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MEETING REPORT

Obstacles and opportunities in managing coexisting obesity and CKD: Report of a scientific workshop cosponsored by the National Kidney Foundation and The Obesity Society

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Abstract

The National Kidney Foundation (NKF) and The Obesity Society (TOS) cosponsored a multispecialty international workshop in April 2021 to advance the understanding and management of obesity in adults with chronic kidney disease (CKD). The underlying rationale for the workshop was the accumulating evidence that obesity is a major contributor to CKD and adverse outcomes in individuals with CKD, and that effective treatment of obesity, including lifestyle intervention, weight loss medications, and metabolic surgery, can have beneficial effects. The attendees included a range of experts in the areas of kidney disease, obesity medicine, endocrinology, diabetes, bariatric/metabolic surgery, endoscopy, transplant surgery, and nutrition, as well as patients with obesity and CKD. The group identified strategies to increase patient and provider engagement in obesity management, outlined a collaborative action plan to engage nephrologists and obesity medicine experts in obesity management, and identified research opportunities to address gaps in knowledge about the interaction between obesity and kidney disease. The workshop's conclusions help lay the groundwork for development of an effective, scientifically based, and multidisciplinary approach to the management of obesity in people with CKD.

Complete author and article information provided before references

Chronic kidney disease (CKD) is a major public health problem. It is becoming increasingly clear that obesity, which affects more than 650 million people globally, is not only highly prevalent in persons with CKD but is also a prime inducer of CKD and other kidney-related and unrelated adverse outcomes (Figure 1) [1–3]. Despite the unabated growth in obesity among adults and children [4, 5], the utility of managing coexisting obesity as a strategy to improve health in persons with CKD is just beginning to be recognized and pursued in earnest.

Because of the complexity and heterogeneity of obesity, best management would benefit from a team-based approach that includes a variety of disciplines providing individually tailored lifestyle-based, pharmacological, and/or surgical therapies. Collaborative advocacy efforts of specialists in kidney disease and obesity would also offer an opportunity to improve insurance coverage and payment policies, thereby expanding access to effective care for all patients.

In order to address the treatment of obesity in the setting of CKD and related issues, the National Kidney Foundation (NKF) and The Obesity Society (TOS) cosponsored a scientific workshop on the management of obesity in adults with CKD on April 29 to 30, 2021. In preparation for the workshop, a planning committee appointed by the NKF and TOS defined the overall agenda, developed the topics and questions to be addressed and a plan to disseminate the workshop outcomes, and invited participants from academia, clinical practice, patient groups, industry, and government. Although COVID-19–related restrictions required that the meeting be held virtually, the program was designed to maximize cross-disciplinary and multispecialty interaction and discussion. Accordingly, the invitees included a range of experts in the areas of kidney disease, obesity medicine, diabetes management, metabolic surgery, endoscopic medicine, transplant surgery, and nutrition, along with people living with CKD and obesity. The goals of the workshop were to develop a clearer delineation of the issues, challenges, and knowledge gaps facing the nephrology and obesity medicine communities in advancing the care of obesity in people with CKD and to identify ways to begin to advance the understanding and effective management of these frequently coexisting and closely linked disorders.

In advance of the workshop, the planning committee provided the participants with an outline of the agenda and access to online prerecorded presentations on several topics related to obesity and kidney disease. The conference agenda and a list of workshop attendees are included in Supporting Information Item S1. The first day of the conference included 3 sessions, each composed of prerecorded presentations with ample time for a live panel and audience discussion. Day 2 included 4 live breakout sessions running in parallel, each focusing on a specific topic defined by the planning committee, followed by a summary of the output of each breakout group and a general discussion among all workshop participants. The conference ended with the development of consensus recommendations and the

