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EFFECT OF WEIGHT LOSS IN PATIENTS WITH CHRONIC KIDNEY DISEASE

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Introduction

The increasing prevalence of obesity has been a major global public health threat. The National Institutes of Health and World Health Organization guidelines define individuals with body mass index (BMI) ≥25 kg/m^2 as overweight and those with BMI ≥30 kg/m^2 as obese. Worldwide, more than 1.9 billion 18 years and older population were overweight and among these, over 650 million were obese in 2016 (1). In the United State, the prevalence of obesity was 39.8% and affected about 93.3 million of adults in 2016 according to the Centers for Disease Control and Prevention (2). Obesity is a well-known risk factor for mortality, morbidity, and disability, and has been linked to a rising number of metabolic and cardiovascular comorbidities, such as diabetes mellitus and hypertension (3). It also has a direct impact on the development of chronic kidney disease (CKD) and end-stage renal disease (ESRD). Chronic kidney disease (CKD) is a condition identified as the gradual loss of kidney function over time. CKD refers to all 5 stages of kidney damage, from very mild damage in Stage 1 to complete kidney failure (ESRD) in Stage 5. The stages of kidney disease are based on the eGFR level, which is a blood test that measures the efficiency of kidneys filter waste from the blood. In addition, microalbuminuria and proteinuria are also markers of CKD and they are used to predict the progression of CKD. Currently, CKD affects 30 million people in the U.S. (15% of the adult population). Moreover, more than 660,000 Americans are being treated for kidney failure, or ESRD (4).

The association between obesity and the rising rates of diabetes and hypertension is well-understood and the pathways that draw the connection between obesity and these two conditions are well-established. This is important since diabetes and hypertension are the leading causes of CKD. Moreover, a number of observational studies suggest that obesity is an independent risk factor for CKD patients with or without those comorbidities. Compared with patients with body mass indexes (BMIs) <25 kg/m2, patients with severe obesity have a 341% increased risk of developing ESRD (5).

Weight loss is an effective tool in the treatment of cardiovascular disease and type 2 diabetes. However, the consequence of intentional weight loss for patients with established renal damage, independently of diabetes and hypertension control, remains unknown. This review will provide a summary of the pathophysiology, review of literature, discussion of important findings, existing controversies about the effect of weight loss in patients with chronic kidney disease.

Background

Pathophysiology

Numerous observational studies have shown that there is an association between obesity and both the development and the progression of CKD (6). Excessive body fat leads to a series of metabolic changes which negatively affect different body systems including the kidney. The exact mechanisms underlying how obesity may cause or aggravate CKD remain unclear. Current scientific evidence suggests that the pathophysiology associated with obesity-related kidney disease may be multifactorial. Several contributing factors of kidney damage have been proposed (6).

The main contributing factors are metabolic effects, which may directly or indirectly affect renal structure and function These include inflammation, insulin resistance, and adipokine dysregulation. Some of the detrimental renal consequences of obesity may be mediated by downstream comorbidities such as diabetes mellitus or hypertension. However, adipose tissue may impact the kidney function directly. Specifically, the endocrine activity of the adipose tissue can affect renal function through the production of adiponectin, leptin, and resistin. Adipokine dysregulation induces the development of inflammation, oxidative stress, abnormal lipid metabolism, activation of the renin-angiotensin-aldosterone system, and increased production of insulin and insulin resistance (6).

These negative consequences of metabolic changes led to specific disorders in the kidneys, including “ectopic lipid accumulation and increased deposition of renal sinus fat, the development of glomerular hypertension and increased glomerular permeability caused by hyperfiltration-related glomerular filtration barrier injury, and ultimately the development of glomerulomegaly, and focal or segmental glomerulosclerosis” described by Kovesdy et al. All these disorders underlie the higher risk of CKD reported in the observational studies (6).

