The relationship between obesity and chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

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Susan L. Furth[1], Helen M. Colhoun[2], Mehmet Kanbay[3], Aleksandra Kukla[4,5], Lee-Ling Lim[6], Helen L. MacLaughlin[7,8], Sankar D. Navaneethan[9,10,11], Rukshana Shroff[12], Peter Stenvinkel[13], Michael Cheung[14], Jennifer M. King[14], Morgan E. Grams[15], Michel Jadoul[16] and Peter Rossing[17,18]; for Conference Participants[19]

[1]Department of Pediatrics, Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA; [2]Institute of Genetics and Cancer, University of Edinburgh, Edinburgh, UK; [3]Division of Nephrology, Department of Medicine, Koc University School of Medicine, Istanbul, Türkiye; [4]Department of Medicine, Division of Nephrology and Hypertension, Mayo Clinic College of Medicine and Science, Mayo Clinic, Rochester, Minnesota, USA; [5]Von Liebig Transplant Center, Department of Transplantation Surgery, Mayo Clinic, Rochester, Minnesota, USA; [6]Department of Medicine, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia; [7]School of Exercise and Nutrition Sciences, Queensland University of Technology, Brisbane, Australia; [8]Nutrition Research Collaborative, Royal Brisbane and Women's Hospital, Queensland, Australia; [9]Section of Nephrology, Department of Medicine, Selzman Institute for Kidney Health, Baylor College of Medicine, Houston, Texas, USA; [10]Institute of Clinical and Translational Research, Baylor College of Medicine, Houston, Texas, USA; [11]Section of Nephrology, Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas; [12]Renal Unit, University College London, Great Ormond Street Hospital and Institute for Child Health, London, UK; [13]Department of Renal Medicine, Karolinska Institutet, Stockholm, Sweden; [14]KDIGO, Brussels, Belgium; [15]Department of Medicine, New York University Langone School of Medicine, New York, New York, USA; [16]Division of Nephrology, Cliniques Universitaires Saint Luc, Université Catholique de Louvain, Brussels, Belgium; [17]Clinical and Translational Research, Complications Research, Copenhagen University Hospital - Steno Diabetes Center Copenhagen, Herlev, Denmark; and [18]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

Obesity and chronic kidney disease (CKD) are complex diseases that are interlinked directly and indirectly. In October 2024, Kidney Disease: Improving Global Outcomes (KDIGO) held a Controversies Conference on the Relationship Between Obesity and CKD: Pathophysiology, Prognosis, and Management. The goals of the conference were to examine the most recent evidence regarding the epidemiology, pathophysiology, and treatment of obesity and CKD as well as to articulate priorities for research. A key conference theme was increasing the awareness of obesity-related CKD. Long-term, early-onset obesity and prolonged exposure to obesity carry the highest risk of developing CKD. Identifying early biomarkers of kidney dysfunction and refining assessment methods in the context of obesity could provide opportunities for preventing loss of kidney function. The foundation for managing obesity in CKD comprises modifications to diet, physical activity level, and behaviors related to both. However, these strategies can be unsuccessful in achieving or maintaining weight loss for a myriad of reasons. Pharmacotherapies, such as those including glucagon-like peptide-1 receptor agonists, are effective in weight reduction and have been shown to have kidney-protective and cardiovascular benefits. Metabolic and bariatric surgery has also demonstrated benefits in reducing obesity-related complications. Appropriateness and choice of management strategies will vary depending on age and comorbidities and may change over time. Patient-led goal setting is a foundation for dietary and physical activity interventions focusing on incremental, achievable changes toward healthy eating and an active lifestyle. Health care professionals require training to deliver these interventions and provide ongoing support with positive messaging using nonjudgmental, stigma-free language. Evaluating the optimal duration of therapy, long-term safety of novel pharmacotherapies, and therapies in the context of early and later stages of CKD is a key priority for research. Multidisciplinary collaboration is important both for optimizing patient care and for advancing research.

Correspondence: *Susan L. Furth, Roberts Center for Pediatric Research, Children's Hospital of Philadelphia, 2716 South Street, Room 20124, Philadelphia, Pennsylvania 19146, USA. E-mail: furths@chop.edu; or Peter Rossing, Clinical and Translational Research, Complications Research, Copenhagen University Hospital - Steno Diabetes Center Copenhagen, Borgmester Ib Juuls Vej 83, 2730 Herlev, Denmark. E-mail: Peter.Rossing@RegionH.dk*

[19]Additional Conference Participants are listed in the Appendix.

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Obesity is a complex chronic disease with multiple contributing factors, including environment, genetics, and social determinants of health. The prevalence of obesity in both adults and children is increasing, and it is expected that by 2035 >1.5 billion people will live with obesity.[1] In parallel, chronic kidney disease (CKD), which affects >800 million people globally, is also on the rise, both in prevalence and as a leading cause of mortality.[2,3] Obesity is a driver for the development of type 2 diabetes (T2D) and hypertension, the 2 leading causes of CKD in most countries.[4] In addition, obesity *per se* may lead to CKD directly.[5,6] Adipose tissue may also affect the kidneys through the production of adipokines, hormones that regulate inflammation and glucose metabolism, as well as through dysfunctional lipid metabolism, and each of these processes can contribute to CKD.[4]

Treating obesity with optimized diet and physical activity is preferred but often unsuccessful for a myriad of reasons.[7,8] For example, reductions in weight are often not sustained. In recent years, trials evaluating metabolic and bariatric surgery (MBS) or pharmacological interventions have demonstrated positive outcomes,[9–11] with substantial reductions in weight that are maintained after MBS or with continued pharmacotherapy. It has been suggested that interventions leading to weight loss can reduce progression of CKD, as evaluated either by proxy through reduction in albuminuria or directly through preservation of kidney function (i.e., estimated glomerular filtration rate [eGFR]). The interpretation of changes in eGFR in the context of changing weight is complicated, however, because the biomarker creatinine, used in eGFR equations, is affected by muscle mass and diet, and weight loss inevitably results in loss of some lean body mass.[12,13]

In October 2024, Kidney Disease: Improving Global Outcomes (KDIGO) held a Controversies Conference on the Relationship Between Obesity and CKD: Pathophysiology, Prognosis, and Management. Participants discussed current evidence and controversies regarding epidemiology, pathophysiology, and diagnosis as well as the optimal means to address obesity in CKD with respect to nutrition, physical activity, pharmacological treatments, and MBS to meet person-centered needs in diverse populations. The format of the conference involved topical plenary session presentations (available on the KDIGO website: https://kdigo.org/conferences/ckd-obesity/) followed by focused group discussions. Participants included 51 health care professionals and 3 patients. Key clinical issues and priorities for research were identified (Table 1).

EPIDEMIOLOGY OF OBESITY AND CKD AND ASSOCIATED RISKS

Current evidence shows that obesity, a chronic disease, has reached pandemic proportions. Since 1990, the prevalence of adult obesity worldwide has more than doubled and adolescent obesity has quadrupled. In 2022, 2.5 billion people (43% of the population older than 18 years) were overweight, and 1 in 8 people were living with obesity.[14] Similarly, 390 million children and adolescents aged 5–19 years were overweight in 2022, including 160 million living with obesity.[15] Thirty-seven million children younger than 5 years were overweight.

The prevalences of both overweight and obesity generally increase with age, reaching a peak between the ages of 50 and 65 years and thereafter showing a slight downward trend. The prevalence of obesity is higher in women than in men of any age.[16] The age-standardized prevalence of obesity in adults has increased in 188 countries (94%) for women and in all except 1 country for men, but with distinct differences across countries.[17]

The long-term effects of obesity on the risk of CKD and adverse cardiovascular outcomes are multifaceted and well-documented in both adults and children.[5] The strongest evidence for this link comes from studies with long observation periods (up to 30 years) in children or young adults with obesity, demonstrating a clear connection to kidney disease[18] and adverse cardiac function.[19]

A high body mass index (BMI) is a well-recognized and strong independent predictor of the risk of CKD and kidney failure, even after adjustments for baseline blood pressure level and presence or absence of T2D.[20] A graded association has been shown between the degree of baseline BMI and the risk of kidney failure in a global meta-analysis of >5 million adults (including representation from multiple Asian countries),[21] as well as in a large community-based sample of individuals in the United States.[20] In a study of a community-based cohort of 2585 men and women from the Framingham Offspring Study with long-term follow-up (mean 18.5 years), each unit increase in BMI was associated with a 1.23-fold increased risk of new-onset kidney disease (as assessed using the Modification of Diet in Renal Disease study equation and defined as GFR ≤59.3 ml/min per 1.73 m^2 for women and ≤64.3 ml/min per 1.73 m^2 for men), with the lowest risk for those with a BMI in the normal range and a higher risk for those at either high or low extremes of BMI.[22] For each BMI category, obesity in women was associated with higher health risks than in men (relative risk [RR] 1.92 vs. 1.49), including a higher risk of kidney cancers (pooled RR 1.87 vs. 1.53).[23]

Obesity affects 1 in 5 children worldwide.[24] A recent meta-analysis of 2033 studies in 45 million children from 154 different countries or regions showed that the prevalence of obesity was 8.5% and overweight was 14.8%, with distinct regional differences.[24] Since 1980, the prevalence of obesity has continuously increased and doubled in >70 countries, with the rate of increase in childhood obesity greater than the rate of increase in adult obesity.[25] Life course trajectories of BMI suggest that ∼50% of children are on an increasing BMI trajectory, with <5% on a decreasing trajectory.[26]

The increasing prevalence of obesity in children raises the specter of increasing prevalence of CKD in the future. Importantly, there is evidence that prolonged exposure to overweight during adult life increases the risk of later CKD