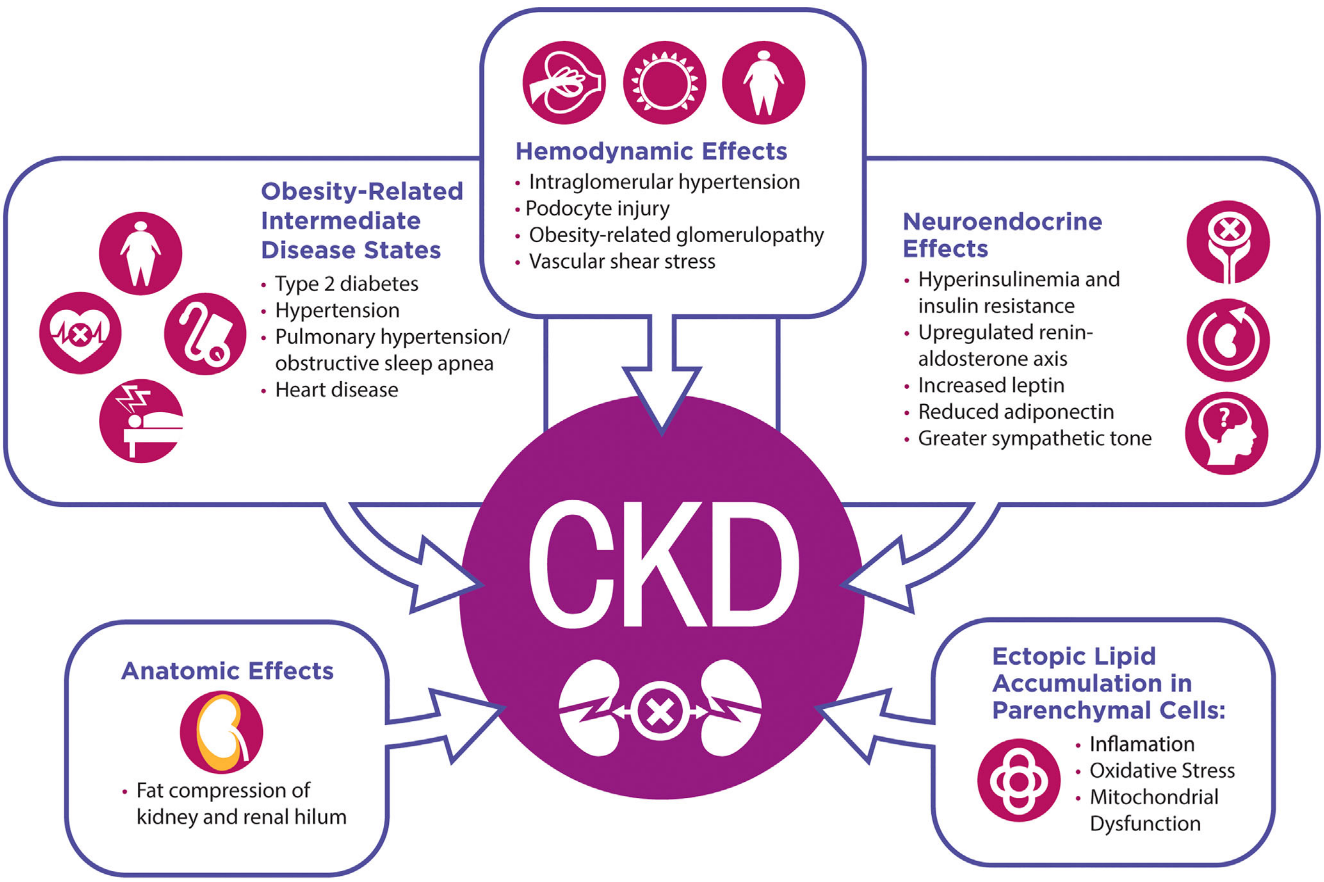
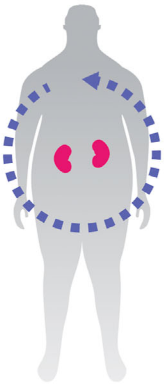


FIGURE 1 Mechanisms through which obesity leads to kidney damage. Abbreviation: CKD, chronic kidney disease



Complications of Obesity	No CKD	1	2	3	4	5	5D	5T
				Stages of CKD				
Increased Risk of Developing CKD	●							●
Increased Risk of CKD Progression		●	●	●	●	●		●
Decreased Access to Kidney Transplantation						●	●	●
Increased Risk of Cardiovascular Disease	●	●	●	●	●	●	●	●
Increased Hospitalizations	●	●	●	●	●	●	●	●
Increased Healthcare Costs	●	●	●	●	●	●	●	●
Decreased Quality of Life	●	●	●	●	●	●	●	●
Decreased Life Expectancy	●	●	●	●	●	●	*	●

FIGURE 2 Obesity-related complications by stage of CKD. *Signifies the unresolved controversy over the impact of obesity on mortality in patients on dialysis related to the "obesity paradox" phenomenon. Abbreviation: CKD, chronic kidney disease

steps necessary for their implementation. Links to the prerecorded lectures can also be found in Item S1. This article summarizes the main topics reviewed, participant feedback, and output of the workshop discussions.

OBSTACLES TO OPTIMAL MANAGEMENT OF OBESITY

There was considerable discussion on the barriers to effective care of obesity, how these barriers affect patients with coexisting CKD, and potential ways to overcome them. At a basic level, identifying which individuals with obesity have CKD remains a major obstacle. The absence of clear and established criteria for treating obesity in people with CKD and evidence that routine screening for kidney disease in people with obesity improves clinical outcomes was also felt to be a major limitation to embracing obesity treatment in this population. Indeed, even deciding on what clearance marker should be used is controversial. Cystatin C is generally considered a more robust marker of kidney filtration than creatinine in the setting of obesity or weight loss, though even it is not entirely independent of lean or fat mass [6–9]. Therefore, equations to estimate glomerular filtration rate (GFR) that combine serum creatinine and cystatin C could potentially improve on creatinine-based equations in helping guide clinical decision-making, research, and public health policy in people undergoing treatment with bariatric/metabolic surgery or antiobesity medications [6, 8].

