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Strategies to Treat Obesity in Patients With CKD

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Abstract

Obesity prevalence continues to increase worldwide, accompanied by a rising tide of hypertension, diabetes, and chronic kidney disease (CKD). While body mass index is typically used to assess obesity in clinical practice, altered body composition (e.g. reduced muscle mass, increased visceral adiposity) are common among patients with CKD. Weight loss achieved through behavioral modification or medications reduces albuminuria, and in some cases, slows decline in estimated glomerular filtration rate (eGFR). Use of medications that promote weight loss with favorable cardiovascular risk profiles should be promoted, particularly in patients with type 2 diabetes, obesity, and CKD. For those who fail to achieve weight loss through lifestyle modification, bariatric surgery should be considered, as observational studies have shown reductions in risk of eGFR decline and kidney failure. Uncertainty persists on the risk-benefit ratio of intentional weight loss in patients with kidney failure, due to lack of prospective trials and limitations of observational data. Regardless, sleeve gastrectomy is increasingly being used for patients with kidney failure and severe obesity with success in achieving sustained weight loss, improved access to kidney transplantation, and favorable post-transplant outcomes. More research is needed assessing long-term cardiovascular and kidney outcomes of most weight loss medications.

Keywords

weight loss; obesity; CKD; kidney failure; bariatric surgery

Clinical Vignette

A 55-year-old man is referred to nephrology clinic by his primary care provider. Past medical history includes severe obesity, type 2 diabetes mellitus, hypertension, hyperlipidemia, and obstructive sleep apnea. He has had a recent weight gain of 10 pounds after he started working from home, despite attempts to lose weight by going to the gym twice a week. His medications include metformin, glipizide, long-acting insulin, metoprolol,

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and lisinopril. His body mass index (BMI) is 42 kg/m^2, blood pressure is 135/80 mmHg, and his physical examination is unremarkable aside from abdominal obesity. Estimated glomerular filtration rate (eGFR) is 45 ml/min/1.73m^2, urine albumin/creatinine ratio is 250 mg/g, and hemoglobin A1c is 7.0%. After explaining potential benefits of weight loss, the nephrologist discontinues glipizide, prescribes a sodium-glucose cotransporter-2 (SGLT2) inhibitor, and refers the patient to a comprehensive weight management center that includes nutritional counseling and bariatric surgery.

Epidemiology of obesity

Obesity continues to be a major challenge across the world(1), with prevalence of obesity (BMI ≥ 30 kg/m^2) increasing in the United States from 30.5% in 1999-2000 to 42.4% in 2017-2018, and prevalence of severe obesity (BMI ≥ 35 kg/m^2) increasing from 4.7% to 9.2% over the same time period (2). Obesity increases risk for kidney disease through many proposed mechanisms including insulin resistance, lipotoxicity, adipocytokine dysregulation, increased blood pressure and enhanced glomerular blood pressure(3, 4). Prevalence of obesity in patients with CKD is particularly high with data from the 2011-2014 National Health and Nutrition Examination Survey (NHANES) showing that 69% had elevated waist circumference, 44% had obesity, and 22% had severe obesity (5). As obesity prevalence continues to rise alongside an aging global population, prevention and mitigation of obesity-associated complications will be critical in global efforts to combat CKD.

Assessing obesity in CKD

Measurement of body weight and height to determine BMI is commonplace, and BMI has strong, consistent associations with health outcomes in the general population(6). However, there are notable limitations to BMI when assessing adiposity. First, BMI is a poor metric for body fat distribution and is unable to differentiate between fat and muscle mass. Asian populations are at risk for developing metabolic complications at lower cut points of BMI, with a proposed lower BMI cut point of 27.5 kg/m^2 for obesity(7). Body composition is often altered in disease states such as CKD, impacting the diagnostic utility of BMI. In a study assessing adiposity in 77 patients with CKD and 20 controls, prevalence of obesity by BMI was 65% in CKD and 20% in controls whereas obesity defined by air displacement plethysmography body fat percentage (≥25% for men, ≥ 35% for women), was 90% in CKD and 60% in controls (8). Thus, approximately 30% of patients with CKD with BMI <30 kg/m^2 may have obesity defined by body fat percentage .

Another important issue is heterogeneity in fat distribution as visceral fat has more adverse metabolic effects than subcutaneous fat (9). Visceral adipose tissue is more strongly associated with adverse cardiometabolic parameters and kidney function decline (10-12). In contrast, lower-body subcutaneous fat may serve as a metabolic buffer, preventing other tissues from accumulating lipotoxicity (10). While visceral adiposity is best captured by imaging, elevated waist circumference (≥102 cm for men, ≥88 cm for women) is a simple alternative that captures some of this risk(11, 13). Among U.S. patients with CKD, prevalence of elevated waist circumference is 69% among those with BMI 25-29.9 kg/m^2 and 26% in those with BMI 22-24.9 kg/m^2 (Figure 1). The value of central adiposity

measurement is highlighted in studies showing that patients with kidney failure and earlier stages of CKD who have low/normal BMI and elevated waist circumference (i.e. sarcopenic obesity) are at the highest risk of kidney failure and death (14-16).

Association between obesity and kidney outcomes

Even with its limitations, elevated BMI has consistently been associated with increased risk of CKD and kidney failure (12, 17-20). In a study of 320,252 adults with BMI measured between 1964-1985 at Kaiser Permanente, adults with BMI 30-34.9 kg/m^2, 35-39.9 kg/m^2, and ≥ 40 kg/m^2 had 160%, 410%, and 510% higher risk of kidney failure, respectively(19). In a study of 3.4 million U.S. veterans with eGFR ≥ 60 ml/min/1.73m^2, BMI had a U-shaped association with rapid loss of kidney function, with the best clinical outcomes associated with a BMI between 25-30 kg/m^2 (20). In a CKD Prognosis Consortium global, individual-level meta-analysis of 5.5 million adults in 39 general population cohorts, BMI levels of 30, 35, and 40 kg/m^2 were associated with 18%, 69%, and 102% higher risk of eGFR decline ≥ 40% (17). Importantly, the association between obesity and risk of eGFR decline ≥ 40% were fairly similar in patients with and without CKD.

Cause of CKD may be particularly important when assessing the prognostic significance of BMI as factors other than obesity play a much more important role for patients with glomerular diseases unrelated to obesity. A single-center study of 560 patients with biopsy-proven primary glomerulonephritides (excluding minimal change disease) found no association between BMI and risk of major adverse kidney events(21). However, other cohort studies focusing on specific types of kidney disease suggest that elevated BMI is a risk factor for CKD progression in IgA nephropathy and adult polycystic kidney disease (22, 23).

