Diabetes, Metabolic Syndrome and Obesity

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REVIEW

The New Challenge of Obesity - Obesity-Associated Nephropathy

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Abstract: In recent years, obesity has become one of the major diseases that affect human health and consume human health resources, especially when it causes comorbidities such as hypertension, diabetes, cardiovascular disease and kidney disease. Many studies have demonstrated that obesity is associated with the development of chronic kidney disease and can exacerbate the progression of end-stage renal disease. This review described the mechanisms associated with the development of obesity-associated nephropathy and the current relevant therapeutic modalities, with the aim of finding new therapeutic targets for obesity-associated nephropathy. The mechanisms of obesity-induced renal injury include, in addition to the traditional alterations in renal hemodynamics, the involvement of various mechanisms such as macrophage infiltration in adipose tissue, alterations in adipokines (leptin and adiponectin), and ectopic deposition of lipids. At present, there is no "point-to-point" treatment for obesity-induced kidney injury. The renin-angiotensin-aldosterone system (RAAS) inhibitors, sodium-dependent glucose transporter 2 (SGLT-2) inhibitors and bariatric surgery described in this review can reduce urinary protein to varying degrees and delay the progression of kidney disease. In addition, recent studies on the therapeutic effects of intestinal flora on obesity may reduce the incidence of obesity-related kidney disease from the perspective of primary prevention. Both of these interventions have their own advantages and disadvantages, so the continuous search for the mechanism of obesity-induced related kidney disease will be extremely helpful for the future treatment of obesity-related kidney disease.

Keywords: obesity, kidney injury, inflammation, oxidative stress, adiponectin, leptin

Introduction

Obesity has become a world health problem that affects health. Especially in such a fast-paced and high-stress living environment, eating disorders or overeating have further contributed to the increase of people with obesity.[1] The prevalence of obesity worldwide has shown a continuous increase over the past 50 years. According to a summary analysis of body mass indices of adolescents and children in various countries around the world from 1975 to 2016, the prevalence of obesity has increased in all countries, with some regional differences.[2] The prevalence of obesity is higher in females than in males.[3] Income level is positively correlated with the prevalence of obesity and overweight, and the prevalence of obesity in high-income countries increased significantly in the past, but the prevalence of obesity and overweight children in some high-income countries, such as the United States, Denmark, and Sweden, has gradually stabilized since 2000. Meanwhile, the prevalence of obesity in low- and middle-income countries has been on the rise. Even in India, where the prevalence of obesity among women of childbearing age is 5.1% and the prevalence of overweight is 15.5%, which is related to the level of urbanization and economic development.[2,4] Current trends suggest that by 2025 the global prevalence of adult obesity will reach 18% among men and 21% among women.[5] Obesity causes several complications such as hyperinsulinemia, disorders of lipid metabolism, nonalcoholic fatty liver, coronary artery disease, cardiovascular disease, various types of cancer and chronic kidney disease (CKD).[6–9] In recent years, with the increase in the people with obesity, obesity has also become an important cause of CKD. An analysis of data from a UK biobank showed that for every 0.06 increase in waist-to-hip ratio estimated using genetic methods, the risk of CKD

Received: 12 October 2023
Accepted: 28 February 2024
Published: 6 May 2024

would increase by 30%; and for every 5 kg/m2 increase in body mass index (BMI), the risk of CKD would increase by 50%.[10] In the UK, about one-third of CKD patients are associated with overweight or obesity.[11] Another 14-year cohort study from Korean adults showed that high baseline levels of BMI and waist-to-hip ratio were independent risk factors for the development of CKD, and obesity was associated with the incidence of CKD.[12] The fact that BMI is associated with obesity-related kidney injury is reflected in the assessment of the degree of obesity. However, BMI is indistinguishable when a person's body composition changes, such as changes in the distribution of muscle and adipose tissue, visceral adipose tissue (VAT), and subcutaneous adipose tissue (SAT). Excessive VAT is associated with more insulin resistance and increased risk of kidney disease compared to SAT.[13,14] Some studies have shown that abdominal or central obesity, reflected as waist circumference or waist-to-hip ratio, is a better indicator of cardiometabolic risk and mortality than BMI, and is more strongly associated with renal impairment.[15,16] Obesity-induced renal injury (as shown in Figure 1) is mainly characterized by inflammation and oxidative stress, lipid accumulation in the glomerulus, and altered renal hemodynamics.[6] In this paper, we describe the mechanisms associated with the development of obesity-associated nephropathy and the current relevant therapeutic modalities, with the aim of finding new therapeutic targets for obesity-associated nephropathy.

Histopathology of Obesity-Associated Nephropathy

The characteristic histopathologic manifestations of obesity-associated nephropathy are glomerulomegaly, focal segmental glomerulosclerosis (FSGS), and hypodensity of podocytes. In a large study of renal biopsies by Kambham et al[17] it was found that, when matched for age and sex, the mean glomerular diameter was larger in biopsy samples from patients with obesity-associated nephropathy compared with normal controls (226 μm vs 169 μm). In an animal experimental model of obesity-associated nephropathy, glomerular cluster volume increases exponentially with body weight, which is associated with an increase in the number and surface area of glomerular capillaries induced by obese glomerular hyperfiltration.[18] The increase in glomerular volume causes figures are alterations in the podocytes, which are reflected in increased width of the peduncle, mild and segmental loss of the peduncle, decreased density and number of podocytes, and even detachment of the podocytes from the basement mem- brane.[19,20] These podocyte alterations are associated with adaptive hypertrophy brought about by glomerulomegaly. Podocytes are unable to proliferate, their