Table 1 | Key knowledge gaps and research priorities in obesity and CKD

Clinical theme	Knowledge gaps and key questions	Research strategies
Epidemiology and pathophysiology	• What are the trajectories of eGFR decline in patients with obesity and o preexisting kidney disease, o kidney transplant, o or premature birth or small for gestational age. • What is the optimal measure or biomarker for monitoring the effect of obesity on kidney function? • What is the role of inflammation in the pathophysiology of obesity and CKD? • In individuals with obesity, how do environmental stressors (including air pollution), socioeconomic stressors (including food deserts), microplastics, heat stress, and the consumption of ultra-processed food influence the risk of CKD?	• Examine the role of obesity in altering the rate of eGFR decline in patients with kidney disease. • Evaluate the role of obesity on graft function and cardiovascular outcomes in kidney transplant recipients. • Measure metabolic changes and energy consumption in relation to obesity in patients with kidney damage. • Identify the age range during childhood when BMI is most predictive of adverse outcomes and discern whether trajectory in children or young adults is more important than a single time point of BMI.
Evaluation of kidney function and adiposity	• In individuals with obesity, what is the best estimation of kidney function compared with the gold standard of measured GFR? • What are the impacts of muscle mass and muscle quality on kidney disease progression in individuals with obesity and CKD? • Would addition of kidney parameters improve the utility of King's College criteria, or is a new scoring system needed to determine treatment needs? • Can assessment of inflammatory markers or visceral organ adiposity aid in predicting outcomes?	• Compare the predictive ability of different anthropometric measures (see Table 2) and body composition tools (alone or in combination) in those with obesity and CKD. • Use different modalities to investigate muscle changes with weight loss. • Incorporate metrics beyond BMI and WC to assess the efficacy of different interventions, especially in those with sarcopenic and visceral adiposity (including patient perspectives). • Identify alternative options to measuring albuminuria (UACR vs. 24-h urine collection) in those undergoing weight loss (including patient feedback).
Nonmedical interventions	• How do we implement and monitor nonmedical interventions for people with CKD and obesity? • Do personalized interventions based on individual risk assessment improve outcomes in CKD? • Which PROMs are most relevant and important?	• Conduct qualitative surveys to understand the challenges that people with obesity and CKD face in implementing nonmedical interventions. • Develop an obesity and CKD core outcome set including PROMs and tools for measurement. • Implement diet and exercise interventions and monitoring plans for people with CKD and obesity on the basis of CKM risks and phenotypes in real-world practice. • Conduct pragmatic implementation trials (population: individuals with CKD and obesity; intervention: personalized based on assessment and patient goals; comparison: usual care; outcomes: changes in eGFR slope, albuminuria, health-related quality of life, and physical function).
Medical interventions	• In patients with CKD, what are the relative efficacies of surgical and newer medical therapies on weight loss, kidney and cardiometabolic outcomes, and safety? • In children, can drug therapy obviate surgery or delay its need until maturity? • What are the efficacy and safety profiles of obesity interventions in groups with need but where data are lacking (extremes of age, diverse demographics, and advanced CKD [including dialysis and kidney transplantation])?	• In studies of weight loss interventions, routinely include people with CKD and outcomes of kidney function. • Conduct head-to-head comparisons of the efficacy and safety of drug therapies before metabolic and bariatric surgery. • Evaluate the efficacy and safety of drug therapies after metabolic and bariatric surgery. • Initiate implementation research on the best approaches to ensure those in need are offered effective therapies with minimal side effects, nonpersistence is minimized, and drug dosage is appropriately tailored. • Capture real-world epidemiologic and health economic data to analyze the full range of benefits and costs of weight loss interventions in people living with obesity and CKD.

(*Continued on following page*)

Table 1 | (Continued) **Key knowledge gaps and research priorities in obesity and CKD**

Clinical theme	Knowledge gaps and key questions	Research strategies
Care models	• How much weight loss is needed to improve health outcomes in people with obesity and CKD? • What are the best approaches for scaling up the assessment and monitoring for PROMs, PREMs, physical function, and functionality in routine practice? • What are the best approaches to enhance the implementation of nonmedical interventions in routine practice from the perspectives of sustainability and health economics?	• Use RCTs, observational studies, and evidence reviews to define the relationships between the percentage of weight loss on clinical outcomes and PROMs in people with obesity and CKD with a duration of at least 12 mo and longer follow-up. • Conduct RCTs to delineate the percentage of weight loss target for CKD outcomes (UACR and eGFR) and health-related quality of life. • Evaluate the effectiveness and sustainability of obesity care interventions that include a combination of behavioral, pharmacological, and surgical interventions, together with dietary and physical activity interventions, in people with obesity and CKD. • Evaluate self-management strategies and behavioral modifications for sustaining health outcomes in people with obesity and CKD. • Evaluate mobile assistive technology tools for sustainable weight reduction in people with obesity and CKD, including in large-scale implementation models.

BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; PREM, patient-reported experience measure; PROM, patient-reported outcome measure; RCT, randomized controlled trial; WC, waist circumference; UACR, urinary albumin-to-creatinine ratio.

in a cumulative manner.[27] A population-based prospective study showed that people with overweight beginning early in adulthood (by age 26 or 36 years) had approximately double the odds of developing CKD by age 60–64 years compared with those who first became overweight at ages 60–64 years or never became overweight, with the strength of this association decreasing with increasing age of first overweight.[27]

At a population level, the prevalence of obesity is higher in populations with CKD G5 (eGFR $<$ 15 ml/min per 1.73 m^2) versus age-matched general populations, showing the association between obesity and kidney failure. An approximately 2-fold higher increase in BMI was reported in patients with incident kidney failure than in the age-matched US population.[28] Controversy remains as to the extent and nature of this association, however, as some studies suggest that BMI has a U-shaped or J-shaped association with CKD progression, with the lowest incidence observed in people with overweight and mild obesity.[29,30]

In exploring the causes of the obesity epidemic and risks of developing CKD, environmental and societal factors are potentially important. Some have suggested that the exposome—which includes factors such as global warming, air pollution, health disparities, microplastics, and lack of clean water—exacerbates the synergistic interactions of environmental factors with chronic diseases such as obesity and CKD.[31–33] Future research on the impacts of strategies combining policy and clinical care pathways may increase knowledge on developing effective interventions to prevent the growing population burden of obesity-related CKD.

PATHOPHYSIOLOGY LINKING OBESITY AND CKD

The progression from metabolic disruptions to development of obesity, CKD, and cardiovascular events and reduced life expectancy can be conceptualized as a "metabolic domino effect" (Figure 1). The complete details of this pathophysiological progression are an important area of future study to identify areas for targeted interventions and preventive measures. T2D and blood pressure account for most of the risk associated with adiposity and CKD.[34] Chronic hypoxia has been proposed as the primary pathophysiological pathway driving CKD caused by T2D or other etiologies. Glomerular hyperfiltration, mitochondrial exhaustion, and a mismatch between oxygen delivery and oxygen demand may contribute to a cycle of hypoxic injury, glomerular loss, and progressive nephropathy (Figure 2).[35] Other metabolic alterations include inflammation, activation of the renin-angiotensin-aldosterone system, oxidative stress, dyslipidemia, insulin resistance, lipotoxicity, gut dysbiosis, changes in adipokines, sodium and fluid retention, and the influence of obesogenic drugs. Adipose tissue accumulation in the kidney and liver positively correlates with increasing BMI, urinary albumin-to-creatinine ratio (UACR), and triglycerides as well as negatively correlates with eGFR.[36] In addition to metabolic effects, the adipose tissue may compromise kidney function by physical compression of the kidneys. Understanding these mechanisms is crucial for developing targeted strategies to mitigate CKD risk in patients with obesity and improve overall kidney health.[37]

The causal relationship between systemic inflammation and CKD is still being clarified. Ongoing trials investigating the effects of targeted interleukin-6 inhibitors, such as clazakizumab[38] and ziltivekimab,[39] in people with CKD with or without obesity may inform whether inflammation has a causal role in disease progression. Systemic inflammation is known to play an important role as a modifier of the paradoxical association between higher BMI and lower mortality in people undergoing hemodialysis.[40]

Genetic factors also influence the association between adiposity and CKD. Modeling based on Mendelian randomization analysis of UK Biobank data showed an effect of selected loci on the association of both general and central adiposity with CKD, although genetics appeared to be a weaker mediator of adiposity and CKD than diabetes or blood pressure.[34]

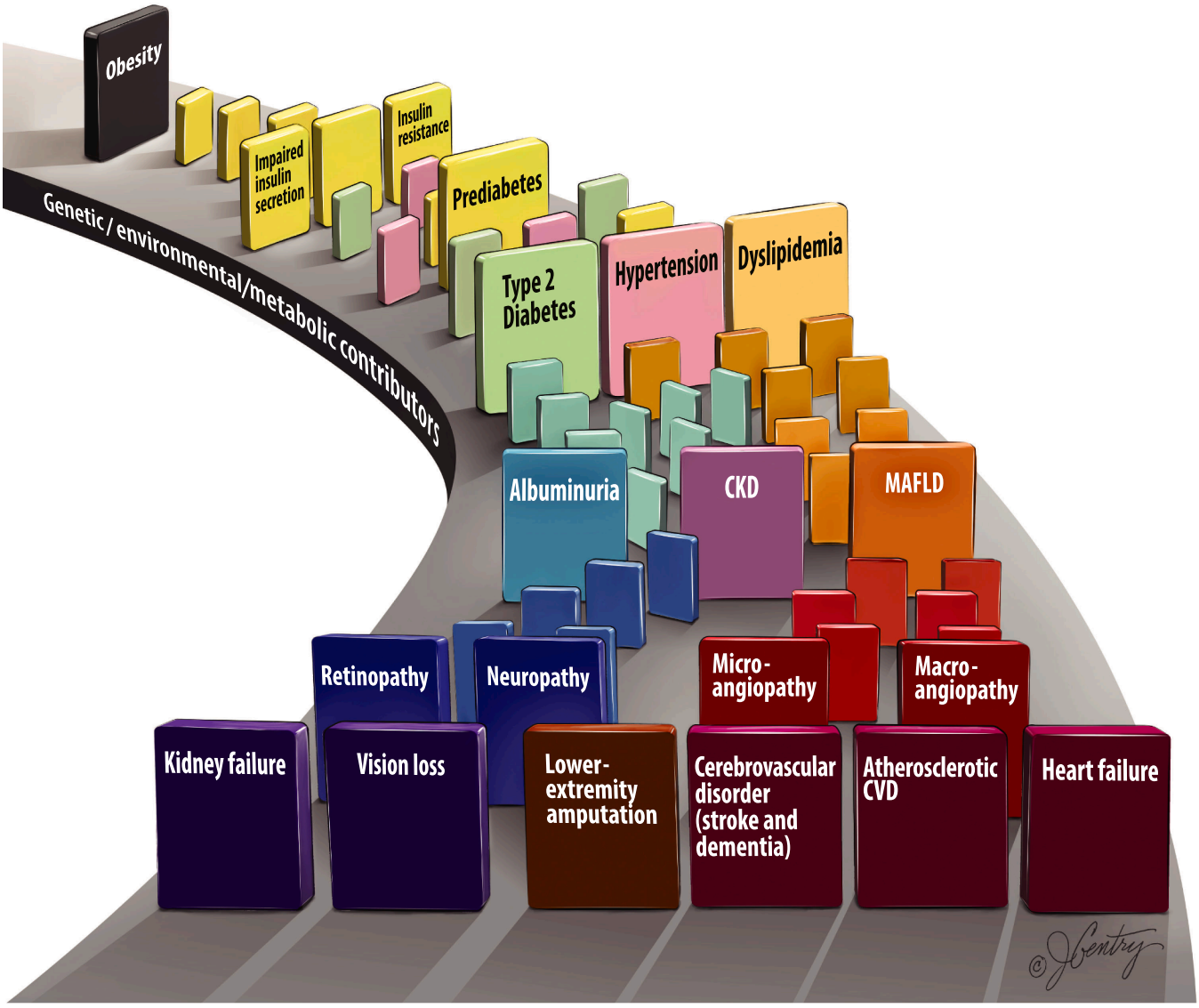

Figure 1 | Metabolic domino as a conceptual model for the flow of events and chain reactions associated with obesity and chronic kidney disease. The order of risk factors and outcomes is schematic and will differ between individuals on the basis of genetic predispositions and lived environments. Changes in diet and physical activity level can lead to obesity and insulin resistance, followed by hyperglycemia, hypertension, and dyslipidemia. Worsening kidney function, as evidenced by albuminuria and reduced glomerular filtration rate, can lead to chronic disease and its sequelae. Progression of the atherosclerotic process can lead to cardiovascular events such as ischemic heart diseases or cerebrovascular disorders. Preclinical and clinical data indicate that treatments inhibiting the renin-angiotensin system, such as angiotensin receptor blockers, can suppress the onset of type 2 diabetes and, when administered even earlier in the metabolic domino, reduce the development of hypertension in at-risk individuals. CVD, cardiovascular disease; MAFLD, metabolic dysfunction–associated fatty liver disease. © Jennifer N. Gentry.