Another theory is that chronic kidney damage may be caused by renal lipotoxicity, which is the increased influx of lipids into the kidney. The hypothesis states that the adipose tissue has a limited expansion capability, and once this limit is reached, the adipose tissue cannot store any more lipids and will thus release them into the bloodstream. The intracellular accumulation of free fatty acids and triglycerides in renal glomerular and tubulointerstitial cells results in chronic kidney injuries (7).

Current literature review

After evaluating the current literature, 8 papers were found worthy of inclusion in the review. The treatment of obesity-related kidney disease requires early recognition of kidney injury and an all-around approach to prevent disease progression. Weight loss remains an essential part of therapy, which can be attained through non-surgical intervention such as dietary management, exercise interventions or medications. Weight loss surgery is also a wide-use method in this population and has been shown to have benefits on kidney functions.

Non-surgical intervention on renal function in obese patients

Non-surgical weight loss programs in overweight/obese patients with kidney disease have resulted in a reduction in proteinuria, although improvement in renal function has not been solidified. However, poor compliance to the diet and exercise treatment is a commonly recognized limiting factor that reduces the efficiency of the treatment.

In a systematic, narrative meta-analysis, Bolignana et al. looked at diet as an intervention for weight loss, including 6 prospective studies, and 5 RCTs, involving a total of 604 patients. The duration of the intervention ranged from 4 weeks to 24 months. It found that two studies showed that weight loss through diet intervention produced a normalization of GFR in hyperfiltration or normofiltration. In other studies, GFR remained stable in patients successfully achieving weight loss but tended to worsen in controls in 6 studies. In two studies focusing on patients with CKD, some of which including Stage 5 CKD obese patients, the GFR was lower after lifestyle interventions or anti-obesity drugs (8).

One recent meta-analysis study assessed the impact of weight loss attained through nonsurgical interventions in patients with preexisting CKD. It included 4 observational studies and 2 randomized controlled trials. In most studies, hypocaloric diets with no protein restriction were used as the dietary intervention. The length of follow-up ranged from 4 weeks to 1 year. For patients who received the nonsurgical interventions, weight loss did not lead to any change in GFR at the end of the study period. Weight loss achieved through nonsurgical interventions only reduced the proteinuria at the end of study period, despite significant heterogeneity appears in the studies (9).

Diet alone may have a positive effect on renal function. In a 2-year randomized controlled trial, Tirosh et al. aimed to address the long-term effects of low-carbohydrate, low-fat, and Mediterranean diets on renal function. 318 participants with serum creatinine <176 μmol/L (eGFR ≥30 mL/min/1.73 m^2) were randomized to low-fat, Mediterranean, or low-carbohydrate diets. Significant improvements in eGFR were achieved in low-carbohydrate (+5.3%), Mediterranean (+5.2%), and low-fat diets (+4.0%) with similar magnitude across diet groups. The increased eGFR was at least as prominent in participants with (+6.7%) or without (+4.5%) type 2 diabetes or those with lower baseline renal function of eGFR <60 mL/min/1.73 m^2 (+7.1%) versus eGFR ≥60 mL/min/1.73 m^2 (+3.7%). Even though the baseline characteristics of participants were relatively healthy, a significant improvement in eGFR could still be observed in addition to robust regression of microalbuminuria, thus underscoring the importance of weight loss on slowing the progression, and perhaps even regressing, CKD at early stages of the disease (10).

Effects of Bariatric Surgery on Renal Function in Obese Patients

Bariatric surgery has been shown as an effective treatment for obese people that help with achieving significant long-term weight loss. Commonly seen surgical interventions include laparoscopic adjustable gastric banding, a sleeve gastrectomy, a Roux-en-Y gastric bypass, and intragastric balloon placement. Studies have demonstrated that impressive improvements in diabetes, hypertension, and dyslipidemia complications (3).

High-quality observational analyses using propensity score matching indicate bariatric surgery has a beneficial effect on kidney health.