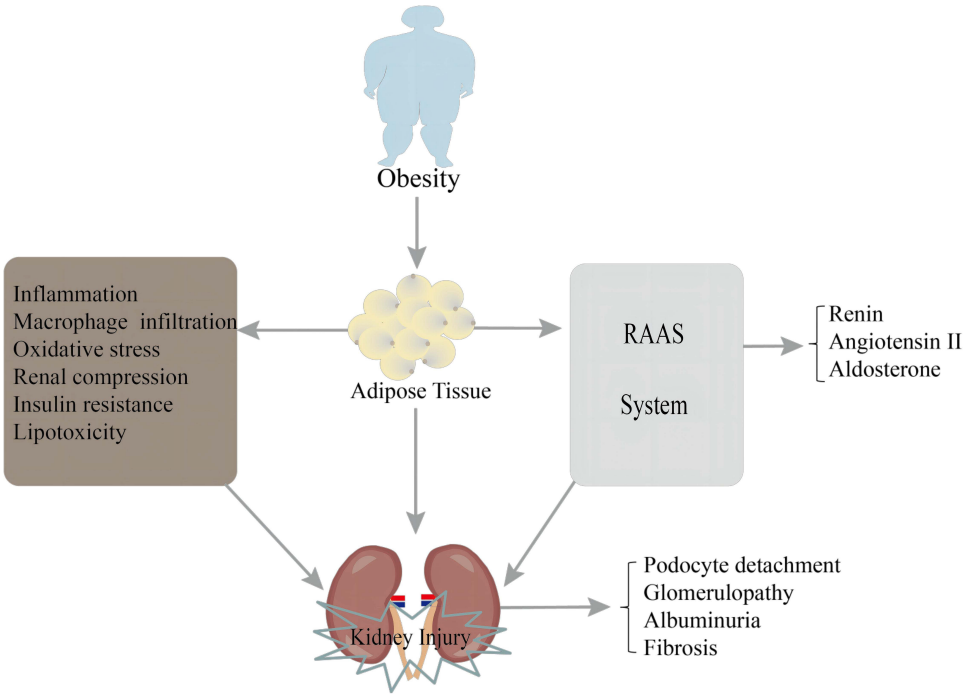

Figure 1 Obesity-induced kidney injury.

hypertrophic capacity is limited, and as the glomerular volume expands, mechanical strain due to tensile tension and shear stress reaches a breaking point, allowing individual podocytes to fail and detach. Reduced podocyte density may reflect an adaptive hypertrophic response to glomerulomegaly and continued podocyte depletion that has not yet reached the threshold for the development of segmental sclerosis.[21,22] This podocyte alteration ruptures glomerular filtration and plays an important role in the development of proteinuria and obesity-associated nephropathy.

Focal segmental glomerulosclerosis (FSGS) is another pathologic feature of obesity-associated nephropathy, but FSGS caused by obesity-associated nephropathy is milder and slower in progression than primary FSGS.[23] Among the five histologic subtypes of FSGS (not otherwise specified, perihilar, cellular, tip variant, and collapsing variant), obesity-associated nephropathy exhibits a preponderance of the perihilar variant.[24] In a Chinese cohort of patients with obesity-related nephropathy, the mean percentage of glomeruli with FSGS was only 6%.[25] In a Spanish study, 95 extremely obese patients with normal renal function (mean BMI of 53.6 kg/m2), with a mean duration of obesity of 20 years, had pathologic findings that showed glomerulomegaly in 38% of cases and FSGS lesions in only 5%.[26] This suggests that unlike primary FSGS, the renal changes caused by obesity-related nephropathy are adaptive FSGS.[27] In adaptive FSGS, podocyte injury is more heterogeneous and less severe, and the pedicle is predominantly intact except for irreversible podocyte denudation. Intercellular proliferation of podocyte injury adjacent to initial foci of podocyte depletion may be mediated by interruption of pro-survival signaling by renin or by increased noxious stimuli (tensile tension and angiotensin). Proliferation of podocyte stress zones in obesity-associated nephropathy promotes the expansion of segmental lesions, ultimately leading to total glomerular fibrosis.[28]