Studies of genetic and environmental interactions will further our understanding of these complex relationships.

EVALUATION OF ADIPOSITY AND ASSESSMENT OF KIDNEY FUNCTION IN PEOPLE WITH OBESITY

Anthropometric measures of obesity

Despite the substantial evidence of an increasing prevalence of obesity and the importance of its associations with CKD, there is currently no gold standard assessment for obesity among people with CKD. BMI is the most widely used and available tool; however, relying solely on BMI can be misleading, and BMI cutoff values are not universal, with BMI >25 kg/m^2 used for Asians versus >30 kg/m^2 for others.[41] There is evidence that distribution of body fat, not obesity as defined by BMI *per se*, is related to various physiological aberrations, such as hyperinsulinemia, hypertension, dyslipidemia, and atherosclerosis. Individuals with central fat distribution, regardless of BMI, have a demonstrated higher risk of diminished eGFR and albuminuria, with a graded association with increasing waist-hip ratio.[42] Conversely, in a population of 1261 middle-aged persons (median age 59 years) without T2D,

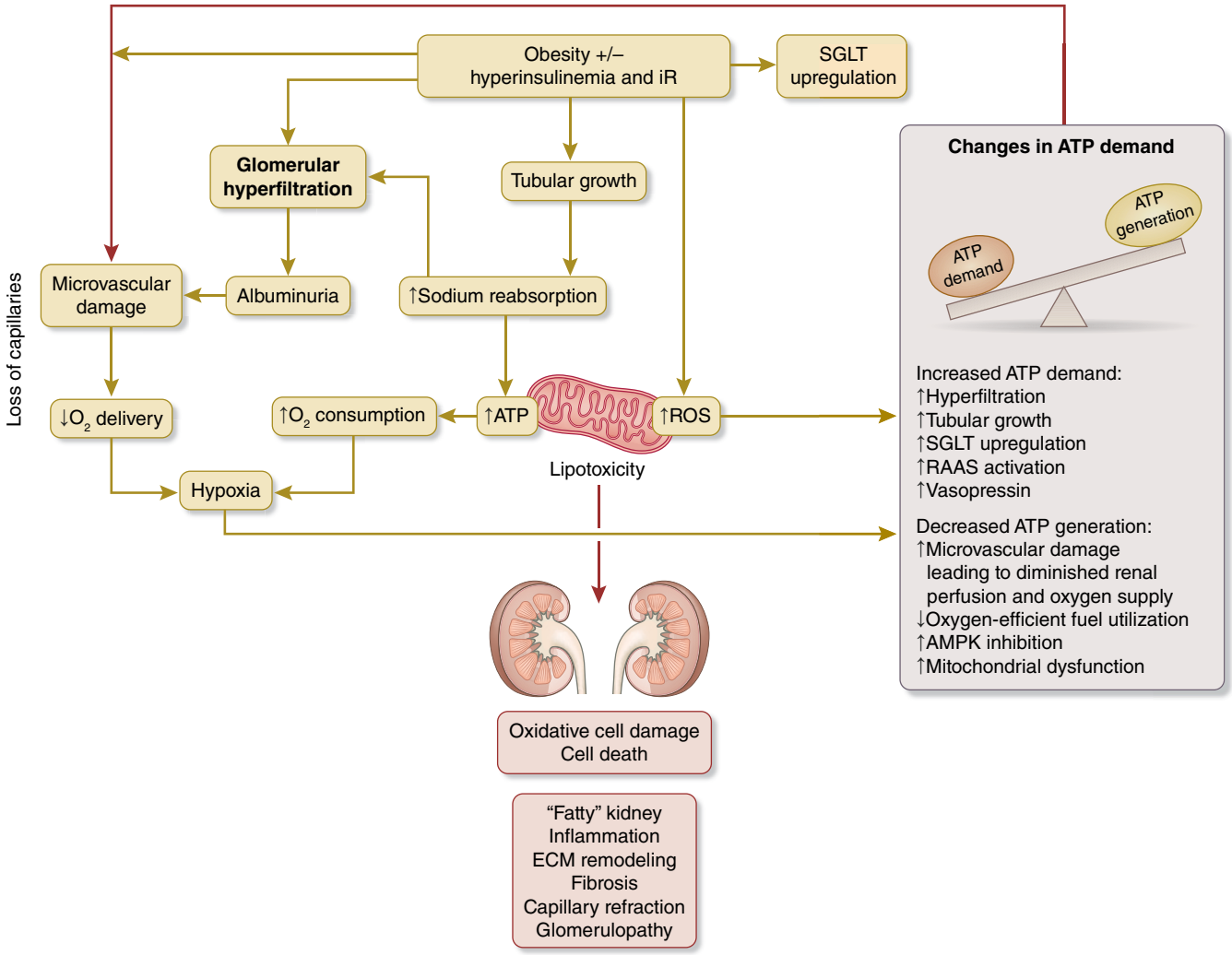

Figure 2 | Hypothesized mechanisms for hyperglycemia-induced hypoxia, leading to kidney tissue damage. Hyperglycemia after insulin resistance may induce single-nephron hyperfiltration, tubular growth, and upregulation of sodium-glucose transporters. This may lead to an increase in sodium reabsorption, increasing adenosine triphosphate (ATP) demand and oxygen (O_2) consumption. Microvascular damage caused by hyperglycemia could decrease renal perfusion and O_2 delivery and shift glucose oxidation toward the less efficient oxidation of free fatty acids, resulting in decreased generation of ATP per O_2 molecule. AMPK, adenosine monophosphate–activated protein kinase; ECM, extracellular matrix; iR, insulin resistance; RAAS, renin-angiotensin-aldosterone system; ROS, reactive oxygen species; SGLT, sodium-glucose cotransporter. Modified from Hesp *et al.* (2020).[35]

cardiovascular disease, or kidney disease, the presence of metabolic syndrome was an independent risk factor for accelerated age-related decline in iohexol GFR over a median of 5.6 years, with a 0.30 ml/min per 1.73 m^2 per year faster mean GFR decline, which was primarily driven by elevated triglyceride levels noted in metabolic syndrome.[43] A recently released consensus statement by the *Lancet Diabetes & Endocrinology* Commission on Definition and Diagnostic Criteria for Clinical Obesity[41] recommends the use of BMI only for population-level studies. It also recommends assessing excess adiposity at an individual level, either via direct measurement of visceral organ adiposity or via use of another anthropometric measure (such as waist circumference, waist-to-hip ratio, or weight-to-height ratio), along with BMI. This statement differentiates preclinical and clinical obesity, which has therapeutic implications. The diagnosis of clinical obesity requires one or both of the following main criteria: (i) evidence of reduced organ or tissue function due to obesity (i.e., signs, symptoms, or diagnostic tests showing abnormalities in the function of ≥1 tissue or organ system) or (ii) substantial, age-adjusted limitations of daily activities reflecting the specific effect of obesity on mobility, other basic activities of daily living (e.g., bathing, dressing, toileting, maintaining continence, and eating), or both. Those who met the definition of clinical obesity would need urgent interventions to prevent adverse consequences.

Several measures have been used to study the adverse consequences of adiposity on kidney function, incident CKD, cardiovascular outcomes, and mortality in those

with preexisting kidney disease.[44] The advantages and limitations of these measures for clinical practice are described in Table 2. Waist circumference and waist-to-hip ratio have been identified as risk factors for eGFR decline and death in individuals with normal or reduced levels of eGFR. However, reported associations between BMI, waist circumference, and kidney disease progression and mortality have been discordant,[45,46] warranting evaluation of adiposity using body composition studies. An additional challenge of using anthropometric measurements is that high fluid retention and hypervolemia can distort not only body weight but also interfere with the accuracy and reliability of assessing obesity. In individuals with CKD, changes in BMI over time may not fully represent an increase in adipose tissue,[47,48] given the influence of multiple factors (such as fluid overload) on BMI. Future studies should compare the predictive ability of different anthropomorphic measures (see Table 2) and body composition tools alone or in combination in those with obesity and CKD.

Clinical phenotypes of obesity

Multiple body composition subtypes (visceral and subcutaneous obesity) and clinical phenotypes of obesity (e.g., sarcopenic obesity) have been identified in the general population. Even though differential risks of individual obesity subtypes with clinical outcomes have been reported,[49–52] there is currently no well-established diagnostic criterion or consensus on the use of appropriate diagnostic modalities for identifying such subtypes; therefore, further studies are warranted. Visceral obesity has been identified as an independent risk factor for CKD and is associated with inflammation and adipokines in CKD.[50] Radiological evaluation may be needed to assess visceral obesity in several situations, although this may not be universally feasible.[51,53]

Sarcopenic obesity, a clinical condition characterized by the co-occurrence of excess adipose tissue and loss of skeletal muscle mass,[54] is associated with an increased risk of CKD and affects 2%–23% of the population with CKD.[52,55] There is a lack of consensus on the definitions of sarcopenia and sarcopenic obesity, with considerable differences among

Table 2 | Comparison of multiple anthropometric and imaging modalities for assessing obesity

Metric	Remarks	Strengths	Limitations
BMI	Measures weight relative to height; used as a general obesity indicator	Simple, widely used, correlates with body fat in population studies	Does not reflect fat distribution or differentiate between fat and muscle mass; affected by high muscle mass
WC	Measures abdominal fat	Easy to measure, correlates with visceral fat, a good indicator of abdominal obesity	Unable to distinguish between subcutaneous and visceral adipose tissue; not adjusted for height or body structure
Waist-to-height ratio	Ratio of WC to height	Better predictor of cardiovascular risk than BMI; accounts for body frame	Lacks cutoff points for different populations; does not differentiate between subcutaneous and visceral fat
Waist-to-hip ratio	Ratio of WC to hip circumference	Correlates with visceral fat and metabolic risk factors; useful in assessing cardiovascular risk	Limited by measurement accuracy; less useful in older adults because of hip shape changes
Percentage of body fat	Represents total body fat as a percentage of body weight	More accurate measure of total body fat than BMI	Requires specialized equipment (calipers, bioelectrical impedance, and DEXA); may vary depending on hydration and other factors
Body shape index	Incorporates WC and BMI	Predicts mortality risk independently of BMI; accounts for central obesity	Complex calculation that is less intuitive than BMI or WC; limited use in clinical practice
Body roundness index	Considers body shape to estimate fat distribution	Provides detailed body shape analysis; can be used to estimate body fat and health risk	Requires specific calculations and validation in different populations; limited research
Relative fat mass	Uses height and WC to estimate body fat	Simple and correlates well with body fat; validated in various populations	Lacks comprehensive data across diverse populations; may not be as accurate for athletes or individuals with varying body composition
Visceral adiposity index	Estimation of visceral fat based on BMI, triglycerides, and HDL	Correlates well with visceral fat and cardiometabolic risk	Requires laboratory results (triglycerides and HDL) that are not easily calculated in routine practice
Weight-adjusted waist index	Adjusts WC for weight	Helps differentiate between weight and abdominal obesity	Not well-established in clinical guidelines; lacks widespread research
Lipid accumulation product	Based on WC and fasting triglycerides	Reflects visceral fat accumulation; associated with cardiometabolic risk	Requires blood tests; may not be as useful in populations with a low prevalence of metabolic syndrome

BMI, body mass index; DEXA, dual X-ray absorptiometry; HDL, high-density lipoprotein; WC, waist circumference.

diagnostic criteria, methodologies, and cutoff values. Nonetheless, the clinical consequences of sarcopenic obesity are considerably worse than those for either sarcopenia or obesity.[56]

Metabolically healthy obesity refers to the presence of obesity in the absence of common metabolic risk factors. A large meta-analysis ($N = 4{,}965{,}285$ participants) illustrated a statistically significant association between the risk of CKD and the phenotypes of being "metabolically healthy" overweight (RR 1.29; 95% confidence interval [CI] 1.27–1.32; $P < 0.001$) or obese (RR 1.47; 95% CI 1.31–1.65; $P < 0.001$),[49] suggesting that both preclinical obesity and clinical obesity (in the absence of metabolic risk factors) are harmful, with additive effects for metabolic risk factors in addition to obesity.

