Adiponectin production is lower in obese than in nonobese patients with nephropathy, via leptin-upregulated TGF-β. This is a paracrine mechanism that promotes collagen type IV synthesis and glomerulomegaly, which can act in a paracrine fashion on the mesangial matrix increase, mesangial cell proliferation, podocyte hypertrophy, and glomerulomegaly, either alone or in combination with various stages of secondary focal segmental glomerulosclerosis (4, 23).

Proposed Mechanisms of Obesity-Related Kidney Injury

The key hormones implicated in mediating the renal changes in obesity are leptin and adiponectin, both of which are produced by adipose tissue. On top of an increased activation of the renal sympathetic nervous system, leptin induces transforming growth factor-β1 (TGF-β1) production by the endothelium, which can act in a paracrine fashion on the mesangium to promote collagen type IV synthesis and glomerulosclerosis via leptin-upregulated TGF-β receptors (30, 31). Adiponectin production is lower in obese than in nonobese individuals, and its plasma levels correlated negatively with urinary albumin excretion in obese nondiabetic African-American subjects (24). Treatment with adiponectin has been associated with protection of podocyte function and reduction in albuminuria (24).

In addition, both interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) are produced by immune cells infiltrating visceral fat, and their levels are highly expressed in the glomeruli of patients with obesity-related glomerulomegaly, suggesting a possible role in the complex pathophysiology of this entity (11).

RAAS activation is also a key player in this process. Increased angiotension II (ANG II; Ref. 21) and angiotensin II type 1 receptor (AT1; Ref. 32) expression in obesity cause a net increase in efferent arteriolar vasoconstriction, an elevation in glomerular pressure and in filtration fraction, potentially contributing to glomerulosclerosis. In addition, aldosterone infusion into rats leads to direct podocyte injury and albuminuria by the activation of NADPH oxidase and the generation of reactive oxygen species (14). Aldosterone blockade lessens renal injury (21).

The structural glomerular lesions attributed to obesity can be seen in extreme obesity without overt clinical renal manifestations. Renal biopsies of 95 extremely obese patients [mean body mass index (BMI): 52 kg/m²] with normal renal function (creatinine clearance >90 ml/min) undergoing bariatric surgery showed a variety of glomerular lesions, including focal segmental glomerulosclerosis in five of them, that correlated only with BMI on multivariate analysis (22). This shows that CKD is only the tip of the iceberg with regard to the spectrum of obesity-related renal injuries.

One relevant question to be asked at this point is whether weight loss can slow the progression of CKD or even reverse the damage caused by the increased fat mass. Another question...
to be addressed relates to whether each weight loss modality, be it lifestyle, pharmacological, or surgical intervention, is effective in reaching this target.

Effect of Weight Loss on Kidney Function

A systematic review conducted by Afshinnia et al. (1) included 522 subjects from 5 controlled and 8 uncontrolled trials involving overweight and obese adults and assessed the impact of different weight-reducing strategies on markers of kidney function. The pooled patient population before interventions was extremely heterogeneous with regards to the degree of urinary albumin and protein excretion; some trials included patients with normoalbuminuria or microalbuminuria, and others included patients with overt proteinuria and even nephrotic-range proteinuria of about 3 g/24 h. Baseline mean glomerular filtration rate (GFR) or creatinine clearance in surgical trials was 140.2 ml/min, while it was 88.0 ml/min in nonsurgical trials.

Overall, dietary restriction-induced weight loss reduced overt proteinuria by 1.7 g [95% confidence interval (CI), 0.7 to 2.6 g] in those patients who had baseline overt proteinuria; this represented a 55% decrease from baseline (95% CI, 23–87%). None of the studies reporting on the effect of bariatric surgery included patients with overt proteinuria. Similarly, and in those patients who mostly had microalbuminuria, all weight loss interventions (dietary and surgical) decreased urinary albumin excretion by 14 mg (95% CI, 11–17), a 52% decrease from baseline (95% CI, 40–64%). Thus weight loss is associated with decreased proteinuria and microalbuminuria. However, there were no data evaluating the durability of this decrease or the effect of weight loss on CKD progression. In the authors’ assessment, it was stated that the quality of evidence for the beneficial effect of weight loss on decreasing proteinuria or albuminuria is moderate.