Proteinuria, the other major clinical marker of CKD, is also affected by obesity. Proteinuria is usually evaluated by a spot urinary albumin-creatinine ratio (UACR) or sometimes a urinary protein-creatinine ratio (UPCR). Muscle mass is increased in individuals with obesity [10]. Because the ratio's denominator (ie, urinary creatinine) reflects muscle mass, UACR and UPCR often underestimate proteinuria in people with obesity, leading to underdiagnosis of increased proteinuria and delayed treatment. Weight loss in patients with obesity may also affect UACR or UPCR through loss of lean mass. Use of 24-hour urinary collections rather than spot urine samples to measure urinary albumin or total protein is a way to avoid these pitfalls.

There is a need to understand how the degree of adiposity influences health risk in CKD and whether this relationship varies by CKD stage (Figure 2). An example of this is the so-called obesity paradox, where obesity is associated with a higher risk of death in early CKD stages but a lower risk in the setting of dialysis [11]. Most studies demonstrating the obesity paradox use body mass index (BMI) to define obesity, but BMI is limited in how well it distinguishes between fat and lean compartments or important differences in fat distribution [12]. These limitations could explain why, in contradistinction to the obesity paradox concept, intentional weight loss in dialysis patients has been associated with lower mortality [13]. Metrics of adiposity of interest beyond BMI include body composition (total fat and lean mass, percent body fat) as well as fat distribution (abdominal visceral and subcutaneous, perinephric, etc). Ultimately, defining obesity using an objective standard that is closely linked to kidney function would greatly advance the care of coexisting obesity and CKD.

The management of obesity in patients with advanced CKD or kidney failure and after kidney transplantation were topics of particular interest. Among the issues that require further study in these populations were high-priority areas such as the health risks of ongoing obesity and acute weight gain posttransplant and the benefits and risks of weight loss from medical therapy or bariatric/metabolic surgery (Figure 3). A few transplant centers in the United States provide obesity management services including bariatric/metabolic surgery to facilitate kidney transplantation, but the overwhelming majority do not.

With respect to commonly used lifestyle-based treatments of obesity, there was agreement that patients experience wide variability in their response to different types of diets, increased physical activity, stress reduction, and improvements in sleep health and normalization of circadian rhythms. As a result, there is no "best" diet for people with obesity with or without CKD, and no diet to date induces sufficient or durable weight loss to demonstrate substantial, long-term improvements in most obesity complications [14]. Compounding the

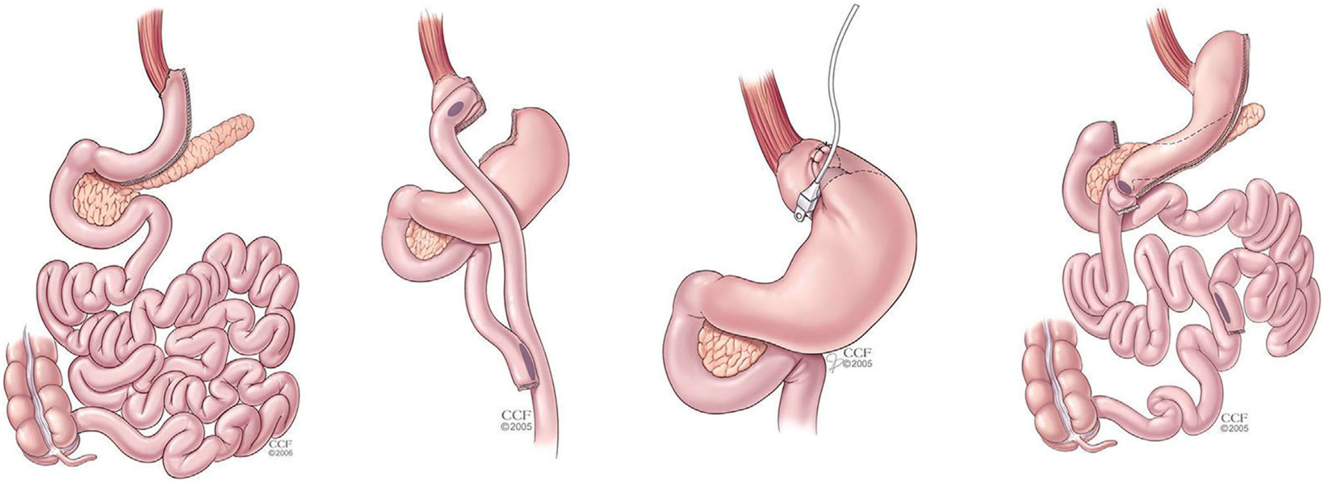


FIGURE 3 The most common metabolic surgical procedures in the United States. Left to right: Sleeve gastrectomy is the most common procedure (58%), followed by Roux-en-Y gastric bypass (19%), laparoscopic adjustable gastric band (3%), and biliopancreatic diversion with duodenal switch (0.6%). Original graphics ©2005 Cleveland Clinic Foundation, all rights reserved; reproduced with permission from the copyright holder