Kidney function assessment in obesity

An accurate assessment of kidney function is often challenging in people with obesity and remains a subject of debate. Gold standard assessment tools, including exogeneous glomerular filtration markers such as iothalamate, ethylenediaminetetraacetic acid, diethylenetriaminepentaacetic acid, and iohexol, are relatively expensive, inconvenient, and time-consuming and are therefore rarely used in clinical practice.[57,58] Serum creatinine and cystatin C, 2 endogenous molecules, are widely used to assess eGFR; however, their accuracy in GFR estimation is unclear among patients with extreme obesity (Figure 3).[59] The reliability of these measures in individuals undergoing weight loss also merits further study.

There has been debate about the utility of indexing to body surface area, which has direct implications for CKD staging and drug dosing. There is a lack of validation of body surface area–estimating formulas (nonindexed) in people with obesity, and indexing has the potential to mask glomerular hyperfiltration in people with obesity.[60] In an analysis of 3611 participants from the CRIC (Chronic Renal Insufficiency Cohort) Study, increases in obesity-associated body surface area were accompanied by higher absolute GFR for a given eGFR.[61] This was further evaluated in a study of 4707 persons referred for measured GFR with a range of BMIs.[62] The analysis of indexed and nonindexed eGFR using creatinine (eGFRcr), cystatin C (eGFRcys), and the combination (eGFRcr-cys) concluded that indexed eGFRcr-cys was more accurate than indexed eGFRcr across the BMI spectrum. Using nonindexed eGFRcr-cys further improved accuracy for some treatment decisions. Studies comparing the effectiveness of indexed versus unindexed GFR for predicting long-term CKD-related clinical outcomes, including CKD progression, major adverse cardiovascular events, or mortality, are needed.

Albuminuria assessment in obesity

The presence of albuminuria is a well-studied and acknowledged risk factor for CKD. However, when assessing

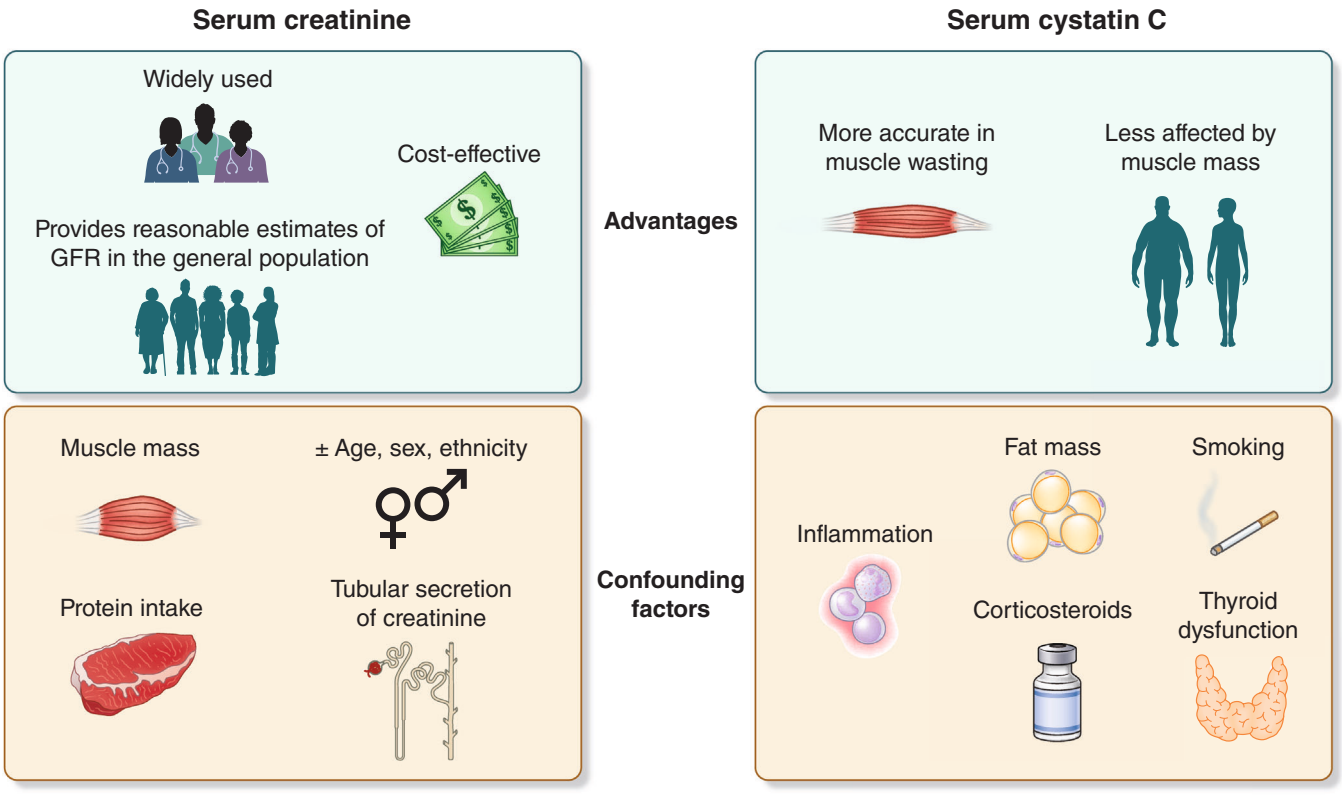

Figure 3 | Comparison of cystatin C and creatinine for kidney function assessment. GFR, glomerular filtration rate. Sex refers to biological attributes.

UACR in the setting of obesity, it is important to remember that urinary creatinine excretion is a direct reflection of muscle mass. This can be particularly problematic in sarcopenic obesity and in those undergoing weight loss.[63] A mild-to-moderate change in urinary creatinine excretion can lead to an under- or overestimation of spot UACR if urinary albumin remains constant.[63] Although determining a lower threshold for UACR may appear to be a solution, such an approach may be misleading in people with sarcopenic obesity.

Considerations relevant to kidney transplantation

In people with kidney failure, including those living with obesity, kidney transplantation provides survival benefits over dialysis therapy.[64–66] However, obesity is associated with lower access to kidney transplantation, as evidenced by lower rates for referral, longer wait times, and lower rates of transplantation.[67] Relative to individuals with a BMI of 18.5–25 kg/m^2, individuals with a BMI of ≥35 kg/m^2 are less likely to be listed for receiving a kidney transplant, especially among individuals younger than 45 years, women, or those of Asian race.[68]

The rationale for this diminished access is the documented higher risk of surgical complications (i.e., longer procedure period and warm ischemia time, higher risk of surgical-site infections, dehiscence, and vascular complications including venous thromboembolism) and postoperative complications (i.e., delayed graft function and acute rejection).[69] However, whether these risks outweigh the known benefits of transplantation over dialysis remains somewhat controversial. Obesity treatment should be considered before transplantation, mediated via pharmacotherapy or MBS, to facilitate timely access to kidney transplantation and potentially improve long-term metabolic risks. However, more data in this area are needed. Multiple studies, mostly retrospective, with small sample sizes and short follow-up periods, have reported potential benefits of intentional weight loss before transplantation among kidney transplant candidates with obesity,[70–72] but large-scale prospective clinical studies investigating this highly relevant issue for clinical practice are needed. It is noted that after MBS, maintaining adequate immunosuppression levels after transplantation can be challenging.[73]

INTERVENTIONS FOR WEIGHT LOSS AND IMPROVING KIDNEY FUNCTION

Tailored diet and physical activity interventions should be a foundation of therapy in people living with obesity and CKD. Also integral to management are behavioral therapy and the consideration of obesity-management medications and surgical interventions. The mechanisms by which weight loss affects kidney outcomes are unclear and may be direct or indirect. Weight change should be considered alongside changes in clinical and patient-reported outcomes, including kidney function, quality of life, blood pressure, functional capacity, and measures of diet quality.

Diet and exercise

Randomized controlled trials (RCTs) have reported the effectiveness and safety of reduced energy intake and increased physical activity to achieve weight loss and improved functional capacity in people living with obesity and CKD.[7,74] However, studies have not consistently shown evidence that behavioral interventions to reduce intake improve metabolic outcomes, including blood pressure, albuminuria, and blood lipids, possibly because of small sample size, short follow-up, or study heterogeneity.[7] Studies addressing kidney outcomes in populations at high risk for CKD have shown that diet and physical activity interventions can reduce the incidence of reaching a high-risk CKD category (orange in the KDIGO CKD nomenclature chart [heat map][75]) and slow eGFR decline.[76–79] Successful interventions, which include dietary modification and physical exercise, incorporate elements of behavioral therapy. In a secondary analysis of the Look AHEAD (Action for Health in Diabetes) RCT, participants with T2D and obesity who received intensive lifestyle intervention achieved a 9% reduction in body weight versus 6% in the usual education group.[76] This was accompanied by a 31% reduced risk of incident very high-risk CKD on the basis of the KDIGO heat map (hazard ratio [HR] 0.69; 95% CI 0.55–0.87).[75,76] In a secondary analysis of the CORDIOPREV (CORonary Diet Intervention with Olive oil and cardiovascular PREVention) RCT, participants with T2D and obesity randomized to a Mediterranean diet had less decline in eGFR than did those randomly assigned to a low-fat diet, independent of weight loss.[78] In the PREDIMED-Plus (PREvención con DIeta MEDiterránea-Plus) RCT, participants with cardiovascular-kidney-metabolic (CKM) syndrome randomly assigned to an energy-reduced Mediterranean diet along with physical activity recommendations and behavioral support had a 40% lower incidence of moderately or severely impaired eGFR (HR 0.60; 95% CI 0.44–0.82), and a 92% higher reversion of moderately to mildly impaired eGFR (HR 1.92; 95% CI 1.35–2.73), than did a control group with education about a Mediterranean diet.[79]

Table 3 summarizes the key studies on dietary interventions for obesity management, including suggestions regarding suitability at different stages of CKD and evidence gaps in certain populations.[76,79–87] Dietary and physical activity interventions focusing on incremental, achievable changes toward healthy eating and an active lifestyle, with positive messaging and ongoing support, can be implemented using patient-led goal setting.[85,88] Health care professionals require training to deliver these interventions using nonjudgmental, stigma-free language and approaches.[89]

Obesity management medications

Several medications are currently licensed for obesity treatment, and, among these, incretin mimetics have the most available data on kidney outcomes. Incretin mimetics currently licensed or in development include glucagon-like

Table 3 | Effective nutrition-based interventions for people with obesity and CKD