Meta-regression analysis showed that, independent of the decline in mean arterial blood pressure or body weight at baseline, each 1 kg of weight loss was associated with 110 mg (95% CI, 60–160 mg) decrease in proteinuria, or a 4% decrease (95% CI, 2–5%) and 1.1 mg (95% CI, 0.5–2.4 mg) decrease in microalbuminuria, or a 4% decrease (95% CI, 2–9%), respectively. The decrease was observed across different designs and methods of weight loss.

In general, changes in creatinine clearance and GFR were directly correlated with the change of body weight. Only bariatric surgery resulted in a significant decrease in creatinine clearance; GFR or creatinine clearance decreased by 23.7 ml/min (95% CI, 11.4–36.2), a 17% decrease from baseline (95% CI, 8–26%). Within nonsurgical interventions that achieved moderate degrees of weight loss, the results were mixed with little if any significant change in creatinine clearance (1). Thus the highest baseline weight, GFR, and creatinine clearance in patients of surgical trials, compared with other studies, suggest that the highest hyperfiltration in the former is actually reversed with more profound weight loss.

The systematic review and meta-analysis by Navaneethan et al. (16) looked at the impact of various forms of intentional weight loss on proteinuria and GFR in 13 different studies. Nonsurgical weight loss regimens (calorie restriction, exercise, and/or antiobesity drugs) were examined in overweight or obese individuals who also had CKD stage 1 to 3 (mostly due to diabetic nephropathy, hypertensive nephrosclerosis, or obesity-related glomerulopathy). After a mean follow-up period of 7.4 mo, the patients achieved a significant reduction in proteinuria by a mean of 1.31 g/24 h from a baseline mean of 2.5 g/24 h. Weight loss, however, did not result in a change in GFR or creatinine clearance at the end of study period. This stabilization of GFR might be considered a beneficial effect because of the tendency of the GFR to decline over time as a natural progression of these diseases. The results of this systematic review need to be interpreted with caution as some of the included studies used the Modification of Diet in Renal Disease (MDRD) and Cockcroft-Gault formulas to report renal function, which are unreliable equations to estimate GFR in obese patients.

The obese patients in the systematic review who underwent bariatric surgery had evidence of glomerular hyperfiltration at baseline (GFR >125 ml/min) related mostly to obesity-related glomerulopathy (16). Weight loss that was attained through surgical intervention resulted in normalization of GFR with an average reduction of 25.6 ml/min (16). Whether this normalization in hyperfiltration translates into long-term renal benefits remains to be seen. The patients undergoing bariatric surgery also had significant improvement in albuminuria; for instance, the median urinary albumin-to-creatinine ratio dropped from 66 to 13 mg/g (2). In the studies with patients who had overt proteinuria, there was also a substantial drop in the urinary protein excretion rate that exceeded 1 g/24 h. After weight reduction that was achieved through either nonsurgical or surgical intervention, the systolic blood pressure level was also significantly reduced.

At the other extreme, and in considering the group of patients with end-stage renal disease (ESRD) on dialytic therapy, weight reduction regimens in obese individuals might uncover a serious problem of protein-energy malnutrition. Several studies in patients on maintenance dialysis have shown that a higher basal BMI is associated, paradoxically, with the greatest survival (27). Therefore, obese ESRD patients must be adequately assessed and followed closely if a decision to lose weight is taken.

Several weight loss strategies were studied in individuals with various stages of CKD. Their effect on renal endpoints will be reviewed here.

Lifestyle Interventions (Diet and/or Physical Exercise)

Calorie restriction and increased physical activity are the mainstay weight-reducing interventions in large populations, and multiple studies have looked at their role in obese patients with kidney disease. Such approaches have been encouraged by preclinical studies whereby food restriction and weight loss in rodents prevented the development of renal disease in nonobese rats and reduced the severity and mortality from glomerulosclerosis in obese rats (25). An earlier study had also documented a reduction in the incidence and severity of glomerular hypertrophy simply by restricting the food intake of Sprague-Dawley rats, even without the need to modify the individual components of their diets (10). However, with the rising popularity of the low-carbohydrate diets, multiple studies have reported conflicting results about the effect of these diets, which are by nature protein rich, on renal disease and health. Few of these studies were randomized controlled trials,
and most of them were small observational studies of short duration.

