Blockbuster Medications for Obesity: A Primer for Nephrologists

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The prevalence of obesity in the United States and across the world continues to climb, imparting increased risk of chronic disease. This impact is doubly felt in nephrology because obesity not only increases the risk of chronic kidney disease (CKD) but also exacerbates existing cardiovascular morbidity and mortality. The role of medical weight loss therapy in CKD has been debated, but increasing evidence suggests that intentional weight loss is protective against adverse kidney and cardiovascular outcomes. This may be particularly true with the advent of novel pharmacotherapies taking advantage of the incretin system, resulting in weight loss approaching that seen with surgical interventions. Moreover, these novel therapies have repeatedly demonstrated protective effects on the cardiovascular system. Here, we review the impact of obesity and weight loss on CKD, and the biological basis and clinical evidence for incretin therapy. This perspective provides recommended prescribing practices as a practical tool to engage nephrologists and patients with CKD in the treatment of obesity-related morbidity.

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Impact of Obesity

The obesity epidemic continues to worsen, with a prevalence of obesity in the United States of 42.4% in 2017-2018,[1] and with recent estimates suggesting prevalence rose 3% during the COVID-19 pandemic.[2] Global obesity prevalence is expected to reach 18% in men and 21% in women by 2025.[3] The reasons for these trends are myriad, with the obesogenic food environment, the built environment (the environment in which people live, work, and play), and decreased physical activity all playing a role. The disease of obesity contributes to health problems including diabetes, hypertension, heart disease, kidney disease, and fatty liver disease, among others. According to the Global Burden of Disease, high body mass index (BMI) accounted for 2.4 million deaths and 70.7 million disability-adjusted life years, of which the leading causes were cardiovascular disease, diabetes, kidney diseases, and neoplasms.

Obesity increases the risk of chronic kidney disease (CKD) by inducing a state of insulin resistance, raising blood pressure, increasing the risk of diabetes, and directly damaging the kidney.[4,5] The association between BMI and risk of end-stage kidney disease (ESKD) in participants from 1964-1985 with 15-35 years of follow-up increased in a graded fashion, with relative risks of 3.57, 6.12, and 7.07 for stage 1 obesity (BMI 30-34.9 kg/m^2), stage 2 obesity (BMI 35-39.9 kg/m^2), and stage 3 obesity (BMI ≥40 kg/m^2), respectively, compared with normal weight (BMI 18.5-24.9 kg/m^2). Data from more contemporary cohorts have also found that obesity is associated with an increased risk of CKD, albeit more modestly. In a global CKD Prognosis Consortium individual-level meta-analysis of 5.5 million patients, the hazard ratio of eGFR decline at BMIs of 30, 35, and 40 kg/m^2 was 1.18, 1.69, and 2.02, respectively, compared with a BMI of 25 kg/m^2.[6] The risk of eGFR decline was similar for patients with eGFR <60, 30-59, and <30. Obesity is also associated with increased risk of cardiovascular disease, including a doubling of the risk of heart failure[7]—a particularly important problem because CKD increases the risk of heart failure 4-fold.[8,9]

As obesity imparts substantial risks to kidney health, the prevalence of obesity is high and continues to increase among patients with CKD. Using 2007-2018 NHANES data in patients with CKD (eGFR < 60 mL/min/1.73 m^2 or albumin-creatinine ratio [ACR] ≥ 30 mg/g),[10] Figure 1 shows that these trends continue to worsen for obesity (BMI ≥ 30 kg/m^2: 43.1% to 49.8%), elevated waist circumference (>102 cm for men, >88 cm for women: 66.8% to 71.6%), and severe obesity (BMI ≥ 35 kg/m^2: 20.7% to 26.3%) from 2007-2010 to 2015-2018.