Nutrition intervention	Physical activity intervention	CKD category	Other support provided	Suggested adaptation for CKD G4–G5
Mediterranean diet with energy reduction				
Encourages whole foods predominantly from plant sources, including grains, fruits, vegetables, pulses, nuts, and seeds Small servings of poultry, fish, or seafood 4–5 times a week; red meat once a week or fewer (fish or poultry to replace beef or lamb) Daily olive oil (in salad dressings and sauces); handful of nuts 3 times a week to once a day Reduce processed foods, sweets, pastries, and cakes ***Energy intake*** Baseline energy intake minus 500–600 kcal/d or total energy intake 1500 kcal/d for women and 1800 kcal/d for men ***Macronutrients and fiber*** 40%–45% carbohydrates (low glycemic index choices) 30–35 g fiber/d 20% protein (plant sources preferred) 35%–40% fat (plant sources preferred)	Simple advice to increase activity to 150 min/wk (Orazio *et al.* [2011])[80]	Post-kidney transplantation	Written information Pictorial guide	For CKD G4 and G5: modify protein intake to 0.8 g protein/kg body weight/d Likely safe if supervised by a clinical team; may require closer monitoring of potassium initially Increase protein intake in CKD G5D from plant sources (pulses and nuts) and poultry, fish, and seafood to meet protein goal of 1–1.2 g/kg body weight/d; maintain fiber intake at 30–35 g/d
	Intensive support for physical activity and behavior change (Díaz-López *et al.* [2021])[79]	Included non-CKD and CKD G1–G3b	List of lower-energy foods Mediterranean diet food group servings Used adapted Mediterranean diet checklist	
	None (Tirosh *et al.* [2013])[81]	CKD G3 (31% of study participants had eGFR 30–60 ml/min per 1.73 m^2)	Dietitian-led group sessions fortnightly for 2 mo and then every 6 weeks up to 18 mo Telephone support Education for spouses	
Low-fat diet with energy reduction				
Consume grains, vegetables, fruits, and legumes, and limit intake of additional fats, sweets, and high-fat snacks ***Energy intake*** Baseline energy intake minus 500–600 kcal/d or total energy intake 1500 kcal/d for women and 1800 kcal/d for men ***Macronutrients*** Fat 25%–30% Protein 1.0–1.2 g/kg of adjusted body weight used in CKD G1–G3b and G5D, or 0.6–0.8 g/kg of adjusted body weight in CKD G4	None (Tirosh *et al.* [2013])[81]	CKD G3 (31% of study participants had eGFR 30–60 ml/min per 1.73 m^2)	Dietitian-led group sessions fortnightly for 2 mo and then every 6 weeks up to 18 mo Telephone support Education for spouses	Modify protein intake in CKD G5D, often as 1–2 servings of 100 g of lean poultry, 100 g of tuna, or 2 eggs
	Moderate-intensity aerobic exercises 3–5 d/wk for 30 min (Kittiskulnam *et al.* [2014])[82]	CKD G1–G4 with proteinuria	Nutritionist and clinician delivered intervention	
	None (Morales *et al.* [2003])[83]	CKD ~G1–G3a with proteinuria	No additional information provided	

(*Continued on following page*)

Table 3 | (Continued) **Effective nutrition-based interventions for people with obesity and CKD**

Nutrition intervention	Physical activity intervention	CKD category	Other support provided	Suggested adaptation for CKD G4–G5
	Home-based exercise 5 d/wk Start at 50 min/wk and increase to 175 min/wk (Look Ahead Research Group [2014])[76]	Non-CKD and CKD G1–G2 with type 2 diabetes (excluded CKD G3–G5)	Included 1–2 meal replacement products per day (energy 1200–1800 kcal/d) Intensive support provided for 18 mo Refresher group program and/or orlistat offered if target weight loss not met Other supports included exercise or cooking classes	
Healthy diet with energy reduction				
Energy intake No specific nutrient intake prescribed; 10%–15% reduction in total daily energy intake from baseline ***Dietary pattern*** Large amounts of fresh, unprocessed plant foods along with moderate levels of lean protein and fats such as omega-3 and monounsaturated fats	In exercise arms: supervised aerobic exercise 30–45 min 3 times a week (Ikizler *et al.* [2018])[84]	CKD G3–G4	2 × 2 design: exercise, energy reduction, or both; or control Dietitian-led dietary intervention: avoid high-calorie meals rich in processed, easily digestible, quickly absorbable foods and drinks as a part of a CKD diet	None for CKD G4 Monitor for hypotension with weight loss For CKD G5D, additional monitoring for electrolytes and dry weight adjustment. Additional protein may be required, often as 1–2 servings of 100 g of lean poultry, 100 g of tuna, or 2 eggs
Low-energy diets using formula meal replacements				
Energy intake 800–900 kcal/d and 75–80 g of protein ***Composition*** 3–4 commercially produced standardized and micronutrient-fortified meal replacement shakes, bars, and soups/d	Remotely delivered exercise support with graded exercise program after dietary intervention ceased (Conley *et al.* [2025])[85]	CKD G1–G3b	Plus 1 piece of fruit and 1 low-energy small meal and 2 cups of nonstarchy vegetables per day Fortnightly dietitian support	Safe with clinical supervision Feasible over short term (up to 3 mo) For CKD G5D, additional close monitoring for electrolytes and dry weight adjustment. Additional protein may be required, often as 1–2 servings of 100 g of lean poultry, 100 g of fish, or 2 eggs
	None (Friedman *et al.* [2013])[86]	CKD G3b–G4[86]	Plus 1 lean meal, 50 g carbohydrate/d	

(*Continued on following page*)

Table 3 | (Continued) **Effective nutrition-based interventions for people with obesity and CKD**

Nutrition intervention	Physical activity intervention	CKD category	Other support provided	Suggested adaptation for CKD G4–G5
Low carbohydrate diet without energy reduction				
Energy intake Total energy was not limited ***Macronutrient intake*** 20 g carbohydrate/d for 2 mo and then gradually increase to maximum 120 g carbohydrate/d No limits on fat and protein Choose vegetarian sources of fat and protein; avoid trans fats	None (Tirosh *et al.* [2013])[81]	CKD G3 (31% of study participants had eGFR 30–60 ml/min per 1.73 m^2)	Dietitian-led group sessions fortnightly for 2 mo and then every 6 weeks up to 18 mo Telephone support Education for spouses	Not suitable for CKD G4–G5
New Nordic renal diet without energy reduction				
Whole food approach: 80% plant-based, 20% animal products 1–2 vegetarian days/wk Fish ≥2 servings/wk Poultry 2 servings/wk No red meat 300 g fruit/d, 20 g nuts/d Protein 0.8 g/kg of body weight/d	None (Misella Hansen *et al.* [2023])[87]	CKD G3b–G4, eGFR 20–45 ml/min per 1.73 m^2	Choose mostly whole grains, legumes, and root vegetables as well as in-season vegetables Food boxes and recipes were delivered to households each week Dietitian home visit was offered	Increase protein intake in CKD G5D from plant sources (pulses and nuts) and poultry, fish, and seafood to meet protein goal of 1–1.2 g/kg body weight/d Maintain fiber intake at 30–35 g/d

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

peptide-1 receptor agonists (GLP-1 RA), combination GLP-1 RA and glucose-dependent insulinotropic polypeptide (GIP) RA, combination GLP-1 RA and glucagon RA, and triple combinations with GLP-1 RA, GIP RA, and glucagon RA. At present, GLP-1 RA and dual GLP-1/GIP RA have the most data to inform obesity management in people with or without kidney disease.[90] In people with CKD, these agents have shown efficacy for weight reduction with an absence of CKD-specific safety signals.[91–94] Of note, trials including participants with CKD excluded transplant recipients and many excluded people with eGFR < 30 ml/min per 1.73 m^2. Dialysis and transplantation are not listed as contraindications to using GLP-1 RA or GLP-1 RA plus other peptides, although there is a lack of evidence of kidney benefits in patients with GFR < 15 ml/min per 1.73 m^2 (including those on dialysis). Emerging retrospective data indicate potential kidney benefits in kidney transplantation, mostly tested in transplant recipients with T2D,[95,96] but RCTs are needed.

An important question is whether obesity management medications are, in practice, used long enough to benefit kidney health. Lack of adherence and nonpersistence with treatment are important barriers[97]; in some real-world studies, nonadherence is as high as 60%.[98,99] Cost and payer preparedness are also important barriers to accessibility for GLP-1 RA.[100] There is a need for both trial and real-world data in this population to inform strategies for realizing potential benefits of these medications.

Effects of incretin-based therapies on the kidney. To date, the only trial of incretin-based therapy with a kidney primary end point was the FLOW (Evaluate Renal Function with *Semaglutide* Once Weekly) trial. The FLOW trial examined semaglutide 1.0 mg/wk in people with T2D and CKD.[92] Prior transplantation, kidney replacement therapy, or eGFR <25 ml/min per 1.73 m^2 were exclusion criteria. Overall, 400 of 3533 total participants had eGFR <30 ml/min per 1.73 m^2. The primary outcome comprised kidney failure (dialysis, transplantation, or eGFR <15 ml/min per 1.73 m^2), ≥50% eGFR reduction from baseline, or kidney or cardiovascular death. Relative to placebo, semaglutide was associated with an overall 24% reduction in the primary outcome and a 21% reduction (HR 0.79; 95% CI 0.66–0.94) in a composite outcome of kidney-specific components. There was no significant variation in this effect based on eGFR category at baseline. The mean annual eGFR slope was 1.2 ml/min per 1.73 m^2 less with semaglutide relative to placebo ($P < 0.001$). The benefits on slope were seen for calculations using both creatinine and cystatin C to estimate eGFR.

The data from FLOW were consistent with prior secondary analyses from trials of semaglutide and other GLP-1 RA in people with T2D. A meta-analysis including data from 8 trials[91] reported a 21% reduction ($P < 0.001$) in the composite kidney outcome (Table 4).[91–94,101–110] This composite consisted of development of severely increased albuminuria, doubling of serum creatinine, or either at least a 40% decline in eGFR, kidney replacement therapy, or death due to kidney disease. Trial-specific effect estimates ranged from a 12% reduction of the composite outcome in EXSCEL (Exenatide Study of Cardiovascular Event Lowering) to a 36% reduction in SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes), indicating a class effect.[91]

For incretin-based therapies, to date the largest study with kidney outcome data in the absence of T2D come from the SELECT (Semaglutide Effects on Cardiovascular Outcomes in People With Overweight or Obesity) trial. The SELECT trial included people with overweight and obesity and prior cardiovascular disease but without T2D at baseline.[93] Patients undergoing hemodialysis or peritoneal dialysis and individuals with eGFR <15 ml/min per 1.73 m^2 were excluded. Of the 17,604 enrolled participants, 1908 (11%) had eGFR <60 ml/min per 1.73 m^2 at study entry, with only 26 (0.15%) persons having eGFR <30 ml/min per 1.73 m^2. Semaglutide 2.4 mg s.c. weekly was associated with a 20% reduction in the primary end point of first occurrence of major adverse cardiovascular events compared with placebo. The reduction in the risk of major adverse cardiovascular events with semaglutide was similar in those with and without eGFR <60 ml/min per 1.73 m^2 and in those with and without albuminuria at study entry.[111]

For kidney outcomes in SELECT, semaglutide 2.4 mg s.c. weekly was associated with a 22% reduction in the prespecified composite kidney end point (HR 0.78; 95% CI 0.63–0.96; $P = 0.02$). The treatment difference of 2.19 ml/min per 1.73 m^2 in eGFR at 104 weeks of the trial was greatest in the 11% who had eGFR <60 ml/min per 1.73 m^2 at baseline (95% CI 1.00–3.38; $P < 0.001$). Although treatment discontinuations in both treatment arms were more common in patients with baseline eGFR <60 ml/min per 1.73 m^2, a lower number of serious adverse events were reported in those taking semaglutide than in those taking placebo.