One randomized controlled trial by Brinkworth et al. (5) evaluated renal function in 68 adults with normal kidney function and no albuminuria who were randomly assigned to receive either a very low-carbohydrate diet (4% carbohydrates and 35% proteins) or a high-carbohydrate diet (46% carbohydrates and 24% proteins). At 1 yr of follow-up, weight reduction was achieved without any adverse renal consequences in any of the two arms (5). These data from this small prospective study are generally supportive of the observational long-term findings in the Nurses’ Health Study, which showed that high dietary protein intake was not associated with a decline in renal function in women with normal renal function during an 11-yr period (12). However, the latter study also showed that women with mild CKD (estimated GFR 55–80 ml·min\(^{-1}\)·1.73 m\(^{-2}\)) who consumed more protein (median 93 g/day) had a 3.5-fold greater relative risk of worsening renal function over 11 yr compared with those who consumed less protein (61 g/day; Ref. 12).

Secondary analysis of a randomized controlled trial was performed comparing the effects of a low-carbohydrate/high-protein diet with unlimited protein consumption as per the Atkins protocol vs. a low-fat diet containing 15% proteins on 307 obese but otherwise “healthy” adults with a creatinine clearance of 133 ± 41.8 ml/min. It showed that the former diet was associated with a clinically insignificant 4.2% reduction in serum creatinine from a mean baseline of 0.9 mg/dl at 3 mo in the setting of an unchanged urinary creatinine excretion, which was paralleled by a decrease in cystatin C. This new steady state for serum creatinine as well as the reduction in cystatin C level, which, unlike serum creatinine, reflects glomerular filtration alone independent of creatinine generation reflects a state of glomerular hyperfiltration. At the same time, a transient increase in creatinine clearance (by 20.8 ml/min) was observed at 12 mo of follow-up but did not persist at 24 mo (9).

Despite the occurrence of increased glomerular filtration with the protein-rich diet, no subsequent reduction in GFR was detected at 2 yr of follow-up, and this could be explained by either decreased adherence to the diet, the need for more sensitive markers of kidney damage, or a longer duration of follow-up (9).

Animal studies have long shown the damaging effects of high-protein diet on kidney structure and function. For instance, in two groups of rats that were randomized to receive either a high-protein food intake (35% proteins) or a normal-protein intake (15% proteins) for a period of 17 mo, rats consuming the high-protein diet achieved 8% greater weight loss than the other group; however, they also had 17% higher kidney weights, three times higher proteinuria, and 27% higher creatinine clearance compared with those on normal-protein diet. Histologically, their glomeruli were also larger with more glomerulosclerosis (29).

Since CKD is often a silent disease, it may be therefore advisable to recommend that all patients undergo a screening serum creatinine measurement and urinary dipstick for albuminuria before initiating a high-protein diet (9).

On another hand, physical activity is often forgotten as an important modifiable lifestyle intervention even in patients with kidney disease. A beneficial role of exercise was demonstrated by Straznicky et al. (26) who randomized 38 overweight or obese individuals with the metabolic syndrome and a baseline estimated GFR ranging between 73.4 and 106.9 ml·min\(^{-1}\)·1.73 m\(^{-2}\) to a hypocaloric diet alone, to combination of aerobic exercise and dietary weight loss, or to no treatment for 12 wk. The modified Dietary Approach to Stop Hypertension (DASH) diet was used with the protein content accounting for 22% of the total daily energy intake and the aerobic exercise consisted of 40-min bicycle riding at a moderate intensity every other day. Body weight decreased ~8% in the diet only group and almost 11% in the combined diet and exercise group. Albuminuria and GFR improved in both groups, but the increase in GFR was augmented in the exercise intervention compared with the diet alone (7 ml·min\(^{-1}\)·1.73 m\(^{-2}\) change with exercise and diet compared with 4 ml·min\(^{-1}\)·1.73 m\(^{-2}\) change with diet alone; Ref. 26).