problem in persons with CKD are current nutrition guidelines, which out of necessity may restrict dietary options and limit dietary protein intake [15]. This advice may make it harder to preserve muscle mass during weight loss [15, 16]. Another issue deserving of further study is the source of dietary protein. For example, protein from animal sources is more likely to promote inflammation and increase GFR and renal plasma flow, which in certain circumstances could have negative effects [17]. Whichever lifestyle-based therapies ultimately prove most beneficial for management of obesity in patients with CKD, the limited resources available for intensive lifestyle interventions create a barrier to effective obesity care.

The optimal weight loss goal is also unknown and deserves to be explored. Intriguingly, several studies of bariatric surgery have found no clear relationship of changes of weight with albuminuria and estimated GFR [18–20]. Whether a similar pattern is seen with lifestyle- or medication-related weight loss is not known.

The recent emergence of safe and highly effective antiobesity medications offers an important new opportunity for obesity treatment. Nephrologists and other clinicians at the workshop who were not obesity medicine specialists emphasized their limited knowledge and lack of experience in using available antiobesity medications. Many workshop attendees voiced concerns about the safety profile of these agents, mostly based on adverse effects of earlier generations of medications used to treat obesity. The more recent introduction of antiobesity medications whose safety profile has been established through their routine use for other diseases—for example, topiramate for seizures and migraines, bupropion for depression, and metformin and the glucagon-like peptide 1 (GLP-1) receptor agonists liraglutide or semaglutide for diabetes—and the substantially greater and more durable efficacy of semaglutide should help increase their acceptance among providers and patients (Table 1) [21–24]. Several GLP-1 receptor agonists have recently been shown to decrease cardiovascular risk in patients with type 2 diabetes, and there is accumulating evidence that they have renoprotective effects, making them particularly attractive for treating obesity in people with CKD [25]. A planned randomized controlled trial of semaglutide designed with a primary renal end point will offer useful information on both renoprotection and weight loss benefits in individuals with CKD, type 2 diabetes, and obesity (ClinicalTrials.gov identifier NCT03819153).

The strongest evidence that treating obesity can improve kidney outcomes comes primarily from observational studies [26–32]. Inferences from small randomized trials of bariatric/metabolic surgery, which induces the most profound and durable weight loss of any treatment strategy, also exist [33, 34]. These studies suggest that patients with obesity who undergo bariatric surgery procedures exhibit lower rates of kidney disease, with some evidence of slowed CKD progression [26–32, 35, 36]. A recent proof-of-concept randomized trial showed that bariatric surgery caused greater regression of moderate albuminuria among patients with type 2 diabetes and mild CKD over 2 years compared with intensive medical treatment alone [37]. Further examination of these effects and the degree to which they reflect improvements in coexisting obesity or are a direct effect of weight loss on kidney function is an important area for future study.

Social determinants undoubtedly pose barriers to optimal management of obesity in people with CKD, though teasing out each individual factor is challenging given their complex interrelationships. For example, Black Americans have on the whole significantly higher rates of obesity than White Americans [38]. However, between 2011 and 2018 Black Americans were the only major racial/ethnic group in which the prevalence of obesity did not grow while Asians were the only subgroup that demonstrated increases in all markers of obesity [39]. Moreover, the higher obesity rates in Black versus White Americans apply only to women [38]. Income may also play a role though again its impact on obesity is also not clear-cut. Obesity rates among men are similar at all income levels, with few exceptions. Among Black and Mexican American men, rates of obesity are higher with higher socioeconomic status, but the same is not