Impact of Weight Loss in CKD

Considering the known effects of obesity on the kidney and heart, weight loss is important to address in CKD. In the past, caution was advised regarding weight loss in CKD because observational studies had noted an "obesity paradox" in conditions such as kidney disease and heart failure where patients who have obesity with these conditions tend to live longer than patients without obesity.[11] There may be several reasons for this. BMI is an imperfect metric reflecting both muscle mass and fat mass. Patients who have sarcopenic obesity with low BMI and high abdominal obesity are at the highest risk of death.[12] Related to this issue is the phenomenon of protein-energy wasting (PEW) and malnutrition in patients with CKD, especially advanced CKD. PEW is an independent risk factor for adverse outcomes, including mortality, so lower BMI in patients with CKD may be reflective of PEW rather than healthy weight loss; multiple scoring systems have

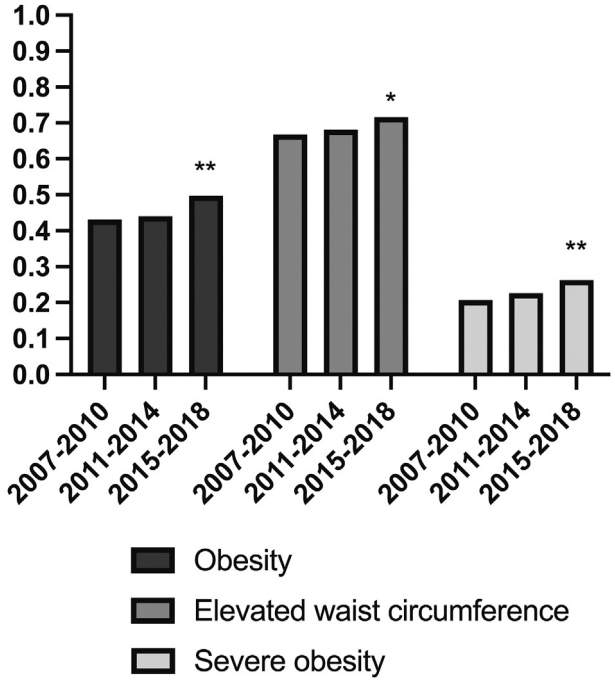

Figure 1. Prevalence of obesity, abdominal obesity, and severe obesity in chronic kidney disease. Prevalence of obesity (BMI ≥ 30 kg/m^2), elevated waist circumference (>102 cm for men, >88 cm for women), and severe obesity (BMI ≥ 35 kg/m^2) in patients with chronic kidney disease. Data from NHANES 2007-2018. Abbreviation: BMI, body mass index. *P = 0.02 for linear trend. **P < 0.01 for linear trend.

been developed to monitor nutrition status specifically in patients with kidney disease.[13] Unintentional weight loss often occurs secondary to illness and could weaken the association between higher BMI and adverse health outcomes if patients with CKD lost weight before entry into a cohort.[14] If obesity increases the risk of CKD, risk factors for CKD that may be unmeasured or measured poorly are likely to be greater in nonobese individuals with CKD (ie, collider bias).

Fortunately, recent prospective randomized controlled trials (RCTs) have shown kidney benefits with weight loss, suggesting that intentional weight loss through lifestyle intervention, pharmacotherapy, and bariatric surgery is safe in patients with obesity and CKD.[15-20] Weight loss in general reduces albuminuria, a risk factor for CKD progression.[15] Intentional weight loss achieved through intensive lifestyle modification was associated with a 31% reduced risk of "very high risk" Kidney Disease Improving Global Outcomes (KDIGO) category CKD in 5,145 adults with type 2 diabetes mellitus (T2DM) though only 5% had eGFR < 60 and kidney outcomes were not prespecified.[18]

