Obesity in CKD
A Promising Path Forward

Allon N. Friedman

Obesity is at the epicenter of the global CKD problem through its adverse direct effects on the kidney as well as associated intermediate disease states (1). Obesity leads to fatty kidney, intraglomerular hypertension, podocyte damage, FSGS, activation of the sympathetic nervous system and the renin-aldosterone axis, kidney lipotoxicity, and increased secretion of adipokines that can be nephrotoxic (1). In terms of intermediate diseases, obesity underlies the majority of cases of type 2 diabetes, the world’s premier cause of CKD and kidney failure, and is a common cause of systemic hypertension (the second most common cause of kidney failure in the United States), obstructive sleep apnea and pulmonary hypertension, and heart disease (1). Obesity is a risk factor for progression of IgA nephropathy, the world’s most common GN, and autosomal dominant polycystic kidney disease, the most common inherited kidney disease (1). In people with CKD, obesity increases disability and death, lowers access to kidney transplantation, and makes permanent well-functioning dialysis access more challenging (1). Obesity is common in the CKD population, and in the United States, nearly one of every two patients with CKD is obese (1). Not surprisingly, identifying effective strategies for managing obesity is becoming a topic of keen interest for nephrologists and obesity specialists as exemplified by a 2021 collaborative scientific workshop organized to address the topic (2).

Available treatment options for obesity include lifestyle management, bariatric (also known as metabolic) surgery, and pharmacologic treatment. Lifestyle interventions are appropriately first-line management. Unfortunately, this strategy fails to provide large and sustained weight loss in most people as exemplified by available clinical trials and general clinical experience. For example, the National Institutes of Health–sponsored Action for Health in Diabetes (Look AHEAD) randomized trial found that by year 8 of follow-up in individuals with obesity and type 2 diabetes, an intensive lifestyle intervention program achieved ≥15% weight loss by year 2 (4). The 15% weight loss threshold is important because it was the amount needed for remission of type 2 diabetes in most people. Thus, lifestyle interventions, although effective in certain people, cannot be counted on to work in the majority of the population. This phenomenon can be explained by the new pathophysiologic paradigm for obesity, which on the basis of recent research understands obesity as a disorder in energy homeostasis (1). Under this biologic model, the body “defends” itself against fat loss by returning the subject to a set point of fat after every period of self-induced starvation.

Bariatric surgery, the second treatment option, has long stood out as offering the largest and most durable weight loss of any available treatment modality. Because of this, most research examining the putative renoprotective effects of weight reduction has used bariatric surgery as a model. In randomized studies, bariatric surgery improves risk factors for CKD like type 2 diabetes, insulin resistance, hypertension, and albuminuria (1). Multiple observational studies also describe an association between bariatric surgery and improvements in surrogate (e.g., change in eGFR) and hard kidney end points (e.g., new-onset dialysis and kidney transplantation) (1,5). One study even observed a large reduction in the risk of overall mortality after bariatric surgery in people with preexisting CKD (6).

Although bariatric surgery is quite safe in the CKD population, there are several imposing barriers to more widespread use (1,2). These include nephrologists’ comfort with the procedure, cost, insurance restrictions, presurgical requirements, and surgeon availability (2). Improving access to bariatric surgery for individuals for CKD will therefore require educating nephrologists on the procedure’s benefits and risks to overcome hesitancy about referring patients, improvements in insurance coverage, and more surgeons. Kidney-oriented randomized clinical trials in this area would also be helpful in establishing an evidence base on which to justify surgical referrals and reimbursement (2). One such trial is in progress in patients with CKD stage 3 and albuminuric diabetic kidney disease (NCT04626323).

Pharmacotherapy is the third pillar of obesity management. Although antiobesity drugs have existed for...
decades, the handful of weight loss medications approved by the Food and Drug Administration (FDA) have historically offered only modest weight loss in exchange for a variety of potential side effects, some mild and some more serious. For patients with CKD, the pickings were even slimmer as most approved medications were contraindicated due to cardiovascular side effects or dosing issues with kidney diseases. Despite this relatively bleak history, things have improved dramatically in the last 2 years.