Hemodynamic Changes in Obesity-Associated Nephropathy

Many studies have shown that obesity is one of the main causes of essential hypertension.[29,30] Hypertension is one of the main risk factors for the development of cardiovascular disease and kidney diseases.[31] Increased renal and perirenal adipose tissue in people with obesity causes compression of the kidneys, leading to increased sodium reabsorption by the kidneys.[32] Early obesity is in a state of hypoxia and increased metabolic demand, manifested by increased renal plasma flow and increased renal glomerular filtration rate. The high filtration stimulates the glomerular-tubular balance, causing increased sodium-water reabsorption by the proximal tubules, which raises blood pressure and contributes to the progression of CKD.[33,34] In addition, plasma levels of natriuretic peptide are associated with the development of hypertension in obese people. Natriuretic peptides are polypeptide hormones produced by the heart, including atrial natriuretic peptide and B- type natriuretic peptide. It binds to natriuretic peptide receptors to regulate water and salt metabolism balance in the body by relaxing vascular smooth muscle and promoting renal sodium excretion and drainage.[35] In people with obesity, the concentration of natriuretic peptide receptor type C in adipose tissue increases and natriuretic peptide receptor C-mediated clearance increases, causing a decrease in plasma natriuretic peptide concentration. That weakens the inhibitory effect on the renin-angiotensin-aldosterone system (RAAS) and the diastolic effect on vascular smooth muscle and increasing sodium and water retention, causing the occurrence of hypertension.[36,37] Activation of the RAAS in obesity is the main mechanism for the development of hypertension. It has been shown that activation of sympathetic nerve activity (SNA) plays a role in the development of obesity hypertension.[38,39] Activation of the SNA in turn stimulates an increase in renin levels, further contributing to an increase in blood pressure.[40] Activation of the SNA may be associated with increased leptin, insulin resistance, and activation of peripheral chemoreceptors due to hypoxia in people with obesity.[41,42] It has been shown that when a high-salt diet was changed to a low-salt diet, blood pressure decreased significantly more in the group of people with obesity than in the non-obesity group, suggesting that obesity-related hypertension is associated with salt sensitivity.[43] The development of salt-sensitive hypertension may be related to glomerular hyperfiltration, metabolic changes and neurohumoral mechanisms caused by long-term chronic obesity.[32] In a cross-sectional study by verhave et al, the high sodium intake was found to be positively associated with urinary albumin excretion in people with obesity, suggesting that increased salt sensitivity due to obesity is associated with renal injury.[44] Many studies have confirmed that plasma aldosterone levels are increased in people with obesity.[45,46] Tuck et al found that reduced plasma renin and aldosterone levels were associated with weight loss through diet control for weight loss.[47] Traditionally, aldosterone production is increased by activation of the RAAS system, which binds to the mineralocorticoid receptor (MR) to exert its sodium-saving and potassium-excreting effects. Later Goodfriend et al

confirmed through a series of experimental studies that elevated levels of plasma free fatty acids (FFAs) stimulate an increase in aldosterone levels.[48,49] Shibata et al found an increase in blood pressure and proteinuria in rats given a high-salt diet and aldosterone infusion, but no significant changes in blood pressure and proteinuria in rats given a low-salt diet and aldosterone infusion, suggesting that the aldosterone-induced increase in blood pressure and renal injury may be dependent on the increasing of salt sensitivity.[50] Activation of the RAAS induces the production of fibrogenic factors (eg, TGF-b) that cause matrix in deposition in the kidney. It has been shown that blocking MR reduces tubulointerstitial fibrosis. Angiotensinogen II (Ang II) can cause functional and interstitial fibrosis in the proximal tubule through phenotypic transformation of renal epithelial-mesenchymal change (EMT) to renal injury.[51,52] In addition, podocytes play an important role in glomerular exertion of filtration function. Obesity causes changes such as hyperfiltration in the kidney, increased glomerular capillary blood pressure and expansion of the basement membrane, causing deformation and detachment of the podocytes, further aggravating renal function injury.[53] In addition to the alterations in podocytes caused by pathophysiological conditions, recent studies have shown that lipid accumulation and inflammatory vesicles in people with obesity are also important contributors to podocyte injury.[54]

Inflammation and Oxidative Stress of Obesity-Associated Nephropathy

The role of obesity in driving inflammation and oxidative stress in CKD was illustrated in a cross-sectional study conducted by Luis et al.[55] Also, in a cross-sectional study conducted by Chen et al in 2324 subjects, it was confirmed that inflammation plays an important role in the increased risk of obesity-induced CKD.[56] The inflammatory response people with obesity is low-grade, chronic and localized and is accompanied by macrophage infiltration, the degree of obesity is proportional to the degree of macrophage infiltration,[57] and there is a greater increase in macrophages in visceral fat compared to subcutaneous adipose tissue.[58,59] Macrophage infiltration plays an important role in inflammation caused by adipose tissue.[60,61] Macrophage infiltration in the people with obesity is closely related to the injury and apoptosis of adipocytes caused by obesity-induced vascular thinning of adipose tissue and hypoxia.[62,63] Macrophages have two phenotypes, M1 and M2, with M1 having pro-inflammatory and M2 anti-inflammatory effects.[64,65] Obesity can contribute to the conversion of M2 to M1 phenotype,[65,66] which causes an increase in pro-inflammatory factors (eg, TNF-α, IL-6, etc.) and leads to an increased production of intracellular reactive oxygen species (ROS). It in turn causes cellular injury and oxidative stress.[63,67] Furthermore, the release of free fatty acids (FFAs) from adipose tissue in the people with obesity promotes the polarization of macrophages within adipose tissue toward the M1 phenotype.[65] Recently, Chen et al showed through animal studies that Kdm6a (histone lysine demethylase 6a) regulates M1 and M2 imbalance within adipose tissue by regulating the expression of Ire1α(a transmembrane protein located in the endoplasmic reticulum that senses endoplasmic reticulum stress).[68] The phenotypic conversion of macrophages is a complex process,[69] but a better understanding of the process could be useful in the treatment of obesity-associated nephropathy in terms of inhibiting the conversion of macrophages to M1 type and achieving a reduction in inflammation. Wang et al[70] by injecting an anti-inflammatory small molecule dye (IR-61) into mice by peritoneal administration, confirmed that IR-61 has the function of directly targeting the mitochondria of adipose tissue macrophages (ATMs) and inhibits macrophage activation by increasing mitochondrial oxidative phosphorylation, and also inhibits the expression of pro-inflammatory factors in visceral fat in mice on high-fat diet (HFD), which achieves inhibition of obesity-induced inflammation and obesity-associated diseases. In addition, miRNAs have been found to play an important role in the polarization of macrophages,[71] and more studies are needed to confirm whether macrophage-induced related diseases are treated by targeting miRNAs.