TABLE 1 US Food and Drug Administration–approved antiobesity medications

Drug (proprietary name)	Mechanism of action	Selected common adverse effects	Kidney-related precautions	Dosing adjustments: CKD stage 3–5	Dosing adjustments: Kidney failure
Liraglutide (Saxenda)	GLP-1 receptor agonist	Nausea/vomiting, diarrhea, constipation, dyspepsia	None	Use with caution with severely decreased eGFR (limited data available)	Use with caution (limited data)
Naltrexone-bupropion SR (Contrave)	Norepinephrine/dopamine uptake inhibitor, opioid antagonist	Nausea/vomiting, constipation, dizziness, increased HR and BP	Excreted primarily via the urine	For moderately and severely decreased eGFR: 1 tablet (8 mg/90 mg) 2×/d	Not recommended
Orlistat (Xenical, Alli)	Lipase inhibitor	Fecal incontinence, oily spotting, fat-soluble vitamin deficiency	Reports of acute and chronic kidney injury, possibly from oxalate nephropathy	None	None
Phentermine (Adipex-P; Lomaira)	Sympathomimetic, anorexic	Hypertension, palpitations, anxiety, dry mouth	Excreted primarily via the urine	eGFR of 15–29: maximum dose, 15 g/d	eGFR <15: avoid use (not been studied)
Phentermine/topiramate ER (Qsymia)	Sympathomimetic, anorexic	As listed above plus drowsiness, mental fogginess, proximal (type 2) RTA, nephrolithiasis	Excreted primarily via the urine	CL_{cr} < 50: maximum dose, 7.5 mg/46 mg 1×/d	Dialysis: avoid use (not been studied)
Semaglutide (Wegovy)	GLP-1 receptor agonist	Nausea/vomiting, diarrhea, constipation, dyspepsia	AKI with severe GI reactions	None	None
Setmelanotide (Imcivree)	Melanocortin 4 receptor agonist	Nausea/vomiting, diarrhea, abdominal pain	39% excretion via urine	Not recommended	Not recommended
Tirzepatide (Mounjaro)	GLP-1 receptor agonist/gastric inhibitory polypeptide	Nausea/vomiting, diarrhea, constipation, dyspepsia	AKI with severe GI reactions	None	None

Adapted from Friedman et al. [1] with permission of the copyright holder (original content © 2021 American Society of Nephrology) and supplemented with information in Gossmann et al. [58]. Medications are listed in alphabetical order.

Abbreviations: AKI, acute kidney injury; BP, blood pressure; CKD, chronic kidney disease; CL_{cr}, creatinine clearance (in mL/min); eGFR, estimated glomerular filtration rate (in mL/min/1.73 m^2); ER, extended release; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; HR, heart rate; RTA, renal tubular acidosis; SR, sustained release.

observed among Mexican American women, where higher income is associated with lower rates of obesity [40]. Additional factors to be considered are familial, cultural, and societal influences. Gaining a better understanding of how each issue, alone or in combination, influences obesity and its management is a matter of great importance for the CKD population [41].

Barriers common to all obesity management strategies (ie, lifestyle, medications, surgery) include lack of obesity management guidelines for individuals with CKD, lack of reimbursement and insurance coverage, and a limited number of referral centers for obesity management resulting in long wait times or restricted access to expertise. Finally, conference participants emphasized the importance of discussing obesity with their patients in a compassionate and nonjudgmental way as would be done for patients with any other chronic disease. This is another area where many practitioners would benefit from enhanced education. Strategies to improvement management of obesity in persons with CKD are shown in Box 1.

STRATEGIES TO IMPROVE PATIENT ENGAGEMENT IN OBESITY MANAGEMENT

Several important factors were identified to help promote patient engagement. Patients with CKD and obesity are generally ill-informed about the potential contribution of obesity to their kidney disease and the kidney-related benefits of effective obesity management. Improving self-recognition of CKD, which is very low in the United States, particularly in earlier CKD stages, is a necessary initial step to correcting this problem [42–44]. Obesity as a risk factor for CKD progression is rarely addressed by nephrologists. Likewise, obesity specialists, who are more likely than nephrologists to see patients in earlier stages of CKD when weight management could have disproportionate long-term benefits on kidney health, may not be aware of the degree to which obesity is linked to CKD and related medical problems. Changing these patterns will require concerted and long-term efforts to educate patients and clinicians alike.

An individual's engagement in his or her own obesity management is affected by many personal considerations. In our current obesogenic environment, sustainability of a healthy lifestyle is becoming increasingly difficult. Recent data suggest that the effects of the modern environment can rewire the brain to a higher set-point for body fat, which is then "defended" despite efforts by patients to improve their lifestyle [45]. Thus, development and maintenance of obesity is at its core a biologically driven process that includes manifestation of eating behaviors (eg, hunger, meal satisfaction, subjective fullness) mediated by internal hormonal signals [46]. Patients with CKD who participated in the workshop felt that information on the biological control of satiety would be an important aid in helping them understand that obesity in most instances cannot be optimally controlled merely by adjusting the type and amount of food consumed. Expanding support groups for patients undergoing medical or surgical treatment of obesity to include persons with CKD could be helpful in this regard.

It is important for practitioners to recognize the social stigma of obesity and make special efforts to use nonstigmatizing and nonprejudicial language and actions when addressing obesity in their patients. Obesity treatments are rapidly evolving, and maximal success will almost certainly derive from individualized, precision care [47]. That care also needs to consider widely different cultural, gender, and societal norms about body size, weight, and obesity, and these issues all need to be factored into how best to communicate with and treat individual patients [48]. It was felt important to honor patient autonomy by having providers provide information on the effects of obesity and the risks/benefits of treatment, and supporting the patient in their decision on how to proceed, whatever it may be. The committee felt it a priority to educate health care providers on offering scientifically valid approaches to weight management that optimize effectiveness and safety of treatment. Box 2 offers strategies to improve CKD patient engagement in obesity management.