There was no evidence of increased safety signals in more frail individuals or those with lower eGFR in FLOW and SELECT, respectively, though there were few participants with eGFR <25 ml/min per 1.73 m^2 in the trials and none receiving kidney replacement therapy. In both trials, there was an initial transient decrease in eGFR with semaglutide. In SELECT, this was a net 1.33 ml/min per 1.73 m^2 per year greater decline in patients randomized to semaglutide, but by week 20, eGFR was similar in both treatment arms overall. There was no increase in albuminuria during this period.

A recent meta-analysis of GLP-1 RA phase 3 and 4 trials[94] that included SELECT and FLOW reported an overall reduction across all trials of GLP-1 RA combined in the composite kidney outcome by 18% compared with placebo (HR 0.82; 95% CI 0.73–0.93; $I^2 = 26.41\%$), as well as a reduction in kidney failure of 16% (HR 0.84; 95% CI 0.72–0.99). The combined end point in that analysis excluded albuminuria and was restricted to kidney failure (i.e., kidney replacement therapy or persistent eGFR <15 ml/min per 1.73 m^2), a sustained reduction in eGFR from baseline by ≥50%, or death due to kidney disease.

Table 4 | Key randomized clinical trial data on kidney outcomes from phase 3 or 4 trials of GLP-1 RA

Trial	Description	Main kidney outcome definition	HR (95% CI) associated with GLP-1 RA vs. comparator
Sattar *et al.* (2021)[91]	Meta-analysis of kidney outcomes with GLP-1 RA in 8 trials in type 2 diabetes[a]	Severely increased albuminuria, doubling of serum creatinine, or at least 40% decline in eGFR, kidney replacement therapy, or death due to kidney disease	0.79 (0.73–0.87), $P < 0.0001$
Perkovic *et al.* (2024)[92]	FLOW: semaglutide 1 mg/wk vs. placebo in type 2 diabetes with CKD	Kidney failure (dialysis, transplantation, or eGFR <15 ml/min per 1.73 m^2), ≥50% eGFR reduction from baseline, or kidney or cardiovascular death	0.76 (0.66–0.88), $P = 0.0003$ Excluding cardiovascular death from the end point: HR 0.79 (95% CI 0.66–0.94)
Colhoun *et al.* (2024)[93]	SELECT: semaglutide 2.4 mg/wk vs. placebo in people with overweight or obesity and prior CVD but without type 2 diabetes	Death from kidney causes, initiation of chronic kidney replacement therapy (dialysis or transplantation), onset of persistent eGFR <15 ml/min per 1.73 m^2, persistent ≥50% reduction in eGFR compared with baseline or onset of persistent severely increased albuminuria	0.78 (0.63–0.96), $P = 0.02$
Badve *et al.* (2025)[94]	Meta-analysis of all GLP-1 RA trials including SELECT and FLOW[b]	Kidney failure (i.e., kidney replacement therapy or a persistent eGFR <15 ml/min per 1.73 m^2), a sustained reduction in eGFR from baseline by ≥50%, or death due to kidney disease	0.81 (0.72–0.92), $P < 0.001$

AMPLITUDE-O, Effect of Efpeglenatide on Cardiovascular Outcomes; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ELIXA, Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010 (Lixisenatide); EXSCEL, Exenatide Study of Cardiovascular Event Lowering; FLOW, Evaluate Renal Function with Semaglutide Once Weekly; GLP-1 RA, glucagon-like peptide-1 receptor agonists; HR, hazard ratio; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; PIONEER 6, A Trial Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects With Type 2 Diabetes; SELECT, Semaglutide Effects on Cardiovascular Outcomes in People With Overweight or Obesity; SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes.
[a]Combined data from ELIXA (lixisenatide),[101] LEADER (liraglutide),[102,103] SUSTAIN-6 (semaglutide),[104] EXSCEL (exenatide),[105] REWIND (dulaglutide),[106,107] Harmony Outcomes (albiglutide),[108] PIONEER 6 (semaglutide),[109] and AMPLITUDE-O (efpeglenatide) trials.[110]
[b]Combined data from ELIXA (lixisenatide),[101] LEADER (liraglutide),[102,103] SUSTAIN-6 (semaglutide),[104] EXSCEL (exenatide),[105] REWIND (dulaglutide),[106,107] Harmony Outcomes (albiglutide),[108] AMPLITUDE-O (efpeglenatide),[110] FLOW (semaglutide),[92] and SELECT (semaglutide)[93] trials.

Semaglutide was tested in a smaller study ($N = 101$) involving patients with overweight or obesity and CKD without diabetes, with albuminuria as the primary end point.[112] Compared with the group receiving placebo, the group treated with semaglutide 2.4 mg had a 52.1% lower UACR (95% CI −65.5% to −33.4%; $P < 0.0001$) at 24 weeks.

Fewer data are available for tirzepatide, dual GLP-1/GIP RA. A secondary analysis of the SURPASS (A Study of Tirzepatide [LY3298176]) Once a Week Versus Insulin Glargine Once a Day in Participants With Type 2 Diabetes) -4 open-label trial comparing tirzepatide versus insulin glargine in individuals with T2D and increased cardiovascular risk reported a smaller decline in eGFR with tirzepatide (data pooled across 3 doses: 5, 10, and 15 mg).[113] Further analysis showed that this was the case whether eGFR was estimated using measures of cystatin C or creatinine.[114] There was also an initial transient decline in eGFR with tirzepatide as seen with semaglutide. A recent pooled analysis across SURPASS trials 1–5 found no difference in eGFR between tirzepatide and pooled comparators at week 40/42.[115] However, reductions in UACR were 19%, 22%, and 26% for tirzepatide 5, 10, or 15 mg, respectively, compared with all pooled comparators. Longer-term data for tirzepatide will be available from the forthcoming SURPASS-CVOT (A Study of Tirzepatide [LY3298176] Compared With Dulaglutide on Major Cardiovascular Events in Participants With Type 2 Diabetes. ClinicalTrials.gov identifier: NCT04255433),[116] which completed in June 2025.

Cotadutide combines GLP-1 RA and glucagon RA. In a small phase 2B study in people with T2D and CKD, cotadutide showed significant reductions in UACR relative to standard of care.[117]

Retatrutide is a triple combination of GLP-1 RA, GIP RA, and glucagon RA for which an analysis of 2 phase 2 trials—one in people with obesity and the other in those with T2D—has been performed.[118] In the evaluation in participants with T2D, at 36 weeks there was no observed difference in eGFRcr between retatrutide and placebo, though UACR was significantly reduced with retatrutide. In the trials of participants with obesity, at 48 weeks, retatrutide was associated with increased eGFRcr and decreased UACR compared with placebo.

For dipeptidyl peptidase-4 inhibitors, a systematic review found that only 1 study out of 5 trials with kidney data indicated a reduced risk of composite microvascular outcomes and albuminuria progression.[119]

Mediation analyses of incretin mimetic therapies have noted that weight loss did not fully explain the kidney benefits. Thus, it is unclear whether interventions such as medications benefit kidney health in the absence of weight

loss and whether there should be a target weight or other outcome measure used in people with CKD.

Nonincretin medications used in obesity. Orlistat is a lipase inhibitor that reduces the absorption of dietary fat. A small open-label study in people with CKD and BMI >30 or >28 kg/m^2 with comorbid conditions (T2D, hypertension, or dyslipidemia) found that weight loss in the group that received orlistat together with individualized support and exercise prescription was associated with a slower decrease in eGFR than in the usual care group (without weight management).[120] However, the authors noted that this result might have been affected by sampling bias. Additionally, concerns about acute kidney injury and oxalate nephropathy with orlistat have been raised,[121] leading to a label warning to monitor kidney function in patients at risk for kidney insufficiency and to discontinue the drug if oxalate nephropathy develops.

Phentermine is a Schedule IV–controlled stimulant that is indicated for weight reduction in the United States, but only for short-term use, and it is not indicated in children. The label advises caution when used in people with kidney impairment. Naltrexone/bupropion is an opioid receptor antagonist also used for weight loss, although it is contraindicated in persons with kidney failure.

Other therapies with known kidney benefits but not licensed as obesity drugs. Sodium-glucose cotransporter-2 inhibitors have beneficial effects on cardiovascular and kidney outcomes in people with and without CKD.[122] Meta-analyses across all sodium-glucose cotransporter-2 inhibitor trials suggest modest weight loss—a mean weight reduction of −1.79 kg (95% CI −1.93 to −1.66 kg; $P < 0.001$)—compared with placebo.[123] In several studies, it has been noted that GLP-1 RA effects on kidney outcomes are independent of, and show no interaction with, background sodium-glucose cotransporter-2 inhibitor use.[124]

Pediatric populations. In the United States, semaglutide, liraglutide, orlistat (120 mg), and phentermine-topiramate have been approved as obesity management medications for adolescents 12 years or older and weighing ≥60 kg, with an initial BMI corresponding to ≥30 kg/m^2 for adults. In contrast, only liraglutide and semaglutide have been approved for this age group in Europe. Data on the impact of obesity management medications on kidney outcomes in children are lacking. In the Semaglutide Treatment Effect in People with Obesity (STEP) TEENS trial, in adolescents with obesity or overweight and at least 1 weight-related coexisting condition, semaglutide was associated with a net difference of −16.7 percentage points (95% CI −20.3 to −13.2 percentage points; $P < 0.001$) in BMI. Data on eGFR or albuminuria were not reported.[125]

Surgical interventions

Before the relatively recent introduction of incretin mimetic therapies, surgical interventions for obesity were one of the few therapies that had shown promise in yielding sustainable weight loss. The most commonly performed MBSs are sleeve gastrectomy or Roux-en-Y gastric bypass (RYGB). Overall, surgical weight loss has been shown to be both relatively safe and effective in inducing weight loss in people with kidney disease and associated with improved kidney outcomes in individuals with eGFR <60 ml/min per 1.73 m^2. Relative to RYGB, sleeve gastrectomy has the advantages of not being associated with kidney stones or oxalate nephropathy and not interfering with the absorption of immunosuppressive medications after kidney transplantation.[126]

Prior studies suggested that weight loss after MBS may decrease glomerular hyperfiltration, as indicated by decreases in GFR (both estimated and measured) in people with eGFR >120 ml/min per 1.73 m^2. However, the arbitrary definition of hyperfiltration as GFR >120 ml/min per 1.73 m^2 can be problematic. In a retrospective propensity score–matched analysis comparing 985 people who underwent MBS with 985 who did not undergo surgery (33% of each group had baseline eGFR <90 ml/min per 1.73 m^2), MBS was associated with a 58% lower risk of eGFR decline and a 57% lower risk of doubling of serum creatinine or kidney failure over a median follow-up of 3.8 years.[127]

CKD G5 and G5D. Patients with kidney failure on dialysis experience a higher incidence of post-MBS complications than do those without kidney disease; however, the absolute complication rates are low relative to the benefit and are not MBS-specific.[128] In a retrospective propensity score–matched analysis of 717,809 patients spanning 2015–2019, the cumulative risk of death within 30 days of MBS was approximately 0.6% in 5817 patients with CKD (vs. 0.2% for those without CKD).[129] Current evidence suggests that MBS before kidney transplantation does not lead to adverse outcomes post-transplantation; however, robust evidence in this area is lacking.[130]

When MBS is performed, exercise training before and after is critical for preserving both muscle mass and fitness, as sarcopenia, especially low muscle strength, is associated with a high risk of complications, including cardiovascular events and mortality, in patients on hemodialysis.[131,132]

Pediatric populations. In many countries, MBS either is not permitted or is permissible only in rare situations in children and adolescents with obesity. In the United States, MBS is recognized by the American Academy of Pediatrics as an effective treatment of severe obesity in childhood.[133] Sleeve gastrectomy is almost always the surgery type used in this population. Few, if any, RCTs exist in these populations. In observational data from the Teen-LABS (Longitudinal Assessment of Bariatric Surgery) cohort, MBS was associated with improved kidney outcomes in adolescents (aged 13–19 years) with severe obesity, including those with CKD (G1–G4) and T2D.[134] The procedure led to significant improvements in eGFR, resolution of albuminuria in some, and reduction of hyperfiltration. For adolescents with CKD G5/G5D or a kidney transplant, data on outcomes of MBS are lacking.