In recent years, the pathogenic effects of nucleotide-binding oligomerized structural domain-like receptor protein 3 (NLRP3) inflammasome on the kidney have attracted extensive attention from researchers. The NLRP3 inflammasome is an intracellular multiprotein complex (NLRP3/ASC/caspase-1 complex) containing NLRP3, apoptosis-associated speckled protein (ASC), and caspase-1.[72] NLRP3 inflammasome can be activated by many exogenous and endogenous substances, and the activation of NLRP3 inflammasome in obesity-associated nephropathy may be related to hyperfiltration caused by the RAAS system, mitochondrial dysfunction, and activation of endoplasmic reticulum.[73] NLRP3 inflammasome acts on the progression of obesity-associated nephropathy through the caspase-1-IL-1β/IL-18 axis after being activated by signaling.[74] Inflammatory cytokines such as IL-1β and IL-18 act in an autocrine or paracrine manner

to induce podocyte damage and dysfunction. Additionally, it may be associated with non-inflammatory effects of NLRP3 inflammasome, such as pyroptosis cell death, cytoskeletal changes and altered cellular metabolism.[75,76] A recent study showed that hyperfiltration remained unchanged in obese subjects whose IL-1β/Caspase-1 levels remained high after undergoing bariatric surgery, suggesting that inflammasome signaling plays a role in the development of obesity-associated nephropathy as early as the glomerular hyperfiltration stage.[77] The exact pathogenic mechanisms of inflammasome at various stages of the development of obesity-associated nephropathy remain to be explored.

Leptin in Obesity-Associated Nephropathy

Leptin is an adipose tissue-derived hormone and the amount of leptin in the blood is proportional to the fat content.[78] Leptin is an important hormone for maintaining homeostasis by acting mainly on the central nervous system to suppress food intake and promote energy expenditure leading to weight loss.[79] It has been shown that leptin gene expression is increased in adipose tissue in people with obesity.[80] In people with obesity, there is "leptin resistance", where weight and intake are not reduced even though leptin levels are increased in people with obesity.[81] The central nervous system is the main part of leptin metabolism and exerts its effects by acting on the leptin receptor (LepR) (Figure 2). The arcuate nucleus of the hypothalamus (ARC) is the main site of leptin regulation.[82] Leptin interacts with the receptor to activate Janus kinase 2 (JAK2), which downstream can cause transcriptional activator 3 (STAT3), insulin receptor substrate (IRS)-phosphatidylinositol 3 kinase (PI3K), sh2-containing protein tyrosine phosphatase 2 (SHP2)-mitogen-activated protein kinase (MAPK), and 5 'adenosine monophosphate-activated protein kinase. Activation of the JAK2 signaling pathway causes increased transcription of suppressor of cytokine signaling 3 (SOCS3), which in turn inhibits the JAK2