BOX 1 Strategies for improving management of obesity in persons with CKD

- Design strategies to help identify CKD in the setting of obesity and weight loss.
- Develop criteria for when and how best to treat obesity.
- Educate nephrologists on the importance, role, and effective management of obesity.
- Educate obesity specialists on why, when, and how to screen for kidney disease.
- Identify useful metrics beyond BMI to assess obesity-related health risks.
- Develop recommendations that balance competing dietary needs in CKD patients.
- Address social factors influencing obesity.
- Formulate strategies to improve insurance coverage and reimbursement for weight management.

Abbreviation: CKD, chronic kidney disease

BOX 2 Strategies to improve patient engagement in obesity management

- Educate patients on the interrelationship between obesity and CKD.
- Educate and reassure patients about the biological underpinnings of their obesity.
- Expand obesity support groups to include the CKD population.
- Use nonstigmatizing and nonprejudicial language when addressing obesity.

Abbreviation: CKD, chronic kidney disease

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STRATEGIES TO ENGAGE NEPHROLOGISTS AND OBESITY SPECIALISTS IN MANAGING OBESITY

Strategies for engaging nephrologists and obesity medicine experts are more likely to be successful if they bridge common ground. An initial step to facilitating engagement would be to recognize that obesity management is aimed at pathophysiology and is not necessarily synonymous with weight loss in the same way that treating CKD is not just about modifying laboratory parameters (eg, albuminuria reduction) but ultimately treating the underlying disease (eg, glomerulonephritis or hypertension) that leads to kidney damage that manifests as albuminuria. Changes in body weight can similarly be considered as a read-out for effective control of the disease of obesity.

Obesity interventions in the earlier stages of CKD and obesity might result in better long-term outcomes by helping prevent the development of more overt kidney disease and its associated complications. Nonetheless, there are many people with advanced CKD and obesity who would also benefit. Thus, nephrologists and obesity medicine experts must appreciate that different strategies may be required depending on CKD stage and severity of obesity. In patients with CKD stages 3 to 4, the goal of obesity management could be to slow down or perhaps even reverse existing disease whereas a more appropriate focus in persons with CKD stage 5 might be to facilitate successful kidney transplantation. Whatever the approach, the focus of obesity treatment should be to optimize effective CKD care and reduce the risk of adverse outcomes, including kidney, metabolic, and cardiovascular dysfunction and reduced quality of life.

Work required by nephrologists to manage obesity is often viewed as too cumbersome, time consuming, or even ineffective. One possible way of addressing this challenge would be to use dietitians, clinical pharmacists, nurse educators, and advanced practice providers as clinical extenders. These affiliated providers could be trained to help promote effective obesity care by educating patients and referring them as needed to obesity medicine specialists, multidisciplinary obesity treatment centers, or other qualified practitioners.

Nephrologists' successful engagement with obesity management will be facilitated by (1) a strong evidence base; (2) development and implementation of collaborative, multidisciplinary approaches to CKD management in patients with obesity that involve obesity specialist physicians, bariatric/metabolic surgeons, nephrologists, dietitians, and transplant surgery teams; (3) improved treatment payment structures that promote optimizing health outcomes; and (4) overcoming systemic barriers to access to antiobesity medications and bariatric/metabolic surgery, especially in underserved populations.

Box 3 offers some strategies to help engage nephrologists and obesity specialists in managing obesity in patients with CKD.

BOX 3 Strategies to engage nephrologists and obesity specialists in managing obesity

- Improve familiarity and comfort with weight loss strategies.
- Use dietitians, nurse educators, and advanced nurse practitioners to assist in obesity management and patient education.
- Develop a clinical trial evidence base.
- Develop collaborative clinical and research efforts.
- Work with payers and policy makers to improve reimbursement and overcome access barriers.

STRATEGIES TO ADDRESS KNOWLEDGE GAPS

Establishing an evidence-based approach to manage obesity in individuals with CKD is a key ingredient to enhancing clinician and patient acceptance of obesity treatment and improving clinical outcomes. The workshop therefore invested considerable time discussing how research initiatives can address key knowledge gaps. Topics included clinical outcomes, study populations, and design methodology.