Lifestyle modification interventions for weight loss in CKD

A 2013 systematic review identified 6 lifestyle intervention randomized controlled trials (RCTs), 1 pharmacologic RCT, and 24 observational studies examining the effect of intentional weight loss on kidney parameters in patients with obesity and altered kidney function (24). In lifestyle intervention RCTs, diet alone or combined with exercise was generally effective at reducing weight, lowering blood pressure and proteinuria although follow-up was of short duration and conclusions on long-term effects on kidney function could not be drawn(25-27). Weight loss groups experienced a 31% reduction in proteinuria whereas proteinuria tended to increase in the control group at 5 months. In more recent years, several lifestyle intervention and medication RCTs with larger numbers of participants with CKD have been published, bolstering the evidence for weight loss benefits on the kidney (Tables 1-2).

The Action for Health in Diabetes (Look AHEAD) trial randomized 5145 overweight/obese adults with type 2 diabetes (237 with eGFR < 60 ml/min/1.73m^2 and 829 with ACR ≥ 30 mg/g), to intensive lifestyle intervention (ILI) or diabetes support education (28, 29). The ILI arm had goals of ≥7% weight loss, 1200-1800 kcal/day (<30% from fat, >15% from protein) and ≥ 175 minutes of moderate-intensity physical activity per week through

frequent offerings of individual/group counseling sessions. After the study was ended early due to a futility analysis, a post-hoc analysis examining kidney outcomes was conducted(29). Mean weight loss at the end of a median of 9.6 years of follow-up was 6.0% for ILI vs. 3.5% in the control arm. Individuals in the ILI arm had a 31% reduced risk of "very-high risk" KDIGO category CKD (Table 1).

No convincing data exists supporting the superiority of a specific dietary pattern or popular diet to promote weight loss in the general population or in CKD(30, 31). An RCT randomized 322 adults with obesity (99 with stage 3 CKD, 23 with albuminuria ≥ 30 mg/g) to follow 1 of 3 restricted-calorie diets (low-fat, Mediterranean, or low-carbohydrate) (32). The primary outcome, 2-year weight loss, was highest for the low-carbohydrate arm (mean −4.7 kg), followed by the Mediterranean-diet arm (−4.4 kg), and then the low-fat arm (−2.9 kg) (Table 1). In a post-hoc analysis, eGFR increased in all intervention arms with no significant difference between diet arms. Among the 99 patients with stage 3 CKD at baseline, eGFR increased by 7.1% (95% CI: 3.4%, 10.9%). Among the 23 persons with albuminuria, ACR decreased by 24.8 mg/g. Without clear evidence favoring a specific macronutrient or dietary pattern on kidney function during weight loss, a prudent approach would be to individualize weight-loss diets while considering laboratory values, comorbidities, and patient preferences with the aid of a registered dietitian nutritionist. Fortunately, medical nutrition therapy (MNT) coverage for non-dialysis dependent CKD (as well as diabetes) is provided by Medicare for up to 3 hours during the initial year of referral and up to 2 hours in subsequent years as a standalone billable service with a referral from a physician(33). MNT coverage is also frequently covered by Medicaid and private payers.

A meta-analysis of 421 patients with non-dialysis dependent CKD in 13 exercise intervention RCTs found that exercise interventions resulted in a slight increase in eGFR although this appeared to be restricted to studies <3 months duration (34). Cardiometabolic benefits of exercise in CKD include decreases in systolic blood pressure (−5.6 mmHg), diastolic blood pressure (−2.9 mmHg), and BMI (−1.3 kg/m^2), although BMI was reduced only in exercise interventions of 6-12 months duration. Other benefits of exercise demonstrated in CKD include improving exercise capacity, functional capacity, and quality of life; no effects on albuminuria have been observed (34-36).

Role of medications for weight loss in CKD

In combination with behavioral modifications to reduce weight through diet and exercise, several drugs are currently approved for weight loss by the Federal Drug Administration (FDA) (Table 3). In a 2016 systematic review and network meta-analysis, average 1-year weight loss effects were highest for phentermine-topiramate (8.8 kg), followed by liraglutide (5.3 kg), naltrexone plus bupropion (5.0 kg), lorcaserin (3.2 kg), and orlistat (2.6 kg)(37). Cardiometabolic effects were greatest for phentermine-topiramate (decreased waist circumference, modest decreased glycemia and blood pressure, minimal decreased cholesterol) and liraglutide (substantial decrease in waist circumference and glycemia, minimal effect on blood pressure and cholesterol). However, attrition rates ranged from 30-45% (37). Given the track record of weight loss drugs having been withdrawn from the U.S. market due to cardiovascular concerns (e.g. fenfluramine, sibutramine), psychiatric

concerns (rimonabant), and malignancy concerns (lorcaserin)(38-40), it is perhaps unsurprising that one study reported that 1.3% of adults eligible for weight-loss medications were prescribed these medications between 2009-2015 with phentermine accounting for 77% of prescriptions(41). Unfortunately, scant safety data exists on phentermine-topiramate and naltrexone plus bupropion in patients with CKD.

Phentermine/topiramate

While phentermine-topiramate has been shown to be very effective for achieving weight loss, RCTs have been of short duration <1 year and trial exclusion criteria have included creatinine clearance <60 ml/min, nephrolithiasis, recent cardiovascular disease or unstable angina, and blood pressure >160/100 mmHg(42, 43). Listed adverse effects on the product label include elevated blood pressure and heart rate for phentermine and increased risk of renal tubular acidosis, nephrolithiasis, and teratogenicity (oral clefts) for topiramate. Post-marketing surveillance data from an observational study found no signal of cardiovascular harm for phentermine-topiramate, and RCT data suggests that phentermine-topiramate actually lowers blood pressure (44). Both phentermine and topiramate are cleared by the kidney, and the product label for phentermine-topiramate recommends a maximum dose of 7.5 mg/46 mg daily for moderate or severe kidney impairment, and avoiding its use in kidney failure (Table 3)(43, 45). Considering the high cardiovascular risk of patients with CKD, long-term RCT data are needed to understand safety of phentermine alone or phentermine-topiramate before recommending their use in CKD.