**Pharmacological Interventions**

Weight-loss medications are usually used as an add-on therapy to diet and exercise, particularly when the latter interventions fail to achieve or maintain adequate weight loss. Several drugs are now on the market but none has been adequately tested in adults with CKD stage 3 or greater. A cross-sectional analysis of over 10,000 participants in the National Health and Nutrition Examination Survey between 1999 and 2006 (NHANES: 1999–2006) concluded that a significant proportion of the CKD population uses medications to promote weight loss which may be harmful at this point, in view of the lack of studies showing their efficacy (17).

Orlistat (also known as tetrahydrolipstatin), which is a reversible inhibitor of gastric and pancreatic lipases, was studied in combination with diet and exercise in a group of obese patients with CKD stages 2–4 with a baseline average GFR of 44.8 ml/min (6). At 12 mo, all of the patients were able to achieve significant reductions in BMI and waist circumference and increase in exercise capacity without any reported adverse effects. Although their estimated GFR decreased by almost 21%, down to an average of 35.5 ml/min, this effect was not attributed to the intervention itself but rather to the progression of their underlying disease. On the other hand, the patients were now considered transplant candidates due to their lower BMI and improved functional ability (6). Patients taking Orlistat should be closely observed for fat-soluble vitamin deficiencies, for interaction with cyclosporine absorption, and for possible acute kidney injury from renal xalosis (13).

**Bariatric Surgery**

The main challenge in severely obese patients is maintenance of weight loss, which can prove difficult using the traditional interventions. Therefore, bariatric surgery now plays an important role, particularly in patients with class II obesity (BMI: 35–40 kg/m\(^2\)) with comorbidities and class III obesity (BMI > 40 kg/m\(^2\)). The rising popularity of bariatric surgery is attributed mainly to its beneficial effects on multiple obesity-related conditions such as insulin resistance, hypertension, dyslipidemia, obstructive sleep apnea, and, most importantly, a significant reduction in mortality that is maintained up to 18 yr postoperatively (2). In addition, there has been substantial support over the past several years for a favorable effect of bariatric surgery in improving all parameters of kidney function in patients with associated proteinuric CKD.
This is exemplified by a controlled prospective trial on 61 extremely obese patients whereby drastic weight loss 1 yr after bariatric surgery led to a considerable improvement in albuminuria or proteinuria and an increase in creatinine clearance; however, only albuminuria continued to improve in the second year (19). These results mirror those of another retrospective study of 25 morbidly obese CKD patients with a mean BMI of 49.8 kg/m² who underwent bariatric surgery. Their estimated GFR improved from an average of 47.9 7 ml·min⁻¹·1.73 m⁻² at baseline to 56.6 7 ml·min⁻¹·1.73 m⁻² at 6 mo and to 61.6 7 ml·min⁻¹·1.73 m⁻² at 12 mo (18).

Some might argue that the parameters used above, like the estimated GFR and the creatinine clearance, might not be an accurate measure of kidney function in obese patients, but Fenske et al. (8) used cystatin C as a marker of kidney function to assess patients pre- and postoperatively. In this study, 34 morbidly obese patients were randomized to undergo three types of bariatric surgery: laparoscopic sleeve gastrectomy, laparoscopic adjustable gastric banding, or Roux-en-Y gastric bypass. At 12 mo of follow-up, the patients in all treatment arms showed significant decrease in the mean arterial pressure and in urinary and serum inflammatory markers that correlated directly with body weight loss. In addition, patients with impaired renal function at baseline (corresponding to serum cystatin C >0.8 mg/l) had a marked improvement in renal function. The estimated GFR increased from 78.2 ± 2.8 7 ml·min⁻¹·1.73 m⁻² at baseline to 86.7 ± 0.9 7 ml·min⁻¹·1.73 m⁻² at 12 mo, while the serum cystatin C level dropped from an average of 0.94 to 0.72 mg/l during the same duration. Patients with lower serum cystatin C at baseline demonstrated no additional decrease after surgery (8).