Research discussions focused on defining the best clinical end points for future clinical trials. End points endorsed by the group included the impact of obesity treatment on body weight and metabolic parameters (eg, blood pressure, markers of glycemic control); development of CKD in at-risk individuals; progression to kidney failure; major cardiovascular events, hospitalization, and mortality; and changes in quality-of-life measures. Several additional clinical outcomes specifically relevant to posttransplant patients included studying weight gain after kidney transplantation and the effects of obesity and antiobesity therapies on graft function and survival. It was felt that clinical trial end points should address questions that are relevant to a wide range of stakeholders, including patients, clinicians, payors, and health care systems. Success will therefore require paying close attention to the effect of antiobesity therapies on avoidance of CKD progression, prevention of dialysis initiation, access to transplantation, patient safety, quality of life, and health care costs.

Studies with mechanistic end points were also considered high priority. Such studies could help define metabolic-, immune-, and inflammatory-mediated processes that contribute to obesity-related CKD and also potentially lead to identification of new therapeutic targets for treatment of CKD. Trials with mechanistic end points could also help determine whether the various adverse effects of obesity directly affect the kidney or are mediated through obesity complications like diabetes and hypertension, and whether there are differential effects of these factors in different subtypes of kidney disease. Additionally, mechanistic studies can help elucidate the degree of kidney health improvement with obesity therapies via weight loss–dependent versus weight loss–independent, treatment-specific effects [18, 49–51]. Knowledge gained from these types of studies could also help define subtypes of both CKD and obesity that help inform the relationships between these 2 disorders [52].

Another important consideration is the patient population to be studied. Trials recruiting patients with CKD stages 1 to 2 would be appropriate to assess the effects of obesity interventions on development of early CKD, identify factors predicting CKD progression, and identify predictors of kidney response to obesity treatment. It is unlikely that such studies would generate sufficient late-phase clinical events like kidney failure, kidney transplantation, or kidney-related death. Thus, changes in albuminuria or estimated GFR may be appropriate clinical markers as end points for such early-stage studies [53, 54]. Because such trials will likely need large sample sizes and require long periods of follow-up in order to offer adequate statistical power for clinically useful results, "piggybacking" CKD outcomes and subgroups on to larger non-CKD obesity outcome trials would be advantageous.

Studies of patients with CKD stages 3 to 5 would be most suitable to evaluate the effects of antiobesity strategies on progression of CKD and kidney failure such as the Randomized Study Comparing Metabolic Surgery with Intensive Medical Therapy to Treat Diabetic Kidney Disease (OBESE-DKD [NCT04626323]). This clinical trial will randomize 60 patients with proteinuric type 2 diabetes, obesity, and CKD stage 3 to metabolic surgery or best medical therapy. The end points to be assessed include directly measured GFR, albuminuria, weight loss, metabolic and cardiovascular parameters, and health care costs.

Trials conducted in patients who are receiving maintenance dialysis could assess the effect of obesity and antiobesity therapies on outcomes relevant to the dialysis milieu, including mortality, hospitalization, eligibility for and success of kidney transplantation, and quality of life. Similarly, studies in patients with kidney allografts could assess the efficacy of various obesity treatments on limiting weight gain after transplantation and improving graft survival.

The workshop participants agreed that a broad range of studies assessing obesity interventions are needed in populations across the spectrum of CKD. These studies should be performed in parallel, given the differences in needs and outcomes between different CKD subgroups and the desire to achieve timely progress. Human physiologic studies are necessary to fully identify mechanisms through which obesity leads to incident CKD and its progression. Observational and small-scale randomized controlled trials can identify and characterize potentially relevant clinical factors (eg, degree of obesity, fat distribution, effect of comorbidities, etc) that influence CKD progression. Some such studies already exist [18], and additional, small-scale RCTs can also help establish the efficacy, safety, and effect on kidney outcomes in patients at different stages of CKD and assess the clinical utility of biomarkers or other surrogate outcomes. Trials are needed to compare the impact of various lifestyle-based, pharmacological, and surgical interventions—alone and in combination—on kidney and related outcomes. Finally, larger scale studies will likely be required to determine conclusively the efficacy, safety, and cost-effectiveness of various obesity interventions in persons with CKD and, ultimately, which antiobesity therapies are most effective and appropriate for particular subgroups of CKD patients.

Integrating gold standard kidney tests into clinical studies of patients with CKD will generate valuable information. For example, directly measuring GFR in patients with concurrent obesity and CKD will provide a degree of accuracy that GFR estimations cannot offer [6, 8, 55, 56]. Kidney biopsies in patients with CKD and obesity may be useful in identifying and validating histological and even molecular markers of CKD progression and providing additional pathophysiologic or treatment insights. Of note, obesity has been associated with a slightly lower risk of bleeding complications and death after percutaneous kidney biopsies [57].

Participation of all stakeholder groups, including patients, in study design would be beneficial. End points should be validated and include quality-of-life assessments and other patient-reported outcomes. Flexible study designs, including adaptive and platform trials, allow incorporation and evaluation of emerging treatment options to keep the results as clinically relevant as possible. Finally, wide dissemination of study results will be critical to capturing the greatest benefit from this research investment. Thus, the involvement of implementation scientists in the design and planning process will be important. A summary of strategies to address research gaps in this field are seen in Box 4.