GLP-1 RAs

Robust cardiovascular safety data exists on the use of GLP-1 RAs with systematic reviews and meta-analyses demonstrating this class improves weight and glycemia, even when compared to dipeptidyl peptidase-4 inhibitors(46). The efficacy and safety of several GLP-1 RAs in patients with type 2 diabetes and CKD have been established in several trials (Table 2), even though these trials were not designed as weight loss trials(47-49). Currently, only liraglutide is FDA-approved at a higher dose for the weight loss indication (Table 3). An RCT comparing liraglutide 3.0 mg daily vs. placebo in 2254 adults with pre-diabetes demonstrated efficacy in reducing weight (liraglutide vs. placebo: −6.1% vs. −1.9%) and risk of diabetes (2% vs. 6%) (50).

In addition to benefits on glycemia and weight, GLP-1 RAs appear to be cardioprotective (51). In a meta-analysis of 4 GLP-1 RA trials, GLP-1 RAs reduced risk of cardiovascular outcomes by 10%, and all-cause death by 12%(52). In a trial that randomized 9340 patients with type 2 diabetes and high cardiovascular risk (23% with eGFR <60 ml/min/1.73m^2, 37% with albuminuria ≥ 30 mg/g) to liraglutide (diabetes dose: up to 1.8 mg per day) or placebo(47, 53), liraglutide reduced the risk of the primary cardiovascular outcome similarly in those with and without CKD (Table 2)(53). Adverse effects of liraglutide and other GLP-1 RAs include higher rates of acute gallbladder disease, and gastrointestinal events leading to discontinuation but lower risk of hypoglycemia, and no increased risk of AKI (47). Other studies suggest that GLP-1 RAs may have beneficial effects on kidney outcomes although this finding has largely driven by improvements in albuminuria in most trials(49, 54, 55).

The European Renal Association-European Dialysis and Transplant Association published a consensus statement summarizing evidence and advocating the preferred use of GLP-1 RA and SGLT2 inhibitors in the treatment of patients with type 2 diabetes and CKD(48). While no SGLT2 inhibitors are FDA-approved specifically for weight loss, modest weight loss (~1-3 kg) has been observed in SGLT2 inhibitor RCTs(56). This effect may be weaker in patients with CKD as the glucosuria effects of SGLT2 inhibitors decrease as kidney function declines(57). In a landmark trial of adults with T2DM and CKD (eGFR 30-89 ml/min/ $1.73m^2$, ACR ≥ 300 mg/g), canagliflozin reduced body weight by 0.8 kg(58). Use of both SGLT2 inhibitors and GLP-1 RA together shows great promise in promoting weight loss and glycemic control(59), though additional data are needed in CKD.

Bupropion-naltrexone

Long-term CVD safety data is unavailable for bupropion-naltrexone as the RCT evaluating cardiovascular safety was terminated after inappropriate release of confidential interim data by the sponsor(60). Systematic exposure of bupropion-naltrexone is expected to be increased based on data for the individual components (bupropion and its metabolites 2-3-fold; naltrexone and its metabolites increased unknown amount)(45). In 1-year controlled trials, bupropion-naltrexone resulted in higher serum creatinine at follow-up (0.07 mg/dl vs. 0.01 mg/dl) and higher rates of doubling of creatinine (0.6% vs. 0.1%), compared to placebo(45). This creatinine rise might be independent of GFR as in vitro drug-drug interaction studies suggest bupropion and its metabolites inhibit organic cation transporter 2. Given its effect on increasing blood pressure and uncertain effects on kidney function, bupropion-naltrexone should probably be avoided in CKD.

Other medications

Another weight loss drug infrequently used is orlistat, an inhibitor of gastric and pancreatic lipase that results in fat malabsorption in the gut and does not require renal dose adjustment (Table 3)(38). Its efficacy for weight loss is modest, and several case reports of oxalate nephropathy have been reported (61). Lorcaserin, a small-molecule agonist of the serotonin 2C (5-HT_{2C}) receptor, was shown in an RCT of 12,000 overweight/obese persons to reduce the risk of a primary kidney composite outcome (Table 2) (62). However, lorcarserin was discontinued from the market due to concerns about possible increased risk of cancer(45). Sibutramine, a monoamine reuptake inhibitor, was withdrawn from the market due to increased cardiovascular risk (39). Unfortunately, sibutramine is available over the internet from other countries; patients with CKD should be discouraged from its use.

There are several medication classes that contribute to weight that deserve mention, including some diabetes medications, atypical antipsychotics, corticosteroids and hormone replacement therapy, antiepileptic medications, antidepressants, antihistamines, and beta-blockers (63). A focus on the weight effects of diabetes medications is particularly important and relevant to CKD as insulin, sulfonylureas, and thiazolidinediones are associated with weight gain. Leptogenic medications that result in neutral weight or weight loss include metformin, GLP-1 RAs, SGLT2 inhibitors, dipeptidyl peptidase-4 inhibitors, and pramlintide (63, 64). In a study of U.S. veterans who participated in a behavioral weight-loss

program, patients on obesogenic medications were 37% less likely to achieve ≥5% weight loss(65).

Role of bariatric surgery in CKD

For many patients with severe obesity, satisfactory weight loss may not be achievable through intensive lifestyle modification or medications, and they may be eligible for bariatric surgery (Medicare requirements: BMI ≥ 35 kg/m^2, ≥1 obesity-related comorbidity, failed medical treatment of obesity)(66). The two most popular procedures currently are Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy(5), with their success driven more by effects on hunger and satiety, rather than by mechanical restriction. Mechanisms underlying their effects on hunger, satiety, food choice may be driven in part by gut hormones such as GLP-1 and peptide YY (67). An RCT comparing intensive medical therapy to intensive medical therapy plus RYGB or sleeve gastrectomy found that bariatric surgery groups had greater 5-year weight loss (RYGB −23%, sleeve gastrectomy −19%, medical therapy alone −5%), less use of insulin (−35%, −34%, −13%), and improved quality life (68).

