Global Science. Local Change.

KDIGO Controversies Conference on the Relationship Between Obesity and CKD: Pathophysiology, Prognosis, and Management

October 10–13, 2024
Prague, Czechia

Scope of Work

Kidney Disease: Improving Global Outcomes (KDIGO) is an international organization whose mission is to improve the care and outcomes of people with kidney disease worldwide by promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines. KDIGO also regularly hosts Controversies Conferences on a focused subject pertaining to kidney disease to review state-of-the-art evidence, set priorities for improving patient care and outcomes, and highlight areas for which additional research is needed.

CONFERENCE BACKGROUND AND RELEVANCE

The prevalence of obesity in both adults and children is increasing, and it is expected that by 2035 more than 1.5 billion people will live with obesity.[1] In parallel, chronic kidney disease (CKD), which affects more than 800 million people globally, is also on the rise, both in prevalence and as a leading cause of mortality.[2, 3] These conditions are interlinked directly and indirectly. Obesity is a driver for development of diabetes and hypertension, the two leading causes of CKD in most countries.[4] In addition, obesity *per se* may lead to CKD directly, as adipose tissue affects the kidneys through adipokines, which may induce CKD.[4] However, further understanding is needed.

Treating obesity with optimized diet[5] and exercise is preferred but complicated, and often reductions in weight are not sustained. In recent years we have seen positive outcomes in trials evaluating metabolic surgery or pharmacological interventions,[6] with substantial reductions in weight that are maintained (for pharmaceutical interventions, as long as they are continued). In particular, new agents based on incretin hormones alone or in combination with other hormones as dual or triple agonists have led to weight reductions of up to 25% in people with obesity without diabetes and 10-15% in

type 2 diabetes,[7, 8] with more potent drugs under development. The surgical and pharmaceutical approaches have mostly been studied in people aged >50 years, but because obesity can start in childhood, we also have to understand the epidemiology and opportunities in children and adolescence. Additionally, having models of care for optimally providing and monitoring interventions is important.

It has been suggested that interventions leading to weight loss also reduce progression of CKD, as evaluated either by reduction in albuminuria or preservation of kidney function (estimated glomerular filtration rate [eGFR]). This suggestion is controversial, as estimating kidney function during weight loss is difficult; the usual marker of GFR, creatinine, is derived from muscles, but weight loss affects lean body mass.[9, 10] Thus, contentious questions yet remain: what is the best way to lose weight, and what is the best method to assess whether weight loss affects progression or regression of CKD? These questions are relevant for people with obesity and CKD with or without diabetes. Data from large outcome studies with incretin-based therapy in type 2 diabetes evaluating CKD as a primary outcome are awaited. A study of semaglutide in type 2 diabetes with CKD was stopped early for efficacy and reduced progression of CKD, cardiovascular disease, and mortality.[11] Studies with CKD as a secondary outcome in obesity with cardiovascular disease without obesity are also awaited.[12]

The speed with which clinical trials in this space are launching and reporting positive data suggests this is an excellent time to meet and discuss the relationship between obesity and CKD. Topics for discussion will include defining the best means for addressing obesity in CKD with respect to lifestyle, pharmacological, and surgical interventions; optimally evaluating the effect of weight loss on kidney function; and ascertaining how effective interventions can be organized and delivered in a sustainable way.

CONFERENCE OVERVIEW

Drs. Susan Furth (Children's Hospital of Philadelphia and the Perelman School of Medicine at the University of Pennsylvania, USA) and Peter Rossing (Steno Diabetes Center Copenhagen and University of Copenhagen, Denmark) will co-chair this conference. The format of the conference will involve topical plenary session presentations followed by focused discussion groups that will report back to the full group for consensus building. This highly interactive conference will invite key thought leaders and relevant stakeholders, including patients, and experts in nephrology (adult and pediatric), endocrinology, cardiology, surgery, and other related disciplines (nutrition, epidemiology, ethics, nursing, social work, etc.) who will comprehensively review the literature and current state of understanding in this area and address clinical issues as outlined in the **Appendix: Scope of Coverage**. The conference output will include the publication of a position statement that will help guide KDIGO and others on the therapeutic management and future research in mitigating adverse effects of obesity on kidney health across the lifespan.