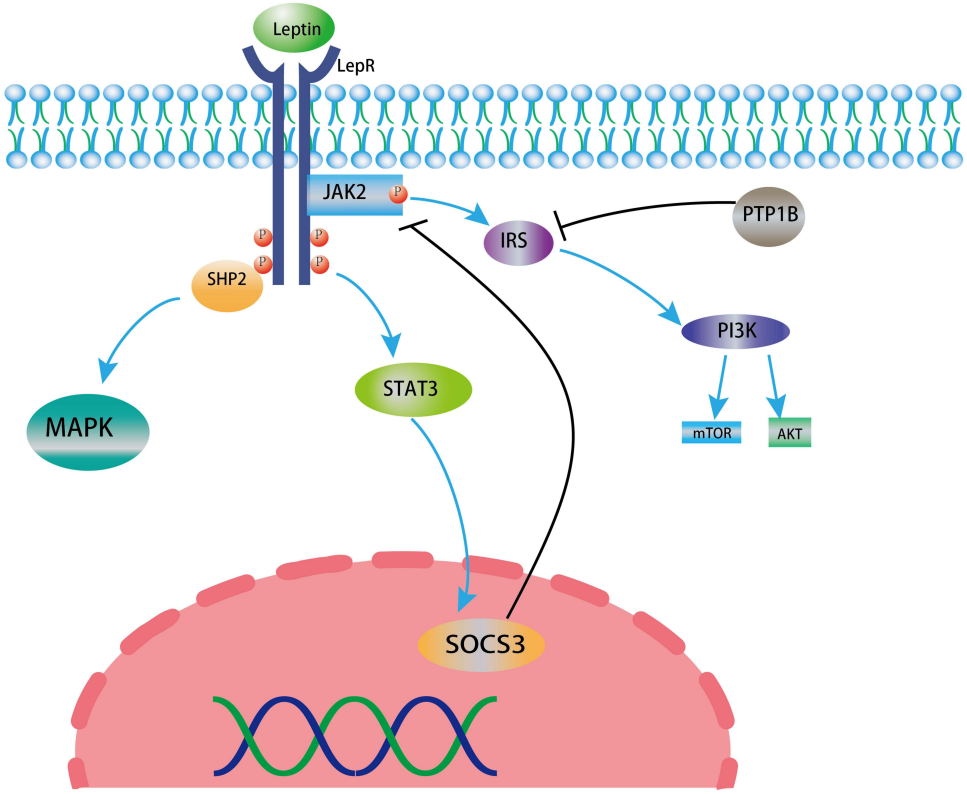

Figure 2 The basic pathway of leptin. Leptin binds to LepR to activate associated JAK2 phosphorylation, causing activation of the SHP2/MAPK pathway and the transcriptional activator STAT3. The SHP2/MAPK signaling pathway has an important role in the cardiometabolic effects of leptin. Activation of STAT3 regulates leptin-induced reduction in food intake and elevated blood pressure, and also induces transcription of SOCS3, which has an attenuating effect on LepR-mediated signaling. Activation of the IRS2-PI3K pathway contributes to the effects of leptin on SNA and blood pressure. PTP1B attenuates leptin signaling by dephosphorylating JAK2.
Abbreviations: LepR, leptin receptor; JAK2, Janus kinase 2; STAT3, transcriptional activator 3; IRS, insulin receptor substrate; PI3K, phosphatidylinositol 3 kinase; SHP2, sh2-containing protein tyrosine phosphatase 2; MAPK, mitog en-activated protein kinase; SOCS3, suppressor of cytokine signaling 3; mTOR, mammalian target of rapamycin; Akt, v-Akt murine thymoma viral oncogene homolog; PTP1B, protein tyrosine phosphatase 1B.

signaling pathway and reduces leptin action.[78,79,83] In addition, protein tyrosine phosphatase 1B (PTP1B) is also involved in the inhibition of leptin signaling.[79] In addition to the regulation of diet and body weight, leptin can also increase sympathetic nerve activity (SNA) in certain tissues, such as cardiovascular sympathetic nerve activity and renal sympathetic nerve activity (RSNA), through receptor action in the central nervous system.[84,85] Harlan et al[82] found in diet-induced mice that deletion of the highest concentration of leptin receptor in the ARC abolished the effect of leptin on increased renal sympathetic excitability. The increase in plasma leptin concentration can cause activation of the RAAS by increasing RSNA and affect renal hemodynamic changes,[32,78,82] which may be related to the involvement of the IRS2-PI3K pathway.[78,86] In addition, it has been shown that leptin is associated with glomerular fibrosis,[87] which is related to the fact that leptin increases TGF-β expression in glomerular cells and activates the JAK/STAT signaling pathway.[88] Also, leptin can affect renal endothelial cells and cause renal fibrosis by increasing reactive oxygen species (ROS).[89] Recently, Liu et al significantly reduced RSNA and elevated blood pressure in HFD mice by siRNA knockdown of Sirt1 (an energy-sensing enzyme located downstream of the leptin signaling pathway), and also reduced leptin-induced levels of tumor necrosis factor α (TNF-α), cytokine interleukin 6 (IL-6), and interleukin 1β (IL-1β), providing a treatment of leptin-induced RSNA and hypertension in the people with obesity.[90,91] In addition, Heiss et al found that the gut microflora-GLP-1 axis could modulate diet-induced hypothalamic inflammation and improve leptin sensitivity.[92]

Characteristics of Adiponectin in the People with Obesity

Adiponectin is an amino acid protein secreted by adipose tissue. It has three structural forms: low molecular weight (LMW), which is trimeric, medium molecular weight (MMW), which is hexamers, and high molecular weight (HMW), which is multimeric. The globular adiponectin differs from the three oligomers in the above in that it is a C1q-like globular structural domain at the COOH terminus of adiponectin, present in the circulation, biologically active, and produced by hydrolysis of full-length adiponectin.[93,94] Adiponectin has both anti-inflammatory and pro-inflammatory effects, which is one of the mechanisms that cause the development of various diseases.[64,95] The reduced secretion of adiponectin in people with obesity may be related to the suppression of adiponectin transcription due to the persistent chronic inflammatory state of the body caused by obesity.[64,96] Adiponectin exerts its function by interacting with adiponectin receptors (Figure 3).