Several observational studies have compared long-term kidney function outcomes in patients who undergo bariatric surgery to matched non-surgery patients with severe obesity(5, 69-71). Overall, results have consistently shown that bariatric surgery is associated with slower eGFR decline and lower risk of kidney failure. In a propensity score-matched cohort study of 985 bariatric surgery (97% RYGB) patients and 985 non-surgery patients, bariatric surgery was associated with a 57% lower risk of doubling of creatinine or KFRT(69). In a propensity score-matched cohort study of 714 bariatric surgery patients and 714 non-surgery patients with baseline stage 3-4 CKD, bariatric surgery was associated with 9.8 ml/min/1.73m^2 higher eGFR at a median of 3 years follow-up (70). This beneficial effect on eGFR might be overestimated using creatinine since creatinine is correlated with muscle mass, which decreases after bariatric surgery. A recent study measured multiple filtration markers before and several years after bariatric surgery and in matched controls with severe obesity(72). Over 8-10 years of follow-up, bariatric surgery was associated with a ~1 ml/min/1.73m^2/yr slower decline in eGFR using creatinine-cystatin C combined equation with consistent findings using other filtration markers like beta-2 microglobulin and beta-trace protein. Similar results have been seen in the Swedish Obesity Study, where patients receiving bariatric surgery (69% vertical banded gastroplasty, 18% banding, 13% gastric bypass) had a 64% lower risk of kidney failure over a median follow-up of 18 years compared to matched controls(71).

Management of obesity in patients with kidney failure

There remains controversy about the role of weight loss interventions in patients with kidney failure (31, 73, 74). Observational studies have found a protective association of elevated BMI (even at >35 kg/m^2) with death in hemodialysis patients whereas this has not been consistently observed in peritoneal dialysis patients (75, 76). It is possible there could be short-term benefits of having excess metabolic reserve in chronic illnesses though caution is advised in interpreting these associations (75). If obesity increases risk of kidney failure via

hypertension and diabetes, then other risk factors (some unmeasured) might be expected to be greater in non-obese individuals with kidney failure(77). Other epidemiologic issues impacting interpretation include reverse causation (i.e. disease resulting in weight loss), survival bias (i.e. unhealthier persons with obesity dying before reaching kidney failure), and inability of BMI to distinguish fat and muscle mass. One study suggested that decline in muscle mass may partially explain the protective BMI-death association in patients on hemodialysis as a decline in serum creatinine was more strongly associated with mortality than weight loss (78). Abdominal adiposity may be a better measure in kidney failure as waist circumference, adjusted for BMI, is associated with increased risk of death in patients with kidney failure on dialysis as well as kidney transplant(15, 16). Transplant programs often exclude patients with severe obesity with BMI center-dependent cutpoints ~35-40 kg/m^2 with justification that obesity is associated with modestly increased risks of transplant graft loss and delayed graft function(79). Whether or not this exclusion is justified is debatable since kidney transplantation is associated with improved survival, even among those with severe obesity, and obesity does not appear to impact survival in patients with kidney transplant(80). Unfortunately, the vast majority of patients with kidney failure trying to achieve BMI requirements for transplant listing fail with medical management of obesity(81-84). For patients on peritoneal dialysis, this can be particularly challenging as large weight gains are common during the 1^{st} year, likely due to glucose load (100-200 gm/day or 400-800 calories/day), increased appetite, and increased fluid gain(85).

In a prospective evaluation of a multidisciplinary weight loss clinic for transplant candidates at the University of Cincinnati, 0/52 patients (90% with kidney failure on hemodialysis) were able to achieve sufficient weight loss over 6 months to be eligible for transplantation (86). In longer-term follow-up (2011-2018) of 243 patients (198 with kidney failure, 45 with CKD) who underwent laparoscopic sleeve gastrectomy, 72% achieved a BMI ≤ 40 kg/m^2, 48% achieved a BMI ≤ 35 kg/m^2, and 45 received a kidney transplant with 10 still on the waitlist(87). Bariatric surgery in patients with kidney failure has been associated with lower mortality (5-year cumulative incidence 26% vs. 40%), higher likelihood of kidney transplant (5-year cumulative incidence 33% vs. 20%)(88), lower rates of delayed graft function (82), and improved long-term allograft survival (89). However, it should be noted that patients who undergo bariatric surgery are carefully selected and typically healthier than ineligible patients. In our opinion, data overall suggest that bariatric surgery should be considered for patients with kidney failure who are candidates for kidney transplantation (aside from their BMI), given the large benefits of kidney transplantation on survival and quality of life(80).

Risks of surgical weight loss

A study using 2015-2016 national bariatric surgery quality data found that 30-day postoperative mortality was 1.4%, 0.4%, and 0.1% for individuals with kidney failure, CKD, and without CKD, respectively (81). There are also risks of micronutrient deficiencies (e.g. thiamine, cobalamin, folic acid, iron, vitamin D, calcium, vitamin A, zinc, and copper deficiencies), protein malnutrition, iron deficiency anemia, fractures, and mental health disorders (e.g. alcohol-use disorders, suicide, self-harm) (66). In terms of kidney risks, bariatric surgery is associated with increased risk of hyperoxaluria and calcium oxalate nephrolithiasis(90). This particular risk is driven by degree of fat malabsorption and is

greatest in biliopancreatic diversion/duodenal switch and “very long limb” RYGB, moderate in conventional RYGB, whereas no increased risk has been observed for restrictive procedures such as sleeve gastrectomy(5, 90). Thus, decisions on bariatric surgery require multidisciplinary team care, careful patient selection, shared decision-making and long-term follow-up.

Clinical vignette, continued

With the help of a dietitian, the patient makes substantial dietary changes shifting from high consumption of processed foods, added sugars and salt to a diet rich in freshly-prepared whole foods with increased consumption of fiber-rich vegetables. A year later, his BMI is 38 kg/m^2 and long-acting insulin and metoprolol were discontinued due to improved blood pressure and A1c. His kidney parameters have improved (urine albumin/creatinine ratio 25 mg/g, eGFR 47 ml/min/1.73m^2), and the patient decides to continue making lifestyle changes while declining bariatric surgery at this time.

Conclusion

Obesity is a major contributor to CKD and kidney failure, and several behavioral modification and medication trials have shown that weight loss improves albuminuria and possibly slows eGFR decline. While intensive lifestyle intervention is recommended for weight loss, use of medications with favorable weight loss effects such as GLP-1 RAs may help patients with type 2 diabetes and CKD achieve weight goals. Bariatric surgery should be considered for patients with CKD and severe obesity who fail lifestyle modifications with potential benefits on slowing CKD progression. Patients with kidney failure who are eligible for transplant aside from high BMI should also be considered for bariatric surgery, which can improve access to kidney transplantation with favorable post-transplant outcomes. Additional research is needed to determine long-term cardiovascular and kidney effects of most weight loss drugs.