Specific weight loss interventions that have been shown to be effective in reducing albuminuria include bariatric surgery, glucagon-like peptide 1 (GLP-1) receptor agonists, and combined agonists of GLP-1 and glucose-dependent insulinotropic polypeptide (GIP).[17,21,22] These will be discussed in detail later. Notably, a randomized controlled trial compared Roux-en-Y gastric bypass (RYGB) to best medical therapy per 2019 American Diabetes Association (ADA) guidelines in 100 patients with eGFR > 30 mL/min/1.73 m^2 and ACR > 30 mg/g.[17] Weight loss was greater for the RYGB group (−25.4%) than the best medical therapy group (−4.5%) at 24 months. The primary outcome, remission of albuminuria, was achieved by 85% in the RYGB group versus 48% in the best medical therapy group. No serious adverse events were noted in the trial, and safety data have shown that although postsurgical risks are increased in CKD patients, absolute risks are acceptably low.[23]

The history of weight loss pharmacotherapy is checkered with drugs withdrawn from the market due to cardiovascular concerns (eg, fenfluramine, dexfenfluramine, sibutramine), but recently approved antiobesity medications and others in development have been shown to be safe and extremely effective.[24] By far the most promising medications for patients with and at risk for CKD take advantage of the incretin system.

Incretin Biology

Since the late 19th century, it has been recognized that glucose loads given orally are better tolerated (ie, without glucosuria) when compared with those given intravenously.[25] In the early 20th century, scientists such as La Barre began to parse the role of duodenal secretions in this physiology, coining the term "incretin" for the portion of duodenal hormone that was thought to stimulate the pancreas to control blood glucose postprandially.[26] Amazingly, La Barre suspected that this biology may one day prove useful in the treatment of diabetes. However, it was not until the 1960s that the term "incretin effect" came to mean the difference in insulin secretion induced by orally versus intravenously administered glucose.[27]

Subsequent work identified the key components of the enteroendocrine system now known as the incretin hormones: GIP and GLP-1.[28] GIP is secreted in the duodenum by K cells in response to food ingestion. GLP-1 is secreted by L cells more distally, in the ileum and colon. GLP-1 levels in the blood rise within minutes of food ingestion, long before nutrients have reached the distal gastrointestinal tract, suggesting a neurohormonal mechanism of GLP-1 regulation that remains incompletely understood.[29] Once released, both GIP and GLP-1 are rapidly degraded by dipeptidyl peptidase-4, with the kidney also participating in clearance of the endogenous incretin hormones.[29]

The incretin hormones regulate blood glucose concentrations through an array of mechanisms. They rapidly signal to the pancreas to increase insulin production, via both direct effects on pancreatic islet cells and through vagal signaling via the portal circulation and the liver.[30] In the β cells, the incretins stimulate glucose-dependent

insulin secretion, increase the production of proinsulin, reduce β-cell apoptosis, and increase proliferation (Fig 2), while in α cells GLP-1 reduces the production of glucagon.[31] These effects diminish at lower blood glucose levels, limiting hypoglycemia.

In addition to effects on glycemic control, the incretin hormones cause weight loss, primarily by driving appetite suppression and decreased food intake. This occurs through peripheral and central mechanisms. GLP-1 slows gastric emptying and reduces gastric acid production; as with signaling to the pancreas, this effect occurs in part via vagal afferents.[29] GLP-1 also plays a role in reducing appetite centrally, as intracerebral administration decreases food intake and weight in rodents via hypothalamic signaling.[32]

Finally, preclinical studies suggest protective effects of GLP-1 and GIP on the organs most at risk of dysfunction in patients with obesity and diabetes: the heart and kidneys. In the heart, for example, administration of GLP-1 increases myocardial glucose uptake, increases left ventricular contractility, and decreases experimentally induced infarct size.[33] Only GLP-1 receptor (and not GIP receptor) has been found in the kidneys. There, GLP-1 induces increased natriuresis and decreases albuminuria.[34] Importantly, GLP-1 may also restore kidney metabolism to prevent or reverse obesity-related kidney diseases.[35,36]