Comparing drug therapies and MBS

Figure 4 outlines the overall relative strengths and drawbacks of pharmacotherapy and MBS. Whether drug therapies or MBS is superior in achieving weight loss and safety end points has not been adequately studied; the current best-in-class U.S. Food and Drug Administration–approved agents (semaglutide and tirzepatide) have not been prospectively compared with MBS at their maximum tolerated doses for obesity management. Evidence from SURMOUNT-1 (A Study of Tirzepatide [LY3298176] in Participants With Obesity or Overweight) has indicated that the maximum dose of tirzepatide (15 mg) leads to weight loss comparable to MBS.[11,135]

Few observational data exist directly comparing surgical and medical interventions. The M6 (Macrovascular and Microvascular Morbidity and Mortality After Metabolic Surgery Versus Medicines) study was a retrospective observational study in the United States from 2010 to 2017, comparing the nephroprotective effect of MBS with that of GLP-1 RA.[136] In that study, patients who underwent MBS had a significantly lower incidence of CKD progression (defined as the onset of ≥50% sustained decline in eGFR compared with baseline, development of sustained eGFR <15 ml/min per 1.73 m^2, initiation of dialysis, or kidney transplantation after the index date) after a median follow-up of 5.8 years. However, it is important to note that none of the patients without surgery were receiving best-in-class medications such as semaglutide and tirzepatide at baseline, and only 19% received these agents during follow-up, limiting the true comparison between medical and surgical management.

Uncontrolled studies comparing surgical and medical interventions using empagliflozin and liraglutide have shown comparable outcomes. MOMS (Metabolic Surgery Compared to the Best Clinical Treatment in Patients With Type 2 Diabetes Mellitus) was a prospective, open-label, randomized study involving 100 patients with T2D, obesity, CKD G1–G3a, and albuminuria A2–A3 ($N = 100$), comparing RYGB with best pharmacotherapy for patients with T2D and obesity (empagliflozin and liraglutide).[135] Albuminuria remission was not statistically different between pharmacotherapy and RYGB after 5 years in participants with diabetic kidney disease and class 1 obesity (BMI 30–35 kg/m^2). RYGB was superior in improving glycemia, diastolic blood pressure, lipids, body weight, and quality of life. However, more studies are needed that include the most effective GLP-1 RA, prospectively escalated to the maximum tolerated dose, to adequately compare medical and surgical therapies.

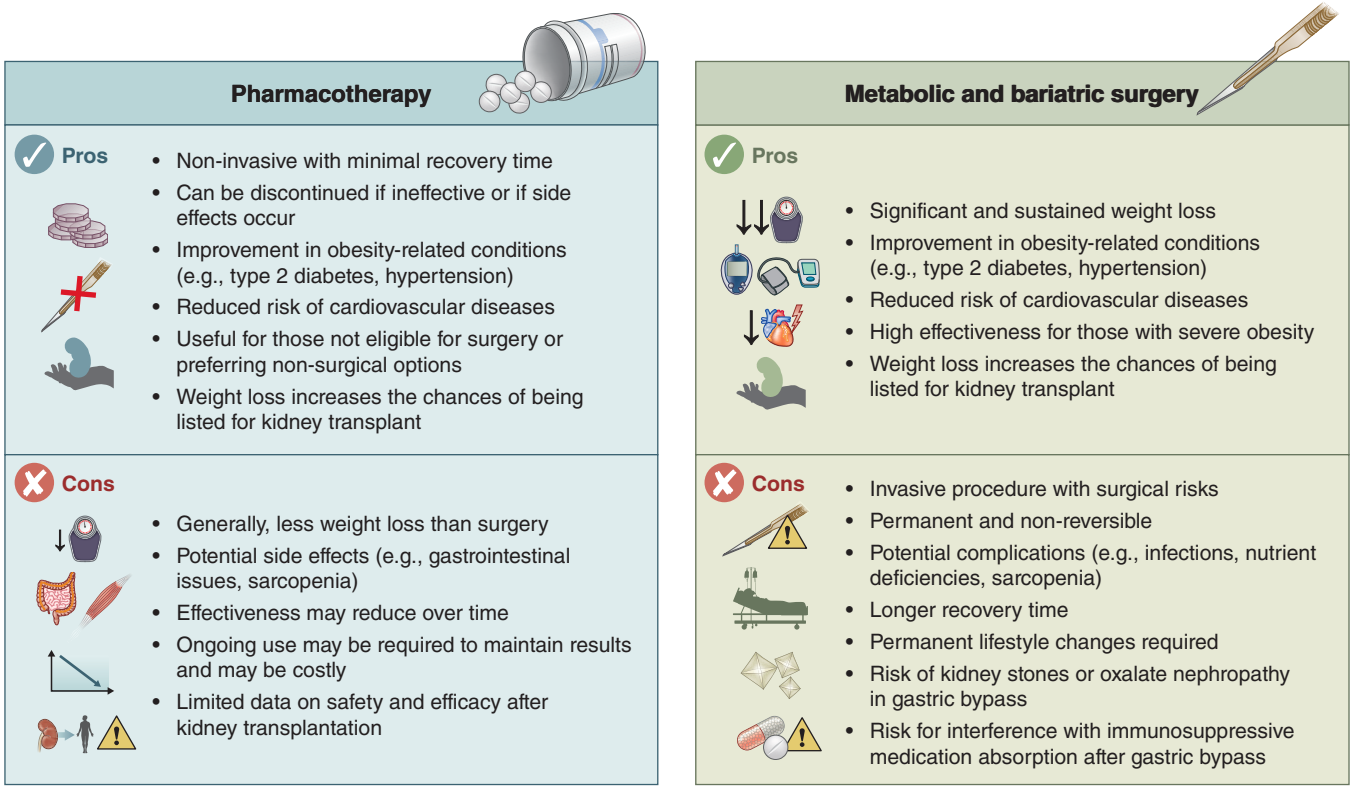

Figure 4| Comparison of pharmacotherapy with metabolic and bariatric surgery for weight loss in chronic kidney disease. Factors such as patient life goals, comorbidities, and ability to engage in physical activity will inform the therapeutic strategy. Metabolic and bariatric surgery may not be appropriate for all age groups.

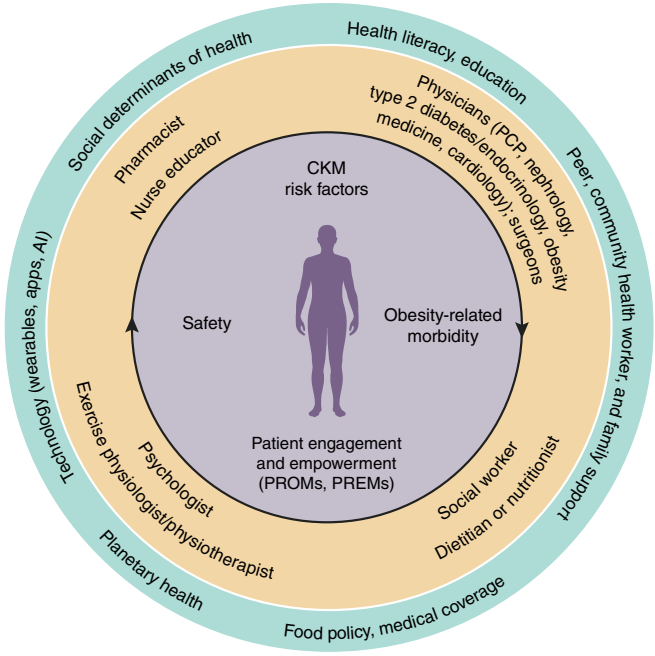

Figure 5 | Person-centered care in action: a collaborative care network for chronic kidney disease and obesity. The inner circle refers to risk factors, comorbidities, and outcomes; the middle circle refers to the team (kidney-specific professional expertise is preferred); the outer circle refers to broader determinants of health and resources. AI, artificial intelligence; apps, mobile health applications; CKM, cardiovascular-kidney-metabolic; PCP, primary care practitioner; PREM, patient-reported experience measure; PROM, patient-reported outcome measure.

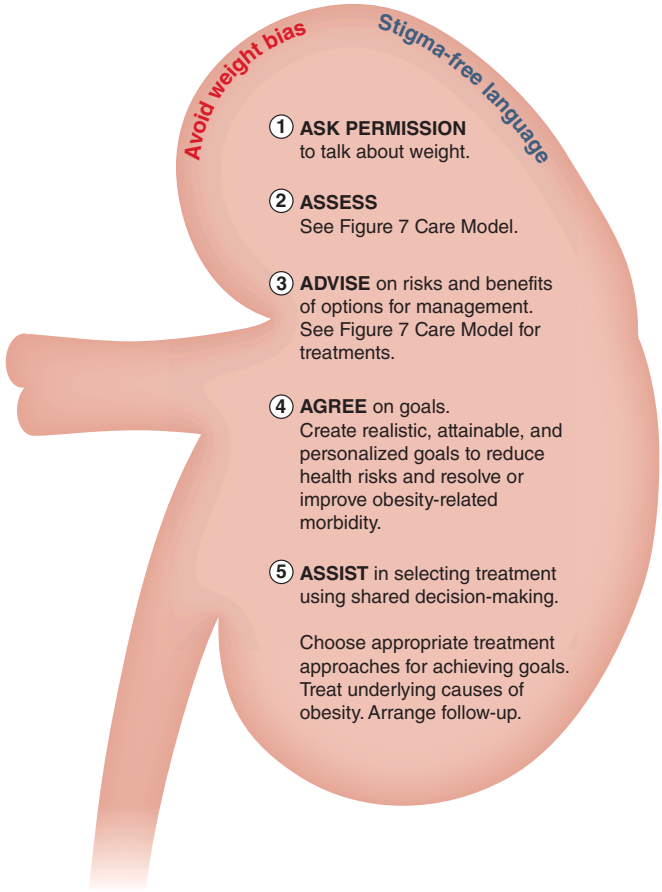

Figure 6 | Care delivery in people with chronic kidney disease and obesity: a framework to guide decision-making. Modified from Vallis *et al.* (2013).[149]

OPTIMAL MODELS OF CARE

Patient participants at the conference emphasized the importance of having multidisciplinary care to support therapy selection and the adoption of changes in nutrition and physical activity level. Indeed, effective interventions for obesity and CKD management require repeated interactions with health care teams, support for behavior change, flexibility, long-term monitoring, and follow-up, and they should be underpinned by behavior change models or theoretical frameworks.[90,137] Individualized interventions must be supported by policy and advocacy at the community, national, and international levels to create long-term change. There is substantial ongoing controversy around models of care; approaches based on implementation science are needed to support the rapid translation of treatments into care for populations globally.