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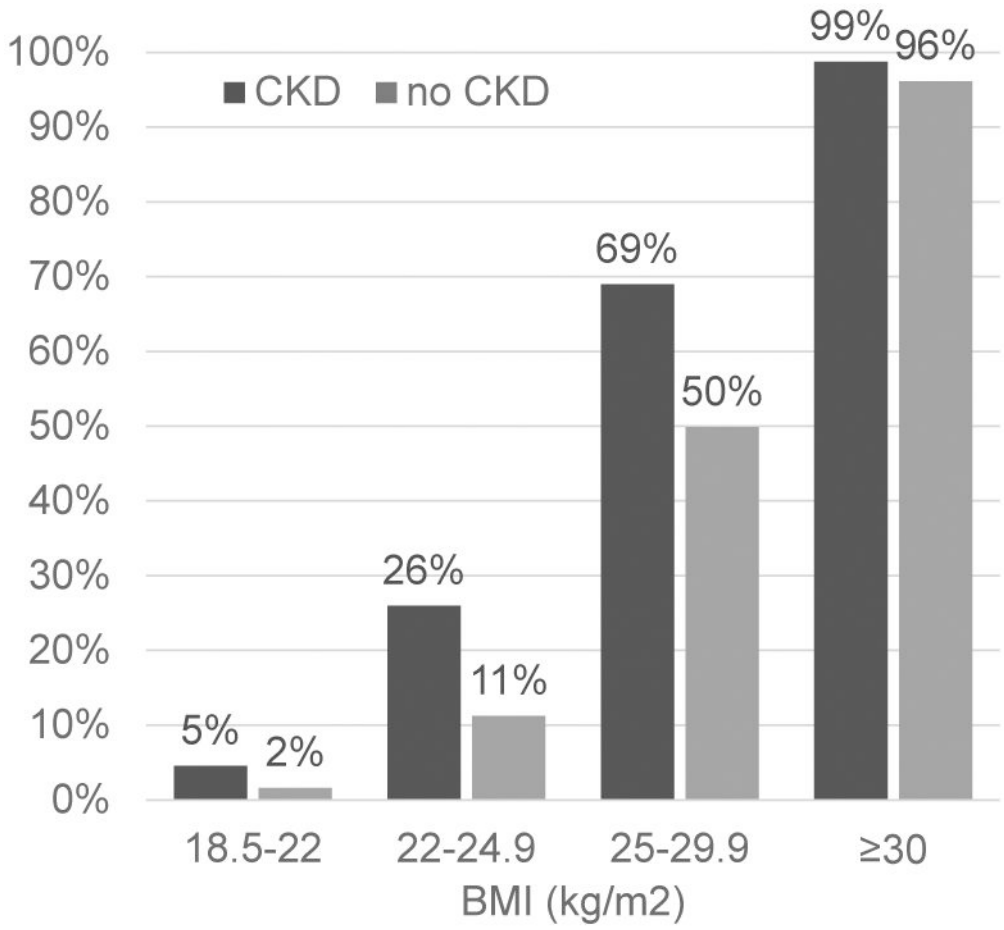

Figure 1. Prevalence of Abdominal Obesity, Stratified by CKD status and BMI: NHANES 1999-2012

Abdominal obesity (waist circumference ≥102 cm for men, ≥88 cm for women) in patients with or without CKD (eGFR <60 ml/min/1.73m^2 or ACR ≥ 30 mg/g). Data from the National Health and Nutrition Examination Survey (NHANES) 1999-2012 cycles.

Table 1.