The results from a cohort of 45 morbidly obese patients who underwent open gastric bypass surgery provide strong support for the notion that those patients with preexisting renal impairment have the greatest renal benefit following successful bariatric surgery. Nine of the patients had resolution, improvement, or stabilization of their renal function after the procedure. One with microscopically confirmed glomerulonephritis had complete resolution of the disease after 9 yr of follow-up and two of the patients who were dialyzed (for focal and segmental glomerulosclerosis) were able to discontinue dialysis for 27 and 7 mo, respectively. The rest of the patients had a stable kidney function throughout the rest of the follow-up (3).

Most of the literature on bariatric surgery in CKD patients notes an increased risk of kidney stone formation mostly due to decreased urinary volume, decreased urinary citrate, increased urinary oxalate and calcium oxalate supersaturation (2). However, several recent reports of the more restrictive procedures demonstrate reduced risk of nephrolithiasis compared with the malabsorptive procedures. Semins et al. (22) followed a group of 18 patients undergoing restrictive bariatric surgery (sleeve gastrectomy or gastric banding) and compared them to normal controls, stone-forming adults, and patients with Roux-en-Y gastric bypass surgery. There was no increased risk of nephrolithiasis in the patients undergoing restrictive bariatric surgery compared with the stone formers and the normal controls, and the urinary oxalate excretion was lower than that of the patients in the Roux-en-Y group (22).

Should all severely obese patients with renal disease be cleared to undergo bariatric surgery? Also, is this intervention appropriate for individuals with all stages of CKD?

To our knowledge, virtually no studies tried to answer these questions, but the most recent report performed by Turgeon at al. (28) with the American College of Surgeons’ National Surgical Quality Improvement Program (ACS/NSQIP) Participant Use Files (PUFs) provides some valuable information. The report compared CKD stage and risk of complications in 27,736 patients who underwent bariatric surgery between 2006 and 2008 (28). Each increment in CKD stage was associated with a 1.3 times increased relative risk of postoperative complications. In absolute terms, however, the rate of complications remained very low, and the mortality rate was not affected at 30 days.

In conclusion, intentional weight loss can improve outcomes, particularly albuminuria and proteinuria, in patients with mild to moderate CKD of different underlying etiologies and particularly those whose renal damage is likely induced by obesity (Table 1). Multiple nonsurgical regimens are available, but close follow-up and monitoring are required for those patients who choose to use high-protein diets or weight-reducing medications. Results from bariatric surgery seem very appealing especially that this intervention has shown reduction in both glomerular hyperfiltration and urinary albumin or protein excretion rate, in addition to significant improvement in multiple comorbidities, quality of life, and obesity-related mortality. The modest, yet apparent, increased risk of perioperative complications with advanced stages of CKD requires more vigilance for earlier screening of obese patients for evidence of renal damage and for earlier referral for surgery. There is a lack of long-term studies that can analyze the impact of various weight loss interventions on patient-centered data.

### Table 1. Effect of various weight loss interventions on kidney parameters

<table>
<thead>
<tr>
<th>Diet</th>
<th>Albuminuria</th>
<th>Proteinuria</th>
<th>Change in GFR</th>
<th>Glomerular Hypertrophy</th>
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</thead>
<tbody>
<tr>
<td>Exercise (+diet)</td>
<td>Afshinnia et al. (1)</td>
<td>Afshinnia et al. (1) mixed results</td>
<td>Gumprecht et al. (10)</td>
<td></td>
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<tr>
<td>Medication (+diet + exercise)</td>
<td>Straznicky et al. (26)</td>
<td>Straznicky et al. (26)</td>
<td>Stern et al. (25)</td>
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<tr>
<td>Bariatric surgery</td>
<td>Navaneethan et al. (16)</td>
<td>Navaneethan et al. (16)</td>
<td>Afshinnia et al. (1) mixed results</td>
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<td>Navarro-Diaz et al. (19)</td>
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<td>Navarro-Diaz et al. (19)</td>
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Summary of the different published studies (reference numbers given in parentheses) reporting on changes in kidney parameters by the various weight loss modalities. GFR, glomerular filtration rate.
such as development of ESRD or mortality. More research is needed in this area.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


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