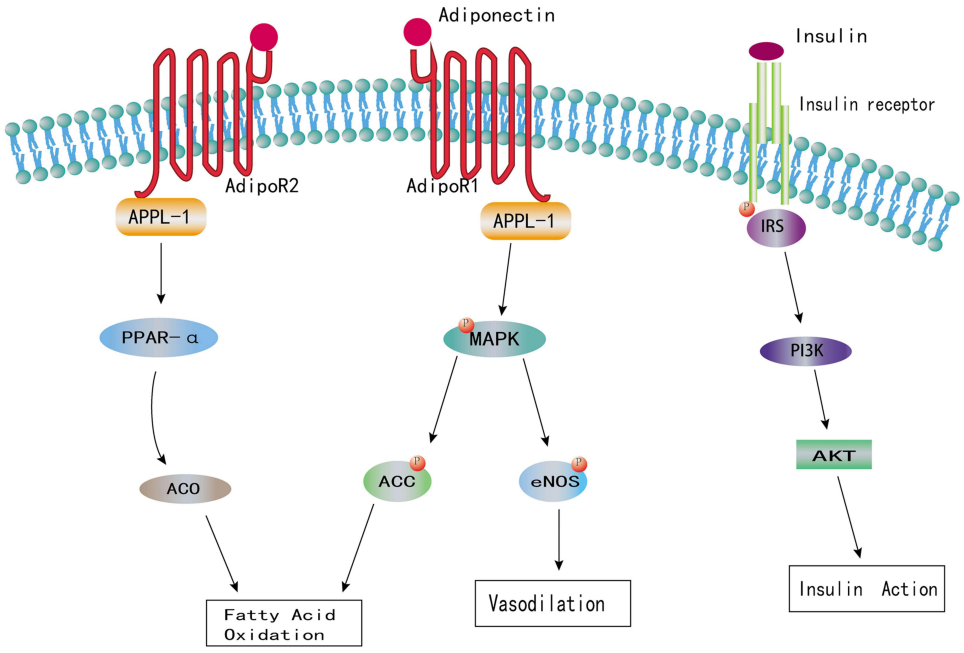

Figure 3 The mechanism of action of adiponectin: Adiponectin and insulin interact with their respective receptors to cause cascade signaling. Adiponectin binds to APL1 and APL2 to activate fatty acid oxidation and inhibit energy expenditure, exerting anti-inflammatory properties. Insulin regulates metabolism by causing glucose uptake and utilization, glycogen and protein synthesis through the PI3K/AKT pathway.

Abbreviations: AdipoR1, adiponectin receptor 1; AdipoR2, adiponectin receptor 2; APPL-1, a protein that interacts with the adiponectin receptor; ACC, acetyl coenzyme a carboxylase; eNOS, nitric oxide synthase; PPAR-α, peroxisome proliferator-activated receptor alpha.

Currently known are adiponectin receptor 1 (AdipoR1), adiponectin receptor 2 (AdipoR2) and T-cadherin (T-cadherin), AdipoR1 and AdipoR2 both have seven transmembrane structural domains distinct from G protein-coupled receptors, which are widely expressed in skeletal muscle and liver and have ceramidase activity, playing an important role in the regulation of metabolic processes.[64,97] The binding of adiponectin to AdipoR1 activates the APPL1 (a protein that interacts with the adiponectin receptor)-AMPK-acetyl coenzyme a carboxylase (ACC)/nitric oxide synthase (eNOS) pathway, enhancing cellular β-oxidation, reducing lipid accumulation, and improving endothelial cell function. Adiponectin binding to AdipoR2 activates APPL1-peroxisome proliferator-activated receptor alpha (PPAR-α), increasing fatty acid oxidation and glucose uptake.[95,98] In addition, adiponectin can act on macrophages to promote conversion to the M2 phenotype and exert the anti-inflammatory effects.[94,99] Adiponectin and its receptors (mostly AdipoR1) are mainly present in glomerular and proximal tubular cells, exerting their protective function on the kidney.[98,100] Studies have shown that obesity is an independent risk factor for the development of CKD.[101,102] Many studies have shown that adiponectin levels are elevated in patients with CKD, especially when the glomerular filtration rate (eGFR) is less than15 ml/min/1.73 m2, which are 2–3 times higher than normal in patients with end-stage renal disease (ESRD).[64,103] Interestingly, Menon et al concluded through an MDRD study, based on a 10-year follow-up of CKD patients, that stage 3 and 4 mortality in CKD patients is strongly associated with increased adiponectin, which is very different from the anti-inflammatory protective function of adiponectin.[104] Rhee et al through a prospective study of 500 patients with chronic kidney disease on regular hemodialysis found that a 10 μg/ml increase in adiponectin concentration was associated with an approximately 25% increase in the risk of death.[105] Recently, Chen et al demonstrated through animal studies that adiponectin can upregulate AdipoR1 in renal tissues and further activate peroxisome proliferator-activated receptor γ coactivator α (PGC-1α) to improve mitochondrial function within renal tubular epithelial cells, which provides an idea for the treatment of diabetic nephropathy.[106] Francisqueti et al showed that the γ Oz-treated group had lower proteinuria levels and increased glomerular filtration rate compared to the control group by using γ-glutamatergic (γ Oz) in obese mice with nephropathy for 10 weeks, it provides a new target for obesity-induced kidney injury.[102]

The Impact of Gut Microbes on People with Obesity

There are many normal flora in the human intestine that have physiological roles in regulating host energy metabolism and immune function.[107] Among them, four bacteria phyla play a major role in the adult gastrointestinal tract, including Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria.[108] Studies in animal models have shown that obesity and high-fat diets can cause changes in intestinal flora, including a decrease in Bacteroides and an increase in Firmicutes.[109] In human studies, RNA sequencing of fecal samples from obese individuals has also shown a reduced proportion of Bacteroidetes compared to lean individuals.[110] Altered intestinal microbes in the obese population disrupt the integrity of the intestinal barrier, causing pathological bacterial transfer into the blood and the initiation of inflammatory responses.[111] Previously, animal studies have shown that a high-fat diet can cause an increase in plasma lipopolysaccharide (LPS) concentrations, which promotes the secretion of inflammatory cytokines, and induce inflammation and oxidative stress in the body.[112] In addition, changes in intestinal flora cause an increase in the storage of triglycerides and the proportion of short-chain fatty acids in the host, regulating lipid metabolism.[111] The altered intestinal flora in the obese population described above causes systemic inflammation and oxidative stress that can have an impact on the kidneys. The development of obesity-associated nephropathy can also cause dysbiosis of the intestinal flora. Therefore, by "reversing" the alteration of intestinal flora (including the intake of probiotics and prebiotics), organ damage and dysfunction caused by intestinal dysbiosis can be reduced.