Lifestyle Intervention RCTs achieving weight loss in Patients with CKD

Author, year (reference #)	Study population	Intervention, Follow-up time	Weight and cardio-metabolic outcomes	Kidney Outcomes
Praga, 1995(91)	RCT of 17 adults (47% diabetes, all w/ preserved GFR, mean age 48 y, BMI 37.9 kg/m^2, proteinuria 3.1 g/d)	Arm 1: Hypocaloric diet; Arm 2: Captopril; Duration: 12 months	BMI decreased in diet arm (37.1 to 32.6 kg/m^2) with no change in captopril arm	Proteinuria decreased in diet group (2.9 g/d to 0.4 g/d) and captopril group (3.4 to 0.7 g/d). eGFR stable in both groups
Nicholson, 1999(92)	Pilot RCT of 11 adults (100% w/T2DM, mean age 54y, albuminuria 435 mg/d, eGFR not reported)	Arm 1: Low-fat vegan diet; Arm 2: Control low-fat diet; Duration: 12 weeks	Vegan arm had greater 12-wk weight loss vs. control (−7.2 kg vs. −3.8) and fasting glucose (−28% vs. −12%).	No significant difference in albuminuria in vegan arm (pre 434.8 mg/d, post 155.2) compared to control (pre 82.9, post 169.2).
Morales, 2003(27)	RCT of 30 adults w/proteinuria >1 g/d and creatinine <2 mg/dL (47% diabetic nephropathy, mean age 56y, BMI 33.4 kg/m^2)	Arm 1: Hypocaloric diet; Arm 2: Standard diet; Duration: 5 months	5-month weight decreased in diet arm (87.5 to 83.9 kg) and increased in control arm (96.1 to 98 kg)	Proteinuria (primary) decreased more in the diet arm (pre 2.8, post 1.9 g/d) than control arm (pre 3, post 3.5 g/d)
Howden, 2013(93)	RCT of 72 adults w/eGFR 25-60 and 1 uncontrolled CVD risk factor (28% diabetes, mean age 61, BMI 33 kg/m^2)	Arm 1: lifestyle intervention (lifestyle program, supervised aerobic and resistance training); Arm 2: usual care (control); Duration: 12 months	12-month changes greater in lifestyle intervention arm vs. control for weight (−1.8 vs. +0.7 kg) and peak VO2 (primary) (+2.8 vs. −0.4 ml/kg/min)	No difference in change in eGFR or ACR between arms
Tirosh (DIRECT), 2013(32)	RCT of 322 adults w/BMI ≥27 kg/m^2, T2DM, or CAD at a workplace in Israel; excluded serum creatinine ≥2.0 mg/dL (14% T2DM, 31% stage 3 CKD, 8% albuminuria, mean age 52 y, BMI 31 kg/m^2)	Arm 1: calorie-restricted low-carb; Arm 2: calorie-restricted Mediterranean; Arm 3: calorie-restricted low-fat; Duration: 2 years	Overall: weight loss (primary) at 2 years highest for low-carb −4.7kg, Mediterranean −4.4 kg, then low-fat arm −2.9 kg. TG decreased and HDL increased more in low carb vs. low-fat.	Overall: Pre-post increase in eGFR similar in all arms (low carb: +5.3%; Mediterranean +5.2%, low-fat +4.0%) CKD stage 3 subgroup (n=99): Combined intervention arms prepost eGFR increase +7.1 Microalbuminuria subgroup (n=23): Combined intervention arms mean ACR decreased −24.8mg/g
Jesudason, 2013(94)	RCT of 45 adults w/T2DM, ACR 30-299 mg/d and eGFR >40 (11% eGFR <60, mean age 61 y, BMI 36 kg/m^2)	Arm 1: Moderate-protein (MP) weight loss diet (90-120 g/d); Arm 2: Standard-protein (SP) weight loss diet (55-70 g/d); Duration: 12 months	Weight loss at 12 months similar in both arms (MP diet −9.7 kg, SP diet −6.6 kg)	Change in measured GFR by ^{99m}Tc-DTPA (primary) at 12 months not significantly different in MP arm (pre 143, post 129) and SP arm (pre 112, post 113). No change in 24-hr urine albumin at 12 months
Look AHEAD, 2014(29)	Multi-center RCT of 5145 adults w/ T2DM; excluded creatinine >1.4 mg/dL (female) >1.5 mg/dL (male) 5% eGFR <60, 16% ACR ≥ 30 mg/g, mean age 59, BMI 36 kg/m^2)	Arm 1: Intensive lifestyle intervention [ILI]: exercise, caloric restriction (<30% fat >15% protein), meal-replacements; Arm 2: diabetes support/education (DSE); Duration: Median 9.6 years	Weight loss at 1-year greater in ILI vs. DSE (8.6% vs. 0.7%) and at study end (6.0% vs. 3.5%). No difference in CVD composite (primary) outcome (ILI vs. DSE) HR 0.95 (0.83, 1.09)	ILI reduced risk of KDIGO “very high risk” category (HR 0.69, 95% CI: 0.55, 0.87). Similar results for other kidney outcomes including ACR≥ 300 mg/g (HR 0.81, 95% CI: 0.66, 1.01), eGFR <45 (HR 0.79, 95% CI: 0.66, 0.96), KFRT (HR 0.80, 95% CI: 0.49, 1.30), doubling of creatinine (HR 0.81, 95% CI: 0.61, 1.07)
Goraya, 2014(95)	RCT of 108 non-diabetic adults ≥18 y w/ stage 3 CKD, CO2 22-24 mmol/L, ACR ≥200 mg/g, K≤4.6 mEq/L (mean age 54 y, weight 84 kg)	Arm 1: Fruits and vegetables to reduce acid load 50%; Arm 2: NaHCO3 0.3 mEq/Kg/d; Arm 3: usual care; Duration: 3 years	At 3 years, weight loss greater in fruit/ vegetable arm (−4.0 kg) than usual care arm (−1.9) and HCO3 arm (no change), and SBP lower in fruit/vegetable arm (128.3 mmHg) than usual care arm (135.4) and HCO3 arm (135.7)	$eGFR_{cyc}$ decline (primary) was slower in fruit/ vegetable arm (pre 42.3, post 36.9) and HCO3 arm (pre 42.6, post 35.2), compared to usual care (pre 42.6, post 28.8). Albuminuria reduced more in fruit/vegetable arm (pre 318 mg/g, post 242) and HCO3 arm (pre 317, post 262), compared to usual care (pre 315, post 300).

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Author, year (reference #)	Study population	Intervention, Follow-up time	Weight and cardio-metabolic outcomes	Kidney Outcomes
Greenwood, 2015(96)	Pilot RCT of 18 adults w/eGFR 20-60, decline in eGFR ≥ 2.9 in past 12 months (mean age 54, BMI 28 kg/m^2)	Arm 1: resistance and aerobic training (3 days/wk); Arm 2: usual care; Duration: 12 months	Exercise intervention improved 12-month weight (between-group differences −5.6 kg), waist circumference (−7.1 cm), VO_{2peak} (5.7 ml/kg/min), PWV (−2.3 m/s)	No significant effect of exercise intervention on 12-month $eGFR_{cr}$ (primary), $eGFR_{cyc}$, or $eGFR_{cr\text{-}cyc}$
Ikizler, 2018(35)	Pilot RCT at 4 US sites of 122 overweight/obese adults w/stage 3-4 CKD (25% diabetes, mean age 60 y, BMI 31-36 kg/m^2)	Arm 1: Caloric restriction (CR) and supervised aerobic exercise; Arm 2: Aerobic exercise only; Arm 3: CR only; Arm 4: Control (usual care); Duration: 4 months	Compared to control, weight improved after 4 months in CR/exercise arm (−2.4 kg), CR only arm (−1.8) but not exercise only (0.5 kg); similar findings for fat mass. F2-isoprostane and IL-6 levels improved whereas VO_{2peak} no improvement in all arms	No significant difference in $eGFR_{cyc}$ or urine ACR after 4 months in any of the intervention arms.

RCTs involving weight loss in patients with CKD. Units for eGFR in table are ml/min/1.73m^2.

Abbreviations: CKD (chronic kidney disease), RCT (randomized controlled trial), BMI (body mass index), CVD (cardiovascular disease), eGFR (estimated glomerular filtration rate using creatinine), ACR (albumin creatinine ratio), T2DM (type 2 diabetes mellitus), CAD (coronary artery disease), HDL (high-density lipoprotein), TG (triglycerides), NaHCO3 (sodium bicarbonate), SBP (systolic blood pressure), CO2 (bicarbonate), K (potassium), $eGFR_{cyc}$ (estimated glomerular filtration rate using cystatin C), MP (moderate protein), SP (standard protein), ^{99m}Tc-DTPA (technetium-99m diethylene-triamine-pentaacetate), ILI (intensive lifestyle intervention), DSE (diabetes support and education), HR (hazard ratio), KFRT (kidney failure with replacement therapy), VO_{2peak} (peak oxygen uptake), PWV (pulse wave velocity), CR (caloric restriction), IL (interleukin)

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Table 2.