Clinical Trial Evidence for Incretin-based Therapies

GLP-1 Receptor Agonists

The promise of the incretin hormones as targets for therapy in diabetes and obesity has been borne out by substantial clinical trial evidence showing not only efficacy for hemoglobin A_{1c} (HbA_{1c}) reduction and weight loss, but also cardiovascular and potentially kidney benefit.[21,37,38] A meta-analysis of 8 trials found that GLP-1 receptor agonists reduced major adverse cardiovascular events (MACE) by 14% as well as a composite kidney outcome (including development of albuminuria ≥ 300 mg/g) by 21% with no significant heterogeneity across GLP-1 receptor agonist structural homology.[37] Importantly, 24% of the patients in these trials had eGFR < 60 mL/min/1.73 m^2, and the beneficial effect on MACE was similar among patients with and without eGFR < 60 mL/min/1.73 m^2. In a trial of 577 patients with uncontrolled T2DM and stage 3-4 CKD comparing once-weekly dulaglutide at two doses, patients in the intervention group had ~3 mL/min/1.73 m^2 higher eGFR at 52 weeks compared with the glargine group.[39]

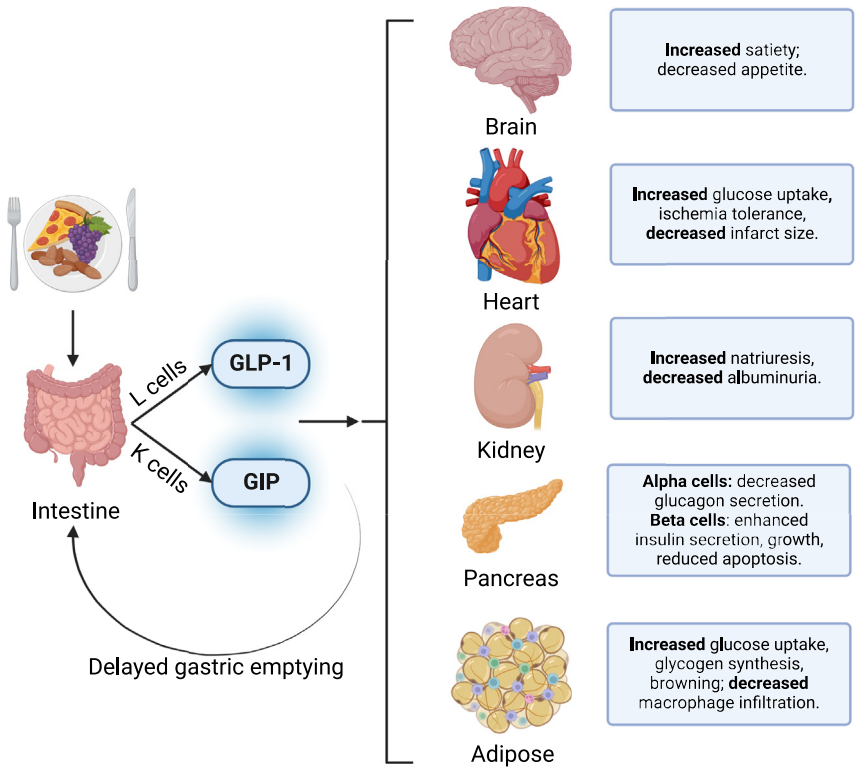

Figure 2. Incretin production and end-organ effects. The incretin hormones, GIP and GLP-1, are produced in the enteroendocrine cells of the gastrointestinal tract in response to food ingestion. They act via both direct and indirect mechanisms to reduce appetite and food intake, and have a variety of end-organ effects leading to both weight loss and cardiometabolic benefits (blue boxes in figure). Created with BioRender.com. Abbreviations: GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1.