Li et al. performed a systematic review of 30 observational studies that examined bariatric surgery in obese subjects with impaired kidney function. The findings from this study indicated that the reduction in the incidence of albuminuria and proteinuria after bariatric surgery was statistically significant (RR: 0.42). The study also found a statistically significant increase in eGFR after bariatric surgery (SMD: 1.04) (3).

Another systematic review and meta-analysis published in 2018 also found similar results. This analysis included 23 cohort studies, comprising 3015 participants. Bilha et al. concluded that compared with renal function before treatment, bariatric surgery significantly decreased serum creatinine level (mean difference (MD), -0.08 mg dl^{-1}) and proteinuria (MD, -0.04 g $24\ h^{-1}$) in the overall group. GFR significantly improved 6 months or more after surgery both in the hyperfiltration and CKD subgroups (11).

One large, prospective cohort study was published in April 2019 by Lin et al. indicated that bariatric surgery was associated with eGFR preservation in obese patients, especially in those with moderate-to-high CKD risk. A total of 1620 obese patients were divided into surgery or non-surgery. During the 1-year follow-up period, the eGFR was measured in all patients. An eGFR decline ≥25% at 12 months was the primary endpoint of the study. This study found that at 12 months, the overall mean eGFRs increased by 4.4 mL/min·1.73 m2 and decreased by 6.4 mL/min·1.73 m2 in the surgery and non-surgery groups, respectively. The Cox regression analysis showed that the BS group had a significantly lower risk of an eGFR decline ≥25% at 12 months. In addition, a BMI decline was significantly correlated with an eGFR change in the patients with moderate or high risks of CKD, but such correlation was not significant among the patients with a low risk of CKD (5).

On the other hand, some results shown by studies on the relationship of CKD risk and improvement on eGFR are mixed. One study included 254 Japanese patients who underwent bariatric surgery were retrospectively analyzed to assess the prevalence of CKD and the effect of bariatric surgery on kidney function. The eGFR was calculated at baseline and 1 year after surgery. Researchers concluded that bariatric surgery resulted in the significant improvement in the eGFR of Japanese patients with morbid obesity, particularly those with pre-CKD (eGFR ≥ 60 ml/min/1.73 m2), while the eGFR values of CKD patients (< 60 ml/min/1.73 m2) were not ameliorated by surgery (12).

Mixed results were observed in another prospective cohort study. This study followed 68 obese patients for 1 year after bariatric surgery. Changes in eGFR were associated with reductions in Fat Mass (P = .010), Body surface Area (P = .049), and % percentage excess weight loss (P<.001). Subgroup analysis indicated that in the eGFR>90 subgroup, eGFR decreased from 143±22 to 122±19 ml/min/1.73 m2. Conversely, in the eGFR<90 subgroup, eGFR had a trend of improvement from 69 to 79 ml/min/1.73 m2 (13).

Current Controversies

Despite that many observational studies demonstrated that bariatric surgery provides a positive impact on overweight or obese CKD patients, the risks associated with surgery for CKD patients are not well-understood. In a small prospective study, 9 patients with BMI >35 kg/m2 and CKD stages 3-4 underwent intragastric balloon (IGB) surgery were followed over 6 months period. This study concluded that the treatment resulted in no changes in eGFR; but it led to a high rate of complications, including acute kidney injury, in obese patients with established

CKD (14). Another large retrospective cohort study performed by Cohen et al. compared the risk of bariatric surgery between patients with CKD and ESRD vs those without CKD. 323,034 patients without CKD, 1694 patients with CKD, and 925 patients with ESRD were included in the study. Patients with CKD and ESRD had a significantly increased risk of 30-day reoperation (CKD OR 2.25; ESRD OR 3.10) and readmission (CKD OR 1.98; ESRD OR 2.97) compared to patients without CKD; mortality risk was elevated in patients with ESRD (OR 11.59) but not in those with CKD (15). However, the existing evidence is essentially limited to retrospective or small prospective data, and the findings need to be tested prospectively in longer-term studies (15).