Medication and Surgical RCTs Achieving Weight Loss in Patients with CKD

Author/Trial, year (reference #)	Study Population	Intervention, Follow-up time	Weight and selected cardio-metabolic outcomes	Renal Outcomes
Stenlof *, 2006(97)	Multi-center RCT of 229 adults w/ T2DM not on meds; excluded "clinically significant renal disease" (mean age 54 y, BMI 36 kg/m^2, A1c 6.7%, mean albuminuria 27 mg/g, did not report proportion w/CKD)	Arm 1: Topiramate 96 mg/d Arm 2: Topiramate 192 mg/d Arm 3: Placebo Duration: 10 months	Weight change at 10 months (co-primary) greater in topiramate arms (96 mg/d 6.6%; 192 mg/d 9.1%) vs. placebo 2.5%; A1c change at 10 months (co-primary) greater in topiramate arms (96 mg/d −0.6%; 192 mg/d −0.7%) vs. placebo −0.2%	Change in 24-hr urine albumin excretion at 10 months significantly greater in topiramate arms (96 mg/d −16.2 mg/d; 192 mg/d −15.7 mg/d) vs. placebo −1.0 mg/24h
MacLaughlin, 2014(98)	Pilot RCT at 3 teaching hospitals of 16 adults w/BMI 35-45 kg/m^2, eGFR 20-60; excluded kidney transplant (45% T2DM, mean age 52 y, BMI 37-40 kg/m^2)	Arm 1: Laparoscopic sleeve gastrectomy (SG) Arm 2: individualized dietary and physical activity prescription + orlistat Duration: 1 year	Improvements for SG vs. non-surgical arm in 1-year changes in weight (adjusted difference −29.0 kg), waist circumference (−29.1 cm). HOMA-IR (−7.7 units), and adiponectin (6.1 mg/L)	No difference in change in eGFR$_{cr\text{-}cyc}$ or urine protein/creatinine ratio for SG vs. non-surgical arm. Change in measured GFR (primary) not reported.
Marso (SUSTAIN-6), 2016(99)	Multicenter RCT of 3297 adults w/ T2DM, A1c≥7%, CVD or CKD; excluded patients on dialysis (24% eGFR <60, mean age 65y, weight 92 kg, A1c 8.7%)	Arm 1: Subcutaneous semaglutide 1.0mg/d Arm 2: Placebo Arm 3: Subcutaneous semaglutide 0.5mg/d Arm 4: Placebo Duration: Median 2.1 years	Overall: Weight loss was greater at 2 years for both semaglutide doses vs. placebo (1.0 mg/ week −4.3 kg, 0.5 mg/week −2.9 kg). Semaglutide reduced risk of MACE (primary) (HR 0.74, 95% CI: 0.58, 0.95) eGFR <60 subgroup (n=795): reduced MACE (HR 0.69, 0.57, 0.85)	Overall: Semaglutide reduced risk of composite kidney outcome (HR 0.64, 95% CI: 0.46, 0.88), largely driven by persistent macroalbuminuria (HR 0.54, 95% CI: 0.37, 0.77). Other kidney outcomes: doubling of creatinine or eGFR <45 (HR 1.28, 95% CI: 0.64, 2.58), KFRT (HR 0.91, 95% CI: 0.40, 2.07)
LEADER, 2018(53)	Multicenter RCT of 9340 adults w/ T2DM, A1c ≥7%, CVD risk factors, CVD, or CKD; excluded dialysis patients (23% w/eGFR <60, 37% w/ albuminuria ≥ 30 mg/g, mean age 64 y, BMI 33 kg/m^2, A1c 8.7%)	Arm 1: Subcutaneous liraglutide 1.8 mg/day (diabetes dose) Arm 2: Placebo Duration: median 3.5 years	Overall: Liraglutide reduced weight at 3 years vs. placebo (−2.3 kg). Liraglutide reduced MACE (primary; HR 0.87, 95% CI: 0.78, 0.97) eGFR <60 subgroup (n=2158): MACE (HR 0.69, 95% CI: 0.57, 0.85) Albuminuria subgroup (n=3422): MACE (HR 0.83, 95% CI: 0.71, 0.97)	Overall: Liraglutide reduced risk of kidney composite (HR 0.78, 95% CI: 0.67-0.92), mostly driven by new-onset persistent macroalbuminuria (HR 0.74, 95% CI: 0.60, 0.91); eGFR <60 subgroup (n=2158): kidney composite (HR 0.84, 95% CI: 0.67, 1.05); Albuminuria subgroup (n=3422): kidney composite (HR 0.81, 95% CI: 0.68, 0.96)
Scirica (CAMELLIATIMI 61) 2019 (62)	Multicenter RCT of 12000 adults w/ atherosclerotic CVD or multiple CVD risk factors; excluded eGFR<30 (20% w/eGFR <60, 16% w/ACR 30-299 mg/g, 3% w/ACR ≥ 300 mg/g, median age 64 y, BMI 35 kg/m^2)	Arm 1: Lorcaserin Arm 2: Placebo Duration: median 3.3 years	Overall: Lorcaserin reduced weight (−2.8 kg) at 1 year vs. placebo. No difference in MACE (primary; HR 0.99, 95% CI: 0.85, 1.14). eGFR <60 subgroup (n=2357): Lorcaserin reduced weight (−3.2 kg) at 1 year vs. placebo. No difference in MACE (HR 1.09, 95% CI: 0.84, 1.42)	Overall: Lorcaserin reduced risk of kidney composite outcome (new or worsening persistent albuminuria, new or worsening CKD, doubling of creatinine, KFRT, or kidney death; HR 0.87, 95% CI: 0.79, 0.96) eGFR <60 subgroup (n=2357): HR 0.75 (0.61, 0.93); ACR 30-300 subgroup (n=1893): HR 0.99 (0.79, 1.24); ACR >300 subgroup (n=385): HR 0.87 (0.55, 1.38)
Tuttle (AWARD-7), 2019(49)	Multicenter RCT of 577 adults w/ T2DM, A1c 7.5-10.5%, stage 3-4 CKD (mean age 65 y, BMI 32 kg/m^2, eGFR$_{cyc}$ 35.3)	Arm 1: Subcutaneous dulaglutide 1.5 mg/wk Arm 2: Subcutaneous dulaglutide 0.75 mg/wk Arm 3: Insulin glargine Duration: 52 wks	Both dulaglutide doses reduced weight at 52 wks (1.5 mg/wk −2.7 kg, 0.75 mg/wk −1.7 kg) vs. insulin glargine (+1.6 kg) Change in A1c at 26 wks (primary) and at 52 wks for both dulaglutide doses non-inferior to insulin glargine	Both dulaglutide doses resulted in higher eGFR at 52 wks (1.5 mg/wk, 34.0 ml/min/1.73m^2, 0.75 mg/wk 33.8 ml/min/1.73m^2) vs. insulin glargine (31.3 ml/min/1.73m^2); No significant difference in ACR at 52 wks for either dulaglutide doses vs. insulin glargine