Although these results are promising, patients with advanced kidney disease and ESKD have been largely excluded from clinical trials. Small pilot studies and case series, however, suggest that most GLP-1 receptor agonists may be both safe and effective even in patients on dialysis.[40-42]

Liraglutide and semaglutide are also approved by the US Food and Drug Administration (FDA) for weight loss regardless of diabetes status. The STEP 1 trial, a double-blind RCT comparing semaglutide (2.4 mg per week) with placebo as an adjunct to lifestyle intervention in nondiabetic patients with obesity, demonstrated a treatment difference (greater weight loss) for semaglutide of 12.7 kg at week 68 compared with placebo.[43] Semaglutide is also available in an oral formulation and has been found to be both safe and effective (though less so than injectable semaglutide) in patients with diabetes and reduced kidney function.[44] Similarly, liraglutide at a dose of 3.0 mg daily was effective for weight loss in patients without diabetes, with an 8.4 kg weight loss compared with 2.8 kg in the placebo group.[45]

Dual GLP-1 and GIP receptor agonist

Co-activation of the GIP and GLP-1 receptors with tirzepatide has been shown to have synergistic effects. Tirzepatide, a once-weekly subcutaneous injectable approved by the FDA for T2DM in May 2022, has been undergoing fast-track review for overweight and obesity treatment. Tirzepatide resulted in greater reductions in HbA_{1c} and weight than semaglutide in an open-label phase 3 trial.[46] An open-label RCT (SURPASS-4) assessing the efficacy and safety of tirzepatide randomized adult participants with T2DM, HbA_{1c} 7.5%-10.5%, and BMI ≥ 25 kg/m^2 at an elevated cardiovascular risk to once weekly tirzepatide (5, 10, or 15 mg) or insulin glargine.[47] Tirzepatide resulted in greater HbA_{1c} reduction for the 10-mg and 15-mg doses with less hypoglycemia and no excess cardiovascular risk. In the SURPASS-5 trial comparing tirzepatide with placebo in patients with uncontrolled T2DM who were taking insulin glargine, the mean treatment differences in body weight were −7.1 kg, −9.1 kg, and −10.5 kg for the 5-mg, 10-mg, and 15-mg doses, respectively.[48]

In addition, post hoc analysis of SURPASS-4 examining eGFR and albuminuria found favorable effects of tirzepatide on kidney outcomes.[22] Tirzepatide slowed eGFR decline (between-group difference 2.2 mL/min/1.73 m^2 per year), reduced albuminuria by approximately 32%, and reduced the risk of reaching the composite kidney end point by (hazard ratio [HR], 0.58 [95% CI, 0.43-0.80]) compared with insulin glargine. The beneficial effect of tirzepatide on eGFR slope appeared to be more favorable among the 338 participants with a baseline eGFR of <60 mL/min/1.73 m^2. Importantly, as with other nephroprotective medications (eg, angiotensin-converting enzyme inhibitors), tirzepatide was observed to induce an early, reversible eGFR dip after treatment initiation.[49]

The SURMOUNT-1 trial randomized 2,539 nondiabetic adults with BMI ≥ 30 kg/m^2 or BMI ≥ 27 kg/m^2 with ≥1 weight-related complications to weekly subcutaneous tirzepatide or placebo.[24] The mean percentage change in weight at week 72 was −15.0%, −19.5%, and −20.9% for 5-mg, 10-mg, and 15-mg weekly tirzepatide doses, respectively, compared with −3.1% for placebo. An astonishing 57% of participants on the 15-mg dose reduced their weight by more than 20%—results approaching efficacy of the sleeve gastrectomy.[24,47] Of note, eGFR < 30 mL/min/1.73 m^2 was an exclusion criterion in SURMOUNT.[50]

Combination Therapy With Sodium-Glucose Cotransporter-2 Inhibitors

Sodium/glucose cotransporter-2 (SGLT2) inhibitors have become powerful tools in the nephrologist's arsenal to prevent progressive CKD and adverse cardiovascular outcomes such that SGLT2 inhibitors are now a standard of care in patients with diabetes and CKD as well as patients with other proteinuric kidney diseases. SGLT2 inhibitor therapy on its own results in 2-3 kg of weight loss.[51] Several placebo-controlled RCTs have examined the synergistic effects of SGLT2 inhibitors with incretin therapies. For example, dulaglutide at 1.5 mg weekly in addition to SGLT2 inhibitors resulted in approximately 1 kg of additional weight loss,[52] while the addition of weekly semaglutide at a relatively low dose of 1.0 mg resulted in 2.8 kg of weight loss in addition to that seen with SGLT2 inhibitors alone.[53] These additive weight loss effects are impressive, but perhaps more importantly the existing evidence suggests that the combination of SGLT2 inhibitors with incretin-based therapies may be even more effective than either group alone in preventing cardiorenal morbidity and mortality in patients at high risk.[54] Clinical trials are underway to test this hypothesis.