The Role of Other Obesity-Induced Effects on the Development of Chronic Kidney Disease

In addition to the basic pathophysiological factors mentioned above, in people with obesity, excessive fat content can cause metabolic disorders and the phenomenon of "ectopic deposition". In the kidney, the accumulation of free fatty acids (FFAs) and triglycerides can lead to inflammation, activation of oxidative stress and alteration of signaling pathways, which can further lead to apoptosis of kidney cells and fibrosis of the kidney.[113] In addition to increasing

macrophage infiltration through the IKKβ and JNK pathways, FFAs can act directly on TLR4 to exert an inflammatory cascade response. Other immune cells such as neutrophils, lymphocytes, and T cells also play a role in the production of inflammation.[114,115] Recently, Watanabe et al showed that adipose tissue neutrophils promote macrophage infiltration and inflammation by activating NF-kB to enable IL-1β expression, revealing a role for neutrophils in adipose tissue inflammation.[116] In addition, disturbed cholesterol metabolism in people with obesity results in cholesterol deposition and impaired renal function.[117] In patients with advanced CKD, HDL levels are reduced and are accompanied by a significant decrease in antioxidant enzyme activity, resulting in impaired anti-inflammatory and antioxidant properties. Moreover, the anti-inflammatory effect of HDL was changed to pro-inflammatory by the modification of oxidative enzymes and apolipoproteins under the effect of systemic inflammation and oxidative stress.[118,119]

Advances in the Treatment of Obesity-Associated Nephropathy

Weight Loss

For kidney injury caused by obesity, weight loss is the most basic treatment.[120] Common methods about weight loss include diet and exercise management, weight loss drugs, weight loss surgery. Many studies have shown that weight loss with diet management resulted in a significant reduction in proteinuria.[121,122] In addition, weight loss can lower blood pressure, reduce renal hyperfiltration, and have a protective function for the kidneys.[123] Studies have shown that a low glycemic index diet and a low-calorie diet not only reduce proteinuria but also have a significant effect on hypertension, insulin resistance, and hyperlipidemia in people with obesity (Table 1).[124,125] In addition, behavioral interventions

Table 1 Studies on the Effects of Different Treatments on Obesity-Induced Kidney Injury

Subjects	Methods	Results	Reference
Human Overweight Chronic proteinuria nephropathies	Hypocaloric diet for 5 months and exclude people taking drugs with anti-proteinuria effects	Weight loss Reduction in proteinuria	Morales et al[121]
Human Obesity-related Glomerulopathy	Energy reduction diet and aerobic exercise	The remission rate of proteinuria in the BMI reduction group was about 56%	Shen et al[124]
Human Obesity	Bariatric surgery	Weight loss Reduce the risk of developing CKD	Friedman et al[127]
Human Obesity	Intragastric balloon plus dietary and exercise	Significant weight loss	Friedman[128]
Human Obesity with proteinuria	Aldosterone antagonists (spironolactone)	More than 50% reduction in proteinuria compared to baseline values	Morales et al[131]
Human Type 2 diabetes Nephropathy	Finerenone (MRAs) combined RAAS blockers	Significant decrease in UACR compared to placebo	Bakris et al[132]
Human Type 2 diabetes Chronic kidney Disease	Finerenone combined RAAS blockers	Slowing the progression of CKD	Bakris et al[133]
Human Chronic kidney Disease	Dapagliflozin (SGLT2 inhibitors)	Decline in mGFR Reduction in bodyweight	Cherney et al[134]
Human Chronic kidney Disease	Dapagliflozin	Reduced risk of hospitalization and prolonged survival in patients with CKD	McMurray et al[135]

(*Continued*)

Table 1 (Continued).

Subjects	Methods	Results	Reference
Animals Obese mice	α-cyclodextrin	Regulated gut microbiota and Reduced fat volume in HFD-fed mice	Nihei et al[136]
Animals CKD rats	Melatonin	Reduces activation of the RAAS and damage to renal tissue	Ishigaki et al[137]
Animals Obese mice	Melatonin	Inhibiting the activation of inflammatory vesicles	Liu et al[138]
Human Obesity	Semaglutide (GLP-1 receptor agonist)	Reducing body weight	Wilding et al[139]

Abbreviations: MRAs, mineralocorticoid receptor antagonists; RAAS, renin-angiotensin-aldosterone system; UACR, urinary albumin-creatinine ratio; CKD, chronic kidney disease; mGFR, measured glomerular filtration rate.

including goal setting, self-monitoring and stimulus control are also beneficial for weight loss.[125] Bariatric surgery has been shown to have a positive effect on obesity-induced kidney disease.[119,126,127] It has been shown that bariatric surgery is accompanied not only by a significant reduction in proteinuria, but also by significant changes in the reduction of hypertension and inflammatory factors, especially 1–5 years after surgery.[128] Recently, endoscopic bariatric therapies have been rapidly developed to reduce gastric volume and delay gastric emptying, mainly through intragastric balloon placement,[129] sleeve gastroplasty, and aspiration therapy.[130]