BOX 4 Strategies to address research gaps and study design issues

- Involve a broad range of stakeholders.
- Tailor end points to CKD stage, subgroup, and study size.
- Implement a wide array of types of studies and implement concurrently.
- Integrate gold standard tests into clinical studies.
- Factor dissemination of results into trial design.
- Encourage flexible trial designs that can incorporate rapidly changing obesity treatments.

Abbreviation: CKD, chronic kidney disease

CONCLUSION

By identifying key questions, challenges, and knowledge gaps, the 2021 NKF-TOS multidisciplinary workshop on obesity and kidney disease helps lay the groundwork for the development of an effective, scientifically based, and multidisciplinary approach to the effective management of obesity in persons with CKD as a means to improve kidney-related and other outcomes as well as improve evaluation and management of CKD in individuals with obesity. This is an urgent issue given the importance of obesity in amplifying the already elevated risks associated with CKD and the growing prevalence of obesity in the CKD population. Future progress in this area will require collaboration between the nephrology and obesity medicine communities to educate patients and practitioners; advance our understanding of the relationship between obesity and kidney disease; appreciate the unique characteristics and needs of patients with these disorders; and develop, test, and implement clinical strategies that optimize the health of the growing population with obesity and CKD.O

FUNDING AGENCIES

The following companies provided a grant to the National Kidney Foundation to support planning and conduct of the workshop: Boehringer Ingelheim, Novo Nordisk, Rhythm Pharmaceuticals, and Pfizer. Workshop sponsors had no role in the development of the workshop agenda or objectives. Sponsors were restricted from viewing any part of the workshop report manuscript until it was accepted for publication and therefore had no role in the content developed for this report. Participation in the workshop was by invitation only. Participants other than those from sponsoring companies were invited to review this report prior to its acceptance for publication.

CONFLICT OF INTEREST

Dr. Friedman serves as a scientific advisory board member or a consultant for GI Dynamics, Gila Therapeutics, AstraZeneca, and Goldfinch Bio and has ownership of Eli Lilly stock. Dr. Schauer has consultancy agreements with GI Dynamics, Keyron, Persona, Mediflix; has an ownership interest in SE Healthcare LLC and Mediflix; has received research funding from Ethicon, Medtronic, Pacira, and Persona; has received honoraria from Ethicon, Medtronic, BD Surgical, and Gore; and is serving as scientific advisor for or a member of SE Healthcare Board of Directors, GI Dynamics, Keyron, Persona, and Mediflix. Dr. Beddhu has received research support from Boehringer Ingelheim, Novo Nordisk, and Bayer, has received royalties from UpToDate, and has received grant funding from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK; R01DK11821 and R01DK128640), National Institute on Aging (R01AG074592), and Veterans Affairs (ORH-14398). Dr. Kramer has served as a consultant to Bayer Pharmaceuticals and AstraZeneca. Dr. le Roux has received grants from the Irish Research Council, Science Foundation Ireland, Anabio, and the Health Research Board; serves on the advisory boards of Novo Nordisk, Herbalife, GI Dynamics, Eli Lilly, Johnson & Johnson, Sanofi Aventis, AstraZeneca, Janssen, Bristol-Myers Squibb, Glia, and Boehringer Ingelheim; is a member of the Irish Society for Nutrition and Metabolism outside the area of work commented on here; has served in an unremunerated capacity as chief medical officer and director of the Medical Device Division of Keyron since January 2011; received gifted stock holdings from Keyron in September 2021, which he divested in full in that same month; and provides ongoing scientific advice to Keyron for no remuneration. Dr. Purnell serves as an advisory board member for Novo Nordisk. Dr. Tuttle has received research and other support from Eli Lilly, Boehringer Ingelheim, Gilead, AstraZeneca, Goldfinch Bio, Novo Nordisk, Bayer, and Travere; and research support from 7 National Institutes of Health grants across institutes (NIDDK; National Center for Advancing Translational Sciences; National Institute on Minority Health and Health Disparities; National Heart, Lung, and Blood Institute) and a Centers for Disease Control and Prevention contract. Dr. Jastreboff serves as a scientific advisory board member or consultant for Novo Nordisk, Eli Lilly, Boehringer Ingelheim, Intellihealth, Scholar Rock, and Pfizer; and has received research support from the American Diabetes Association, Eli Lilly, Novo Nordisk, and NIDDK (R01DK099039 and R01DK117651). Dr. Kaplan serves as a scientific and medical consultant to Amgen, Gelesis, Gilead, Johnson & Johnson, Eli Lilly, Novo Nordisk, Pfizer, and Rhythm Pharmaceuticals. The remaining authors declare that they have no relevant financial interests.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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