Practical Prescribing of Weight Loss Medications in CKD

Treatment of Obesity as a Chronic Disease

Nephrologists should consider and treat obesity as a chronic disease, recognizing the biological underpinnings of obesity and trying to avoid weight bias.[55] The root causes for the obesity epidemic are multifactorial, encompassing environmental, genetic, metabolic, hormonal, and behavioral factors. Medical nutrition therapy and exercise are cornerstones to sustained weight loss. Careful history-taking is important to identify factors such as obesogenic medications, socioeconomic barriers, inadequate sleep hygiene, sedentary lifestyle, adverse childhood experiences, mood, anxiety, binge-eating disorder, and cultural practices.[56] Multidisciplinary collaboration with dietitians, obesity specialists, and surgical teams can help to individualize care plans.[57] Patient-driven goal setting and frequent self-monitoring are key and can be aided through the use of web-based and smartphone applications.[55] Unfortunately, powerful compensatory mechanisms exist to counteract lifestyle interventions,

depressing energy expenditure and resulting in increased hunger and weight regain, necessitating the addition of pharmacotherapy to treat obesity in many patients.[58]

Preference for GLP-1 Receptor or Combined Agonists

When considering weight loss pharmacotherapy in patients with CKD, incretin-based medications should be considered a first-line therapy. For patients with obesity, T2DM, and CKD, GLP-1 receptor agonists are recommended by the ADA as preferred if HbA1c is above target or if SGLT2 inhibitors cannot be used.[59] For patients who wish to achieve both weight loss and glycemic goals, the ADA lists multiple incretin-based medications as very high (semaglutide and tirzepatide) or high efficacy (dulaglutide and liraglutide). Of particular importance to patients and nephrologists managing the increased risk of cardiovascular morbidity in the CKD population, the incretin mimetics also convey cardiovascular risk reduction.

Management of Adverse Effects

GLP-1 receptor agonists delay gastric emptying, making the most common side effects gastrointestinal (eg, nausea or vomiting, decreased appetite, abdominal pain).[60] In subcutaneous semaglutide trials, 42% of those treated reported gastrointestinal events.[61] Most gastrointestinal adverse effects are mild and do not require drug discontinuation. The side effects with tirzepatide are similar. In the SURPASS-2 trial comparing different tirzepatide doses (at 5-mg, 10-mg, and 15-mg doses) versus semaglutide (1 mg) in patients with T2DM, the total adverse events and gastrointestinal adverse events were similar. A higher number of serious adverse events occurred in patients receiving tirzepatide than semaglutide, the most common of which was coronavirus 2019 infection; no deaths were considered to be related to either study drug.[46]

Patients should be educated about the mechanism of action for GLP-1 receptor agonists and the importance of eating slowly, eating smaller meals, and avoiding high-fat, sugary, calorie-dense foods to minimize gastrointestinal side effects. If an increase in dosage leads to the onset of new adverse effects in patients who were tolerating the prior lower dose, the dose can be reduced until symptoms improve. Typical regimens for initiation and titration are shown in Table 1.