Author/Trial, year (reference #)	Study Population	Intervention, Follow-up time	Weight and selected cardio-metabolic outcomes	Renal Outcomes
Husain (PIONEER 6), 2019(100)	Multicenter CVD safety RCT of 3183 adults w/T2DM, CVD risk factors, CVD or CKD; excluded kidney failure, stage 4-5 CKD (27% w/eGFR <60, mean age 66 y, BMI 32 kg/m^2)	Arm 1: Oral semaglutide (14mg) Arm 2: placebo Duration: median 15.9 months	Overall: Semaglutide reduced weight at 15.9 months vs. placebo (−4.2 kg vs. −0.8 kg). No difference in MACE (primary; HR 0.79, 95% CI: 0.57-1.11) eGFR <60 subgroup: MACE HR (0.74, 95% CI: 0.41, 1.33)	Not reported

* Terminated early as sponsor decided to develop controlled-release formulation; results presented for modified-intention-to-treat analysis of 229 patients completing 10-month follow-up

Abbreviations: CKD (chronic kidney disease), RCT (randomized controlled trial), BMI (body mass index), CVD (cardiovascular disease), eGFR (estimated glomerular filtration rate), ACR (albumin creatinine ratio), T2DM (type 2 diabetes mellitus), SG (sleeve gastrectomy), BMC (best medical care), HOMA-IR (homeostatic model assessment of insulin resistance, MACE (major adverse cardiovascular event), KFRT (kidney failure with replacement therapy), HR (hazard ratio)

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Table 3.

Prescribing information of weight loss drugs approved by the FDA in combination with lifestyle modifications

Drug	Mechanism of action	Dose	Most common side effects	Kidney and other less common side effects	CKD dose adjustment	Approved duration of treatment
Liraglutide Available formulations: 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg, 3 mg by subcutaneous injection, pre-filled, multi-dose pen (6mg/mL, 3ml)	GLP-1 receptor agonist; GLP-1 stimulates insulin secretion, inhibits glucagon, regulates appetite and calorie intake	0.6 mg SC daily and weekly increase the dose to 3.0 mg SC daily	GI symptoms, decreased appetite, hypoglycemia, dizziness, abdominal pain, increased lipase	Increased HR, renal impairment in post marketing data, usually in association with nausea, vomiting, diarrhea, dehydration; use caution when initiating or escalating dose in patients with renal impairment, acute pancreatitis, gallbladder disease, medullary thyroid carcinoma, hypersensitivity reactions, suicidal ideation	No dosage adjustment necessary in mild to moderate renal impairment; limited data in dialysis; only 6% metabolites excreted in urine	Chronic
Naltrexone/bupropion Available formulations: 8mg/90mg ER	Anorexiant, exact mechanism in weight loss is not fully known; bupropion (dopamine/ norepinephrine reuptake), naltrexone (opioid antagonist)	8mg/90mgdaily and weekly increase in the dose to 32mg/360mg per day	GI symptoms, headache, dizziness, dry mouth	Elevation of BP and HR, palpitations, urinary urgency, increased creatinine (possibly due to inhibition of OCT2), neuropsychiatric disorders, seizures, hepatotoxicity, angle-closure glaucoma	Moderate to severe impairment: max 1tab BID; avoid in dialysis as not studied; 87% bupropion excreted in urine, up to 79% of naltrexone excreted in urine	Chronic
Orlistat Available formulations: 120 mg, 60 mg	Pancreatic and gastric lipase inhibitor Acts in stomach and small intestine	120 mg TID with meal or less than 1 hour after fat containing meal 60 mg TID with fat containing meal	GI symptoms (oily rectal leakage, flatulence, fecal incontinence)	Decreased drug concentration of cyclosporine, decreased absorption of fat-soluble vitamins (e.g. vitamin D), oxalate stones, pedal edema, hypersensitivity, Leukocytoclastic vasculitis, liver injury	No adjustment; major route of excretion is in feces;<2% in urine; administer cyclosporine 3 hours after orlistat	Chronic
Phentermine Available Formulations: 15, 30, 37.5 mg/day	Anorexiant, exact mechanism is not established; norepinephrine releasing agent stimulates CNS	15 to 37.5mg q am; 8 mg TID (30min before meal)	Insomnia, tremors, changes in libido, dependence, dry mouth, taste alterations, GI distress, anxiety, restlessness	Elevation of BP and HR, palpitations, cardiac ischemia, PPH and valvular heart disease reported in combination with fenfluramine or dexfenfluramine (role of phentermine in valvulopathies has not been established but cannot be ruled out)	eGFR 15-29: 15mg /d; eGFR <15 and dialysis: avoid; urinary excretion 62%-85% under uncontrolled urinary pH conditions	Short term 3 months
Phentermine/topiramate-ER Available formulations: 3.75 mg IR/23mg ER, 7.5 mg IR/46mg ER, 11.25 mg IR/69 mg ER, 15 mg IR/92 mg ER	Anorexiant, GABA receptor modulation plus norepinephrine releasing agent, precise mechanism of action is not known	3.73 mg/23 mg daily in am, progressively increase the dose to 15 mg/92mg per day	Paresthesia, dizziness, dysgeusia, insomnia, constipation, dry mouth	Nephrolithiasis, metabolic acidosis, elevated creatinine≥0.3 mg/dl, hypokalemia, increased HR, hypotension if on BP meds, cognitive impairment, risk of suicidal thoughts, insomnia, angle closure glaucoma, teratogenicity (oral clefts)	eGFR <50: maximum dose 7.5mg/46 mg per day; avoid in dialysis as not studied; close to 80% phentermine excreted in urine; 70% of topiramate excreted unchanged in urine	Chronic

This table details prescribing information from FDA-approved weight loss drugs. Diethylpropion, phendimetrazine, and benzphetamine not included as similar in mechanism and side effects to phentermine, which is the most commonly used drug in the class. Data source: US Food and Drug Administration.[45]

BP: blood pressure, HR: heart rate, TID: three times daily, QID: four times a day (quarter in die), BID: twice a day OTC: over the counter, GI: gastrointestinal, IR: Immediate release, ER extended release. eGFR: ml/min/1.73m^2, SC: Subcutaneous, CNS: central nervous system, PPH: primary pulmonary hypertension