Optimal care models for people living with obesity and CKD should aim to integrate the best kidney care with the best obesity care by adopting a stigma-free, person-centered approach linking primary and secondary care and involving a multidisciplinary team trained to deliver long-term obesity and kidney care. Where possible, the multidisciplinary team should include nephrologists, endocrinologists, obesity medicine physicians, cardiologists, kidney dietitians, bariatric dietitians, nurses, pharmacists, psychologists, and exercise professionals. Metabolic, kidney, and patient-reported outcomes, including diet quality, quality of life, physical function, and patient-reported experience measures, can provide valuable insights into physical and mental health and treatment satisfaction.[138,139] People living with obesity and CKD should have access to holistic structured assessment that incorporates components of physical, mental, and socioeconomic determinants of health.[139,140] Obesity is a key component of CKM syndrome (recognizing that the liver is connected to cardiovascular health and also affects metabolic functioning).[141,142] Providing education on CKM syndrome may enhance understanding and engagement in dual obesity and CKD management and support individualized goal setting.

Figure 5 depicts a multidimensional approach to obesity and CKD, including acknowledgment of broader contexts and optimal integration of a multidisciplinary team. Evidence has shown that person-centered care delivered by an appropriately trained multidisciplinary team can improve CKM risk factors, patient-reported outcomes, and patient-reported experience measures, leading to reductions in the risks of future CKM conditions and premature death.[75,143,144] Technology integration, such as clinical decision support systems, wearable devices, and mobile

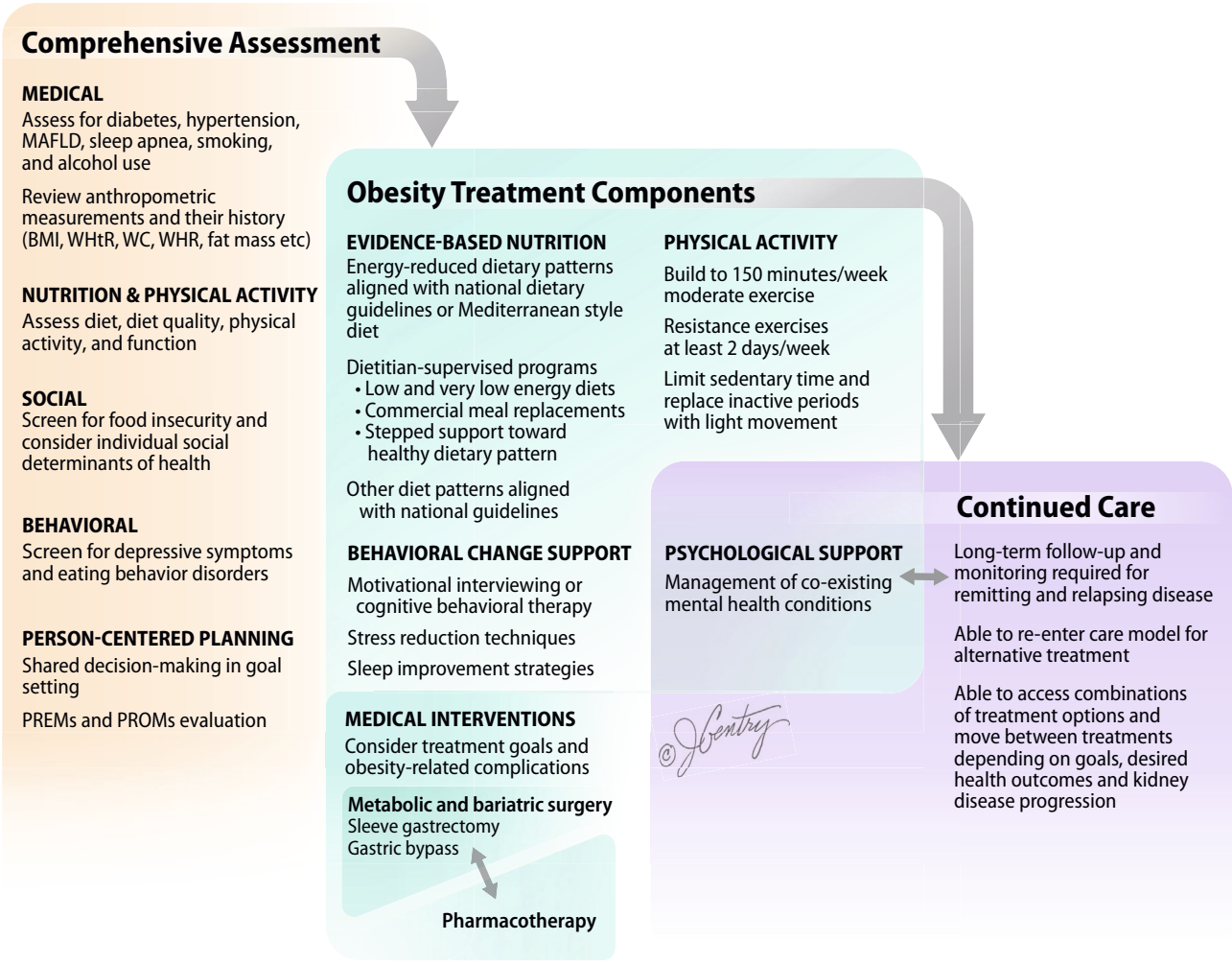

Figure 7 | Care model in people with chronic kidney disease (CKD) and obesity, including nonmedical, medical, and surgical interventions and the relationship between treatment options. All interventions include nutrition, physical activity, and behavior change, with additional psychological, surgical, and pharmacological treatment considered on the basis of comprehensive assessment. Consider using digital or virtual technologies and centralized expertise to train and support local teams in providing expert involvement in assessment, decision-making, and follow-up. BMI, body mass index; MAFLD, metabolic dysfunction–associated fatty liver disease; PREM, patient-reported experience measure; PROM, patient-reported outcome measure; UACR, urinary albumin-to-creatinine ratio; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio. © Jennifer N. Gentry.

applications, can enhance communications and timely referrals between primary and specialist care teams, empower self-management, and facilitate shared decision-making.[75,143,145] However, there are ongoing concerns with digital care, including data privacy and confidentiality, health literacy, accessibility, user-friendliness, and cost-effectiveness.[75,145] Precision medicine approaches incorporating genomic and phenotyping information to guide management are being advocated, although examples of effective care models remain to be demonstrated.[146–148]

To reduce health inequality in access to evidence-based interventions, especially in resource-limited settings, standardization of evaluation and management procedures is needed. Figures 6 and 7 propose an inclusive management framework for people with obesity and CKD.[149] The framework outlines a comprehensive evaluation followed by an individualized management plan including person-centered goal setting and the optimal integration of dietary modification, physical activity, pharmacotherapy, and surgical interventions. Its implementation will depend on the presence of CKM risk factors, available resources, and shared treatment goals. In all settings, dietary modification and physical activity interventions remain as foundation therapies for CKD and complement medical and surgical interventions for obesity.[90,150] Adopting a weight-neutral approach that focuses on health outcomes and health behaviors may be useful to support people who do not wish to focus on

weight *per se*. A structured care model that integrates evidence-based technologies and principles of precision medicine will enable person-centered decision-making and thus may offer a sustainable strategy for managing the complexity of obesity and CKD. To this end, public health policies that create a health-enabling ecosystem with the capacity to facilitate the implementation of this integrated obesity and CKD management framework, along with health economic evaluation, are eagerly awaited.

CONCLUSIONS AND FUTURE DIRECTIONS

Obesity and CKD are increasingly prevalent conditions that often coexist, presenting significant challenges for prevention and management. As highlighted throughout this conference, there is growing awareness that CKD may be present in individuals living with obesity, yet many questions remain regarding early detection, optimal screening strategies, and the most effective ways to assess obesity-related kidney risk. Addressing these uncertainties is critical to improving long-term outcomes, particularly given the increasing rates of obesity among children and young adults.

There is broad consensus that dietary changes, increased physical activity, and behavioral modifications form the foundation of obesity management in CKD. However, the most effective strategies for sustaining meaningful, long-term changes remain elusive. Pharmacotherapies such as GLP-1 RA offer substantial benefits, yet questions persist regarding their long-term safety, particularly for younger individuals and those with advanced CKD. Patients with a kidney transplant require careful consideration to avoid dehydration and to ensure the tolerability of these therapies alongside immunosuppressive regimens. Although RCTs in this area are unlikely, expert opinion and retrospective data may provide valuable guidance moving forward.

A multidisciplinary approach—incorporating nephrology, endocrinology, hepatology, and dietetics—will be essential in refining treatment strategies and expanding the evidence base. Notably, limited data exist on how successful interventions for weight loss affect kidney function, particularly in advanced CKD. Future research should explore whether targeted interventions can not only slow progression but potentially reverse kidney dysfunction, addressing whether it is ever too late to intervene.

The urgency of preventing obesity early in life cannot be overstated. The long-term metabolic and kidney consequences of early-onset obesity are profound, emphasizing the need for preventive strategies and early interventions. At the same time, significant gaps remain in our understanding of global epidemiology, treatment efficacy, and health care implementation, particularly in underrepresented regions.

Although many uncertainties remain, ongoing collaboration, research, and innovation will help strategies for managing obesity and CKD evolve, with the aim of improving patient outcomes across the lifespan.

APPENDIX

Additional Conference Participants

Radica Z. Alicic, USA; Urmila Anandh, India; Carla Maria Avesani, Sweden; Juan Jesus Carrero, Sweden; Juliana C.N. Chan, Hong Kong; Alexander R. Chang, USA; Ricardo V. Cohen, Brazil; Beatriz Fernández-Fernández, Spain; Sharlene A. Greenwood, UK; Mads Hornum, Denmark; Thomas H. Inge, USA; Trond Geir Jenssen, Norway; Vivekanand Jha, India; Holly Kramer, USA; Elaine Ku, USA; Kelly Lambert, Australia; Wells W. Larsen, USA; Adrian Liew, Singapore; Jayme E. Locke, USA; Andrea O.Y. Luk, Hong Kong; Magdalena Madero, Mexico; Johannes F.E. Mann, Germany; Enrique Morales, Spain; Jacinda M. Nicklas, USA; Irene L. Noronha, Brazil; Niels Olsen, Brazil; John Ortiz, USA; Michelle M. O'Shaughnessy, Ireland; Esteban Porrini, Spain; Jorge Rico Fontalvo, Colombia; Ivan Rychlík, Czech Republic; Naveed Sattar, UK; Laura Solá, Uruguay; Maria Jose Soler, Spain; Stella Stabouli, Greece; Paul E. Stevens, UK; Duane Sunwold, USA; Rita S. Suri, Canada; Irma Tchokhonelidze, Georgia; Matias Trillini, Italy; Yusuke Tsukamoto, Japan; Katherine R. Tuttle, USA; Angela Yee-Moon Wang, Singapore; Mai-Szu Wu, Taiwan.

DISCLOSURE

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