Additionally, GLP-1 receptor agonists may increase the risk of cholelithiasis and biliary disorders[62] and should not be given to patients with personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 due to the potential increased risk of thyroid malignancy.[63] All GLP-1–based therapies include a package warning against use in those with a history of pancreatitis due to postmarketing reports of severe pancreatitis in a small number of patients. Meta-analyses of GLP-1 receptor agonist RCTs have not found evidence for increased risk of pancreatitis or pancreatic cancer.[64,65]

Considerations When Initiating Therapy

In addition to the management of potential adverse effects, prescribers are often confronted with the problem of whether to change the patient's existing medication regimen. Although incretin mimetics do not cause hypoglycemia on their own, they may contribute when administered with other medicines for diabetes (in particular sulfonylureas or insulin). In patients with well-controlled blood sugars, the dose of sulfonylurea should be reduced or the sulfonylurea stopped when incretin therapy is initiated. Similarly, a 15% to 20% reduction in the basal insulin dose is generally recommended to avoid hypoglycemia.[66]

Nephrologists and patients should also pay careful attention to antihypertensive doses and consider self-monitoring blood pressure. There is no direct interaction between incretin mimetics and antihypertensives, but the increased natriuresis and weight loss induced by therapy may necessitate reduced dosages or even discontinuation of medications to avoid hypotension.

Weight Regain after Medication Cessation

Long-term medical treatment for obesity is often required because weight regain follows cessation of pharmacological treatment. An extension trial to evaluate changes in body weight after treatment withdrawal in the STEP 1 trial (semaglutide vs. placebo) followed 327 participants.[67] These participants regained two-thirds of their prior weight loss with corresponding worsening of cardiometabolic parameters within the following year.[67] Though the total weight regained after medication discontinuation was substantial, the mean total weight loss was still 5.6% in the semaglutide arm, and nearly half of the participants in the semaglutide arm still had clinically meaningful weight loss of 5% or more from baseline at week 120.

A New Era of Obesity Therapy

Despite these limitations, incretin-based therapies represent a revolution in the treatment of patients with obesity, including those with comorbid kidney disease. Unanswered questions remain, though. First, although the preclinical work and intermediate outcomes suggest that GLP-1 agonism should be beneficial for hard kidney outcomes, no study has been completed to conclusively demonstrate benefit in patients with CKD. The FLOW trial, investigating the kidney and cardiovascular effects of semaglutide in patients with CKD (eGFR 25-75 mL/min/1.73 m^2) and T2DM, recently reported its baseline population characteristics and will help to shed light on this issue.[68,69]

Second, study of the safety and efficacy of these medications in patients with ESKD on dialysis has been limited to pilot studies and case reports. Patients on dialysis have a high cardiovascular risk and disease burden from diabetes and obesity. Recent observational studies suggest that,

