and above the direct and indirect mechanims generating obesity, there are predisposing factors that enhance the risk of developing ORG such as intra-uterine growth restriction, low birth weight, impaired renal development and congenital renal abnormalities, causing discrepancy between body mass and nephron ratio and thus increasing the risk of glomerular hyperfiltration and hypertension throughout later life in obesity [27].

Clinical features and Diagnosis

Clinically, Obesity nephropathy generally starts slowly, with microalbuminuria or significant proteinuria as the major symptoms, with or without renal failure, and a few individuals have microscopic hematuria or nephrotic syndrome [28]. Other clinical complications include hypertension, hyperlipidemia, and obstructive sleep apnea (OSA) [29-31]. The diagnosis of obesity-related kidney disease should meet the following criteria: 1) body mass index [BMI] > 30 kg/m2 (should be > 28 kg/m2 for the Chinese population) and waist circumference >90 cm for men and >85 cm for women; 2) proteinuria at various clinical levels (>0.3 g/24 h), severe proteinuria is rare, hypoproteinemia and edema are rarely present, and renal function is normal or mildly abnormal; 3) light microscopy showed a significant increase in glomerular volume with or without focal segmental glomerular sclerosis (FSGS), and electron microscopy shows fusion of epithelial cell peduncles; and 4) other primary or secondary glomerular diseases are excluded (such as IgA nephropathy and diabetic nephropathy) [32].

Management of obesity nephropathy

Therapeutic strategies including weight loss, lifestyle modifications, and pharmacological drugs, may help restore body weight and prevent or slow down CKD progression

- **Lifestyle interventions**

Lifestyle interventions are the first line of management in all patients with obesity nephropathy. Weight loss through caloric restriction and exercise is associated with decreases in body weight and fat proportion, as well as reduced inflammation and oxidative stress in patients with moderate-to-severe CKD [33]. Meloni C and al show that weight loss slows the progression of renal damage, which shows a significant reduction in the urine albumin excretion rate and improves the GFR [34]. As such, targeting weight loss above all, in the management of obesity nephropathy is crucial in order to decrease the global burden of this disease, and other affections accelerated by adiposity excess and metabolic syndrome.

- **Antiobesity medications**

Antiobesity medications (AOMs) may provide a valuable adjunct to lifestyle interventions, which typically have a limited effect on WL, to help people achieve and maintain healthy behaviors that are consistent with sustaining WL.

RAAS Blockade

Bear in mind that the RAAS is an antihypertensive regulatory system produced by the kidneys, generating vascular contraction and and sodium retention, resulting in elevated blood pressure. Adipose tissue can induce angiotensin II secretion, which stimulates aldosterone secretion and produces water and sodium reabsorption in renal tubules, elevating the renal filtration rate and causing proteinuria. Therefore, RAAS inhibitors may represent an interesting therapeutic alternative to act on the renal component of obesity, although no particular guidelines have provided specific recommendations for patients with obesity-related kidney disease. Whence, more clinical data are needed to support the protective effects of RAAS blockade on these patients [35].

**** SGLT2 inhibitors (SGLT2i)***

Currently, SGLT2i emerged as effective glucose-lowering agents with a good safety profile. They proved to have major positive outcomes on weight loss inspite of they are approved primarily to treat patients with T2DM. Indeed, SGLT2 inhibitors reduce the risk of ESKD, cardiovascular events, and mortality in patients with T2DM and CKD [36]. Despite of inducing weight loss, SGLT2 inhibitors are still not approved for people with CKD and obesity with no significant proteinuria and/or T2DM. Nevertheless, they act on different aspects of the metabolic syndrome and can indirectly benefit patients with obesity [37].

**** GLP 1-RA (Glucagon like peptide1 receptor agonist)***

GLP-1 is a 37-amino acid peptide produced through cleavage of preproglucagon by the prohormone convertase 1 (PC1) and released from enteroendocrine L cells in the intestinal mucosa of the ileum and colon as well as from specialized neurons in the nucleus of the solitary tract. Native GLP-1 has a short half-life of 2 to 5 min because of its rapid cleavage at the alanine 2 residue by the protease dipeptidyl-peptidase-4 (DPP-4), resulting in the inactive peptides GLP-1(9-36 amide) or GLP-1(9-37) [4]. GLP-1 acts via binding to the GLP-1R, a receptor expressed in the pancreas, intestine, stomach, brain, lung, and the heart with the particular insulinotropic effect exclusively restricted to conditions of hyperglycemia which is safe especially for diabetic patients [38]. In the brain, GLP-1R is expressed in the cerebral cortex, hypothalamus, hippocampus, thalamus, caudate-putamen, and globus pallidum decreaseing thus body weight via centrally mediated inhibition of food intake beyond its effect on glycemia [39]. The US Food and Drug Administration (FDA) and European Medicines Agency (EMA) have approved AOMs that have been shown to achieve clinically significant WL when used as adjuncts to lifestyle interventions. Until

recently, only liraglutide is FDA approved at a higher dose for weight-loss indication. Nevertheless, they have moderate efficacy, with significant limitations related to adverse effects, cost, or restrictions on use [40]. One potential new AOM is the glucagon-like peptide 1 (GLP-1) analogue semaglutide, which has been developed with these characteristic features in mind [41]. In view of its effects on the reduction of cardiovascular events, all-cause mortality, and renal disease progression in patients with T2DM, the European Renal Association (ERA) published a consensus and advocated the use of GLP-1 Ras in the treatment of patients with T2DM and CKD [42].

- **Bariatric surgery (BS)**

BS is another treatment option, safe for CKD patients and leading to profound weight loss [43]. It remains the most effective and sustainable form of management of weight in patients with clinically severe obesity [44], and is associated with meaningful postsurgical benefits in patients with CKD such as stabilized eGFR and significantly slower progression to ESKD [45,46]. In a retrospective observational study, Coleman *et al*., reported an improved survival in patients with CKD and class II and III obesity who underwent a BS than in people who do not have surgery, Although there is modest perioperative short term risk which was countred by a large long-term protective effect of on mortality [47].

CONCLUSION

The prevalence of CKD become greater with the rapid increase of the overweight and obese population in recent years as well as many studies have demonstrated a strong association between weight, risk of CKD occurrence, and progression. Pathophysiology of obesity nephropathy is multifactorial, both due to direct and indirect mechanisms. Clinical symptoms are various and not specific miming several kidney diseases. Treatment is essentially based on AOMs, notably RAAS, SGLT2 i and, more recently, GLP RA; in addition to lifestyle interventions. BS is reserved for patients with severe morbid obesity, patients who have poorly tolerated AOMS, particularly GLP RA, or those whose long-term medication costs represent a barrier to sustainable results.

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