In addition to surgery risk, there is limited evidence on the long-term benefits of bariatric surgery for CKD patients. The majority of observational studies conducted on CKD patients who underwent bariatric surgery have a follow-up period from 4 months to 24 months. Only one study conducted by Friedman et al. evaluated the CKD risk at 1 and 7 years after surgery in patients with different baseline CKD risks. Improvements were observed in CKD risk at 1 and 7 years after surgery in patients with moderate baseline CKD risk (63% and 53%, respectively), high baseline risk (78% and 56%, respectively), and very high baseline risk (59% and 23%, respectively) (16). While the findings from this study support the connection of bariatric surgery and CKD risk, there are no other long-term studies conducted on this subject matter. Whether the beneficial effect on kidney function after that period is still persistent remains unknown. Therefore, further prospective long-term studies are needed.

Implications for Dietary Practice

For patients with impaired kidney functions, the dietary requirement is based on the stage of kidney disease. The goal of nutrition intervention is to preserve kidney function and maintain adequate nutritional status. For CKD patients who are overweight or obesity, weight loss may offer additional benefits on renal functions besides cardiovascular benefits (9).

Current researches on weight loss through diet intervention in CKD patients showed a reduction in proteinuria, a significant decrease in systolic blood pressure in obese patients, and improvement in lipid panel and glycemic control after weight loss (8)(9). Although, there is inadequate evidence on improvement in renal function, CKD patients who are overweight or obese can still benefit from weight loss through nonsurgical intervention.

Evidence demonstrated that weight loss through bariatric surgery could prevent further decline in renal function by reducing proteinuria, albuminuria and improving eGFR in obese patients with CKD (3)(5)(11)(12)(13). Bariatric surgery is also associated with improvements in blood pressure, glycemic control, and lipids in obese CKD patients (3). Despite increases in short-term post-operative complications, the benefits of bariatric surgery-induced weight reductions on CKD cannot be underestimated. Bariatric surgery should be considered CKD patients with obesity if medications and lifestyle changes do not result in any improvement. It has shown the potential for preventing further decline of GFR and thus the progression to ESRD. Nevertheless, in order to make definitive, accurate recommendations to those patients, the potential risks and long-term benefits of bariatric surgery should be further evaluated in large, longer follow-up studies.

Conclusion

Obesity has become a worldwide epidemic and it is associated with increased risks for diabetes, cardiovascular disease and also for chronic kidney disease. Obesity is now recognized as a strong risk factor for CKD, while the exact mechanism of obesity-related kidney disease remains unclear. Current evidence suggests that the pathophysiology underlying that is probably multifaceted and several factors may contribute to it such as hemodynamic, metabolic effect, and renal lipid accumulation.

Conservative weight loss intervention such as diet and exercise changes have led to a reduction in proteinuria, while the evidence about improvement in renal function is not adequate. Bariatric surgical interventions have gained more attention for treating obesity and it has been shown to prevent further decline in renal function and ameliorate kidney health in CKD patients.

Although many studies demonstrated that bariatric surgery provides a positive impact on overweight or obese CKD patients, the risks and long-term benefits associated with surgery for CKD patients are not well-understand, which prevents decisive conclusions for recommending specific interventions in the CKD population. Moreover, the majority of current studies depended on surrogate markers for kidney disease progression, such as GFR and proteinuria. Whether weight loss has positive impacts on other clinically important endpoints such as progressions to end-stage renal disease and mortality is unclear.

Long-term and large-scale studies need to be done in obese patients with CKD to determine whether the benefits from weight loss are sustained from both nonsurgical and surgical interventions. The risks associated with the treatments should also be studied in large randomized controlled trials. In addition, future research is needed to further investigate the pathophysiology of obesity-related kidney disease. This can improve the current treatment guidelines for overweight/obese CKD patients and assist in early identification and better prevention of kidney disease in obese patients.

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