APPENDIX: SCOPE OF COVERAGE

Breakout Group 1: Pathophysiology and epidemiology

1) What is the prevalence of obesity among individuals with CKD in different populations and different subgroups (e.g., adults and children with CKD) around the globe?
   a) What is the prevalence of CKD in persons who are overweight/obese?
   b) What is the evidence for the prevalence of obesity in patients with CKD relative to the prevalence in the general population for that region?
   c) What are the age and sex related differences in obesity in patients with CKD?
   d) What are the effects of obesity in special high-risk populations, e.g., those with *APOL1* risk-variant genotypes?

2) What are the potential molecular mechanisms (e.g., hyperfiltration, inflammation) linking obesity and its treatment to the development and progression of CKD?
   a) Do pathomechanisms between CKD and obesity overlap with that of CKD and diabetes or other common risk factors (e.g., HTN)?
   b) Is obesity associated with specific forms of CKD (e.g., obesity-related glomerulopathy)?
      - What is the role of reverse epidemiology?
      - Also consider genetic, neurohormonal, inflammatory, and hemodynamic/molecular mechanisms?
      - What is the unique pathology underlying obesity-related glomerulopathy? If detected early, is pathology potentially reversible before progression to CKD?
      - What is the impact of gut microbiota on obesity risk in CKD?
      - What is the role of fatty liver (e.g., MASLD) as a risk factor for CKD/ CKD progression; is it a good surrogate for obesity?

3) What is the effect of childhood-onset obesity on incident CKD and adverse outcomes later in life?
   a) What is the prevalence and burden of childhood-onset obesity?
   b) What is the relative contribution of social determinants of health to the burden of obesity in children and adults?
   c) What is the evidence for the prevalence of obesity against the socioeconomic status of the individual and the national gross domestic product?

4) Is there a need for case finding programs?
   a) What are the early biomarkers of CKD in obese individuals?
   b) Should CKD screening be contemplated in obese individuals (adults and children)?

5) What are the long-term effects of obesity on adverse cardiovascular outcomes (in children and adults) in later life?

   Focus on:
   - Kidney outcomes
   - Cardiovascular and cerebrovascular disease
   - Mechanisms of obesity-related adverse outcomes

Breakout Group 2: Evaluation of kidney function and adiposity

1) What are the appropriate measures (BMI, waist circumference, waist-to-hip ratio, or their combination) used to define overweight and obesity in those with CKD? Consider CKD G1-G4, CKD G5 and G5D, kidney transplant candidates attempting to lose weight for transplant listing and kidney transplant recipients

2) What are the different cutoffs for BMI and waist circumference to categorize obesity in those with CKD? Do they differ based on age, gender, race, and stage of CKD?

3) What are the different *types of obesity* (abdominal obesity, peripheral obesity, visceral organ fat accumulation, sarcopenic obesity, metabolically healthy vs unhealthy obesity, etc.) in those with CKD?
   - Does the clinical significance differ based on the type of obesity (sarcopenic obesity or visceral adiposity versus others)?
   - Is there a protective effect with higher BMI in those with kidney disease (reverse epidemiology)?

4) What are the strengths and limitations of different measures to assess kidney function (e.g., eGFR, albuminuria, tubular function markers, etc.) in those with obesity and CKD? Can we rely on traditional kidney function measures in those with obesity and CKD?

5) What are the strengths and limitations of different filtration markers in the setting of obesity? Do they differ based on the type of obesity?

6) What factors should be considered when selecting a marker for estimating GFR, e.g., when do we choose serum creatinine versus cystatin or their combination?

7) What are the different clinical scenarios in which measured GFR or 24-hour urine studies (including proteinuria, albuminuria) should be assessed in those with obesity and CKD? When should we consider de-indexing GFR in clinical practice in CKD patients with obesity?

8) Can we rely on available risk prediction equations (such as the Kidney Failure Risk Equation) to predict kidney and cardiovascular outcomes in those with obesity and CKD?

9) What are other biomarkers (e.g., markers of inflammation) or measures (intra-renal fat, perirenal) that can be used to predict outcomes in obesity and CKD, and are these markers modified by obesity?

10) What are the indications for kidney biopsy in those with chronic kidney disease, and is kidney biopsy safe in those with obesity?

11) What is the BMI cutoff to be eligible for kidney transplantation waitlisting? Should we also consider the use of anthropometric or body composition indices other than/together with BMI for evaluating transplantation eligibility?