Table 1. High Efficacy Injectable Incretin Mimetics

Name	Dose Initiation	Titration	Max Dose[a]	Contraindications	Warnings/Precautions	Common Adverse Reactions
Indication: BMI ≥ 30kg/m² or BMI ≥ 27kg/m² With Weight-related Comorbid Condition						
Liraglutide (Saxenda)	0.6 mg SC/d	Increase by 0.6 mg wk, after at least 1 wk	3 mg/d	Personal or family history of medullary thyroid cancer, MEN syndrome type 2, known hypersensitivity to drug or product components, pregnancy	Thyroid c-cell tumors, acute pancreatitis, acute gallbladder disease, serious hypoglycemia, heart rate increase, renal impairment, hypersensitivity reactions, suicidal behavior and ideation	Nausea, hypoglycemia, diarrhea, constipation, vomiting, headache, decreased appetite, dyspepsia, fatigue, dizziness, abdominal pain, increased lipase
Semaglutide (Wegovy)	0.25 mg SC/wk	Increase by 0.5 mg wk, after at least 4 wk	2.4 mg/wk	Personal or family history of medullary thyroid cancer, MEN syndrome type 2, known hypersensitivity to drug or product components	Thyroid c-cell tumors, acute pancreatitis, acute gallbladder disease, hypoglycemia, AKI hypersensitivity, diabetic retinopathy, complications in T2DM, heart rate increase, suicidal behavior and ideation	Nausea, diarrhea, vomiting, constipation, abdominal pain, headache, fatigue, dyspepsia, dizziness, abdominal distension, eructation, hypoglycemia in patients with T2DM, flatulence, gastroenteritis, gastroesophageal reflux disease
Indication: T2DM						
Dulaglutide (Trulicity)	0.75 mg SC/wk	Increase by 1.5 mg wk, after at least 4 wk	4.5 g/wk	Personal or family history of medullary thyroid cancer, MEN syndrome type 2, known hypersensitivity to drug or product components	Thyroid c-cell tumors, pancreatitis, hypoglycemia, hypersensitivity reactions, AKI, severe GI disease, diabetic retinopathy complications, acute gallbladder disease	Nausea, vomiting, diarrhea, abdominal pain, decreased appetite
Semaglutide (Ozempic)	0.25 mg SC/wk	Increase by 0.5 mg wk, after at least 4 wk	2 mg/wk	Personal or family history of medullary thyroid cancer, MEN syndrome type 2, known hypersensitivity to drug or product components	Thyroid c-cell tumors, pancreatitis, diabetic retinopathy complications, hypoglycemia, AKI, hypersensitivity reactions, acute gallbladder disease	Nausea, vomiting, diarrhea, abdominal pain, constipation
Liraglutide (Victoza)	0.6 mg SC/d	Increase by 0.6 mg, after at least 1 wk	1.8 mg/d	Personal or family history of medullary thyroid cancer, MEN syndrome type 2, known hypersensitivity to drug or product components	Thyroid c-cell tumors, pancreatitis, serious hypoglycemia, renal impairment, hypersensitivity, acute gallbladder disease	Nausea, diarrhea, vomiting, decreased appetite, dyspepsia, constipation

(Continued)

Table 1 (Cont'd). High Efficacy Injectable Incretin Mimetics

Name	Dose Initiation	Titration	Max Dose[a]	Contraindications	Warnings/Precautions	Common Adverse Reactions
Tirzepatide (Mounjaro)	2.5 mg SC/wk	Increase by 2.5 mg, after at least 4 wk	15 mg/wk	Personal or family history of medullary thyroid cancer, MEN syndrome type 2, known hypersensitivity to drug or product components	Pancreatitis, hypoglycemia with concomitant use of insulin secretagogues or insulin, hypersensitivity reactions, AKI, severe gastrointestinal disease, diabetic retinopathy complications, acute gallbladder disease	Nausea, diarrhea, decreased appetite, vomiting, constipation, dyspepsia, abdominal pain

This table shows dosing information, contraindications, warnings/precautions, and common adverse reactions listed on the highlights of prescribing information section for each medication.[61] Abbreviations: AKI, acute kidney injury; BMI, body mass index; GI, gastrointestinal; MEN, multiple endocrine neoplasia; SC, subcutaneous; T2DM, type 2 diabetes mellitus.
[a]No adjustment for decreased kidney function (including end-stage kidney disease), is necessary for any of the drugs listed in the table.

among the small percentage of patients who receive them, GLP-1 receptor agonists were associated with lower all-cause mortality.[36,70] Future work should include this vulnerable population to better understand whether incretin therapies impart benefit.

Finally, the use of safe and effective weight loss therapy in CKD is in its infancy. The coming years are likely to see the advent of so-called triple agonists (GLP-1/GIP/glucagon) and combination therapies with the promise of even greater effects on weight loss and cardiometabolic health. Already the combination of semaglutide with the long-acting amylin analogue cagrilintide has shown greater effect than semaglutide alone,[71] and the REDEFINE study[72] will explore the effect of this combination in patients with obesity and high CVD risk, including those with an eGFR greater than 15 mL/min/1.73 m^2. Given these innovations and the deeply entangled relationship between obesity and the development of kidney disease, nephrologists and their patients should not only be aware of these medications, but excited to put them to use in the battle against the cardiorenal complications of metabolic dysfunction.

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