The first major breakthrough came in June 2021 when the FDA approved a 2.4 mg/wk subcutaneous administration of semaglutide (Wegovy) for weight loss. Semaglutide is a long-acting glucagon-like peptide-1 (GLP-1) receptor agonist that reduces food intake by suppressing appetite and slowing gastric emptying. Semaglutide had previously been approved for the treatment of diabetes under a different brand name (Ozempic) and lower subcutaneous dose. The Research Study Investigating How Well Semaglutide Works in People Suffering From Overweight or Obesity (STEP 1) Study Group published the results of a randomized controlled trial comparing once weekly semaglutide 2.4 mg with placebo over a 68-week follow-up period in 1961 adults with obesity and without diabetes with an average age of 47 years, mean body mass index of 38 kg/m², and eGFR of 96 ml/min per 1.73 m² (7). Using an intention-to-treat model, individuals in the semaglutide arm lost a placebo-subtracted average of 12% of baseline weight (14% in the on-treatment analysis). Of note, 75%, 55%, and 35% of individuals on semaglutide lost ≥10%, ≥15%, or ≥20% of weight, respectively. Semaglutide use was also associated with placebo-subtracted declines in systolic BP of 5.9 mm Hg, in diastolic BP of 2.4 mm Hg, in glycated hemoglobin of 0.3%, and improvements in fasting blood lipids, C-reactive protein, and quality-of-life measures. Serious adverse events occurred more frequently in the semaglutide arm (10% versus 6%), with the difference primarily being increased gastrointestinal and hepatobiliary complications.

Even more impressive was the second breakthrough, which occurred in May 2022 when the FDA approved the use of tirzepatide (Mounjaro) for the indication of obesity. Tirzepatide is a first-in-class medicine that activates both the GLP-1 and glucose-dependent insulinotropic polypeptide receptors, leading to increased satiety and reduced food intake. The randomized Study of Tirzepatide (LY3298176) in Participants With Obesity or Overweight (SURMOUNT-1) trial compared weekly escalating doses of subcutaneous tirzepatide with placebo in 2539 adults without diabetes with an average age of 45, body mass index of 38 kg/m², and eGFR of 98 ml/min per 1.73 m² (8). By week 72, placebo-subtracted weight loss at the lowest dose (5 mg) was 14% and was 20% at the highest dose (15 mg). Impressively, 78% of individuals on the tirzepatide 15-mg dose lost ≥15% of baseline weight, 63% lost ≥20% of baseline weight, and 40% lost ≥25% of baseline weight. Similar to the STEP 1 trial, clinically significant improvements in BP, glycated hemoglobin, lipid levels, quality-of-life scores, and other intermediate metabolic parameters were also observed. Serious adverse events were similar in both arms.

These advances are of great relevance to the nephrology community for several reasons. First, they offer the first nonsurgical path to effective management of obesity. Second, both semaglutide and tirzepatide can safely be dosed in persons with advanced CKD and kidney failure. Third, their side effects are primarily gastrointestinal in nature, unlike the previous generation of antiobesity drugs where hypertension and other sympathomimetic effects that are contraindicated in the CKD population were common. Moreover, this is likely just the beginning of a revolution in the pharmacologic treatment of obesity, as a variety of drugs to address this problem are now in active clinical development (9).

Still, from the standpoint of the CKD population, several important questions remain to be addressed. Because the semaglutide and tirzepatide trials described above did not include appreciable numbers of people with CKD, it is not certain that these drugs will be as effective in inducing and maintaining weight loss in the setting of CKD as they are in the general population. It is not known if there are subgroups of patients with CKD who will respond well or not at all. Drug tolerability is another issue because patients with advanced CKD and especially those on dialysis commonly suffer from gastrointestinal-related disorders. Importantly, we do not yet know if these medications offer renoprotection and improve important kidney-related end points, although post hoc data suggest that GLP-1 receptor agonists may have such effects (10). For more definitive answers, we will need to wait for studies such as A Research Study to See how Semaglutide Works (FLOW), (NCT03819153), which will compare the effects of semaglutide versus placebo on kidney-specific end points in a large population of persons with type 2 diabetes and CKD. Other randomized trials will likely also be necessary to establish efficacy and tolerability across the spectrum of CKD. In the meantime, nephrologists and their patients should be optimistic at the new era of effective obesity management that is unfolding before our eyes.

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Author Contributions
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