Breakout Group 3: Medical (pharmaceutical and surgical) interventions

1) What is the evidence on efficacy on kidney outcomes and overall safety of drug interventions for treating obesity (glucagon-like peptide-1 [GLP1] receptor agonists [GLP1RA], GLP1/glucose-dependent insulinotropic polypeptide [GIP] dual agonist) with lifestyle interventions alone or in combination with bariatric surgery in people with and without type 2 diabetes?

   Consider:

   a) CKD G1-G4

   b) CKD G5 and G5D

   c) Kidney transplant candidates attempting to lose weight for transplant listing

   d) Kidney transplant recipients

2) What is the evidence on the efficacy for kidney outcomes and overall safety of surgical interventions for treating obesity in people with and without type 2 diabetes?

   Consider:

   a) CKD G1-G4

   b) CKD G5 and G5D

   c) Kidney transplant recipients

3) Should anti-obesity interventions (GLP1RA, GLP1/GIP dual agonist, surgery) be differentially chosen or introduced based on thresholds of BMI depending on kidney function status?

   Consider:

   a) Surgical risks based on the stage of CKD

b) Risks of malnutrition/sarcopenia with both medical and surgical treatments in various stages of CKD

c) Risks specifically related to gastric bypass versus sleeve gastrectomy (e.g., oxalate nephropathy, impact on immunosuppression absorption in transplant recipients)

d) Risks dependent on concurrent medications

4) When should anti-obesity interventions be discontinued?

Consider:

a) Special considerations for safety monitoring in the presence of CKD

b) Thresholds for temporary discontinuation by CKD stage or other events during CKD

5) What are patient perceptions of the weight loss requirement before being accepted onto the kidney transplant listing?

a) Consider patient views on weight loss requirements in terms of improving their health.

b) Discuss the barriers that patients with kidney failure face in obtaining support for weight loss.

c) Explore patient preferences for weight loss methods relative to current data on the most effective options.

d) Discuss how patients believe nephrologists or transplant centers can best support them in their weight loss efforts.

6) What evidence is required to tailor the optimal sequence of interventions (i.e., lifestyle intervention alone versus combined with medical therapies and/or surgery on the basis of CKD stage, transplant candidacy, and comorbidities (diabetes, heart failure, etc)?

Breakout Group 4: Non-medical interventions and optimal models of care

1) Which non-medical interventions are effective and safe for weight loss in people living with obesity and CKD?
   a) To achieve at least 5% or 10% body weight loss
   b) Should diet and exercise interventions vary across different stages of CKD?
   c) What are the unique considerations for people with obesity and CKD, e.g., safety or risk of hyperkalemia, hypoglycemia, sarcopenia?
   d) What are the social and cultural considerations and adaptations required, and what language can we use to prevent weight stigma?
   e) What is the role of psychological support and/or behavior-based therapies as adjunct treatment across all types of interventions (medical/surgical/diet and exercise)
   f) Which interventions are acceptable to patients and participants (include medical, surgical, and diet and exercise)?

2) What are the recommended benchmarking metrics and quality indicators of success for non-medical interventions in people with CKD and obesity?
   a) Prevention of morbidities (includes body composition, bone health)
   b) Risk factor reduction (includes diet measures)
   c) Patient reported outcome measures and patient reported experience measures
   d) Physical function and functional capacity

3) In people living with the obesity and CKD, what are the impacts of diet and exercise interventions on CKD progression and on known risk factors for CKD progression listed in (a)?
   a) Blood pressure, glycemic control, insulin resistance or sensitivity, blood lipids, inflammation, MASLD, and albuminuria. Others?
   b) Is there a method to score or collate this collective risk reduction?
   c) Is there any evidence regarding cardiovascular outcomes, kidney outcomes, survival, and kidney transplant waiting time?

4) What is the optimal model of care for delivery and monitoring of medical and non-medical interventions for treating obesity in people with CKD?
   a) Multidisciplinary team involvement (dietitians, endocrinologists, primary care physicians, psychologists, and nephrologists). Which specialties are essential? Is there any reference model now?
   b) Initiation of medical and non-medical interventions in primary care versus specialist care settings: challenges and solutions
   c) What evidence is required to tailor the optimal sequence of interventions (i.e., lifestyle intervention alone versus combined with medical therapies and/or surgery based on CKD stage, transplant candidacy, and comorbidities (diabetes, heart failure, etc)?
   d) Frequency of monitoring, follow-up, and pathways in and out of specialist care
   e) Health literary, self-management skills, patient activation and engagement
   f) What technology supports engagement and remote delivery of care?

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