Renin-Angiotensin-Aldosterone System (RAAS) Inhibitors

In the treatment of obesity-induced kidney injury, the control of proteinuria is an important way to slow the progression of kidney disease.[120] RAAS inhibitors are the basic drugs for early protection of kidney function, and typical drugs are angiotensin-converting enzyme inhibitor (ACEI) and angiotensin-receptor blockers (ARB), which can reduce proteinuria, improve renal blood flow and reduce blood pressure to protect kidney function. In a meta-analysis of RAAS inhibitors on chronic kidney disease outcomes, RAAS inhibitors did not appear to have a more beneficial effect on renal prognosis with ACEI or ARB compared with other blood pressure-lowering drugs. However, compared with placebo, RAAS inhibitors were able to reduce blood pressure and urinary protein excretion with significant renoprotective effects, demonstrating the important role of blood pressure control in improving end-stage renal disease and urinary protein.[140] In a clinical trial study by Morales et al showed that RAAS system inhibitors combined with spironolactone (mineralocorticoid receptor antagonist, MRA) consistently reduced proteinuria, lowered blood pressure, and delayed the progression of nephropathy.[131] Finerenone (selective MRA) has been shown to reduce proteinuria in patients with CKD in the short term.[132] Bakris et al showed a significantly lower incidence of the primary composite outcome (including renal failure, at least 40% reduction in eGFR at baseline, and death from nephropathy causes) with finerenone compared to placebo in a randomized double-blind trial than in the placebo group.[133]

Sodium-Dependent Glucose Transporter 2 (SGLT-2) Inhibitor

SGLT2 inhibitors act on proximal renal tubular SGLT2 to promote urinary glucose excretion by inhibiting glucose and sodium reabsorption, while also lowering blood pressure, improving glomerular hyperfiltration, and slowing the progression of nephropathy. As a novel hypoglycemic drug, SGLT2 inhibitors not only lower blood glucose, but also reduce the risk of proteinuria and death in obesity and diabetes and slow the progression of nephropathy.[23,141] In a recent clinical trial of DAPA-CKD, results suggested that dapagliflozin significantly reduced the risk of cardiovascular hospitalization and the risk of adverse renal outcomes, regardless of concomitant cardiovascular disease.[135] Interestingly, another 6-week randomized double-blind clinical trial of dapagliflozin in non-diabetic patients with combined CKD showed no significant difference in the short-term effect of dapagliflozin compared with placebo on proteinuria, but there was a significant reduction in eGFR and body weight, and the impact about renal outcomes needs to

be explored in longer-term trials.[134] Recently, in another DAPA-CKD trial with a median follow-up of 2.4 years, results showed that dapagliflozin reduced the incidence of adverse events and all-cause mortality in chronic kidney disease and cardiovascular disease in diabetic and non-diabetic patients.[142] In addition, many studies have demonstrated that SGLT2 inhibitors improve renal function by reducing pro-inflammatory factors and oxidative stress and regulating lipid metabolism.[143]

Other Treatment Modalities

In addition to the above common drugs, there are some other drugs or modalities that have been proved to have impact on renal function. Early studies have confirmed that gut microbes play a role in the development of obesity,[144,145] so regulating the gut microflora has also become one of the potential methods for treating obesity. Probiotics have been considered to have a positive effect on the gastrointestinal tract, and many studies have demonstrated that probiotic treatment reduces obesity-related inflammation and fat storage.[136] Recently, it has been found that food can be used as a probiotic carrier for the treatment of obesity, with common foods such as fermented dairy products and fruit juices.[146] Melatonin has been shown to have anti-inflammatory, antioxidant and endothelial protective functions in addition to regulating biological rhythms.[113,147] Ishigaki et al improved renal RAAS activation and renal injury by 5/6 nephrectomized (Nx) rats as a chronic progressive CKD model, and after 4 weeks of melatonin treatment, the melatonin-treated group reversed the decrease in intrarenal antioxidant activity, the increase in oxidative stress and the increase in markers of renal interstitial fibrosis compared to the control group.[137] In obesity-induced renal injury, melatonin exerts renoprotective effects by reducing pro-inflammatory factors and adipokines.[148] In addition, some studies have confirmed that melatonin can also reduce obesity-associated nephropathy by inhibiting inflammatory vesicles.[138] Meanwhile, the novel hypoglycemic drug GLP-1 receptor agonist may protect renal function by reducing RAAS system activation, acting as an anti-inflammatory and anti-fibrotic agent, and having a sustained weight loss effect, but the long-term prognosis for the kidney still lacks relevant clinical trials and needs to be explored.[139]

Conclusion

With the increasing prevalence of obesity and other health problems associated with obesity, more and more people are expressing their concern about obesity and its related diseases. The pathophysiological mechanisms of obesity-induced kidney injury are mainly inflammation and oxidative stress, alteration of adipokines, lipid deposition. Those mechanisms cause the alteration of signaling pathways, the glomerular and tubular vascular endothelial and cellular injury and the activation of RAAS system, which further cause kidney injury and fibrosis. Among them, macrophage infiltration and phenotypic transformation play an important role in the inflammatory response caused by obesity, leptin mainly acts on the activation of renal RAAS system through the increase of sympathetic nerve activity (SNA) caused by acting on hypothalamic leptin receptors. Adiponectin, as an anti-inflammatory factor, plays an anti-inflammatory, antioxidant and endothelial function-protecting role, in people with obesity. The decrease of adiponectin is more likely to cause kidney injury. In addition, lipid deposition and disorders of cholesterol metabolism can directly or indirectly cause injury to the kidney and cause the progression of kidney disease.

Practical Application

Clinically, the risk of kidney-related diseases is reduced by means of weight loss, and on the other hand, drugs such as RAAS system inhibitors and SGLT-2 inhibitors are used to lower blood pressure and reduce proteinuria to improve renal function. Both of these interventions have their own advantages and disadvantages, so the continuous search for the mechanism of obesity-induced related kidney disease will be extremely helpful for the future treatment of obesity-related kidney disease.

Disclosure

The authors report no conflicts of interest in this work.

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