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CKJ Review

CKJ REVIEW

Approaches to patients with obesity and CKD: focus on nutrition and surgery

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ABSTRACT

Obesity is recognized as a public health challenge. During the last three decades, the global age-standardized prevalence increased from 8.8% to 18.5% in women and from 4.8% to 14.0% in men, with an absolute current number of 878 million obese subjects. Obesity significantly increases *per se* the risk of developing disability and chronic diseases, including chronic kidney disease (CKD). Specifically, obesity acts as a major, modifiable cause of CKD onset and progression toward kidney failure; as such, it is considered by the International Society of Nephrology a major health priority. This review analyses the effectiveness, safety and practicability of non-pharmacological anti-obesity interventions in CKD as the different patient phenotypes that may take advantage of personalized approaches.

Keywords: bariatric surgery, chronic kidney disease, ketogenic diet, lifestyle, obesity

EPIDEMIOLOGY OF OBESITY IN CKD

Obesity and risk of de novo CKD

During the last three decades, obesity increased worldwidw [1], and, accordingly, the risk of developing chronic diseases, including chronic kidney disease (CKD), increased too [2]. A systematic review and meta-analysis evaluated the risk of chronic kidney disease (CKD) onset in 630 677 individuals with normal renal function over 6.8 years; in obese subjects, the risk of developing low glomerular filtration rate (GFR <60 mL/min/1.73 m^2) and abnormal albuminuria (>30 mg/day) was, respectively, 28% and 51% higher versus non-obese subjects; the onset of CKD was also evaluated by comparing healthy (without metabolic syndrome) and unhealthy obesity; either subgroup resulted significantly associated, with 30% and 63% higher risk of CKD *de novo*, respectively, and with no difference between the two conditions [3]. These data are consistent with a recent meta-analysis that found a 29% higher risk of CKD onset in metabolically healthy obesity and overweight [4]. Obesity, being a major cause of CKD onset and progression have to be considered a major public health priority [5].

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Table 1: Prevalence of obesity in different settings of CKD.

CKD settings	Prevalence of obesity, %
CKD [7]	
Obesity Class I	22
Obesity Class II	11
Obesity Class III	11
Diabetes mellitus with CKD [9]	
Type 1	28
Type 2	49
DKD [9]	
DKD stage 1	54
DKD stage 2	46
DKD stage 3a	44
DKD stage 3b	44
DKD stage 4	47
DKD stage 5	44
ESKD [10]	
Female	44
Male	36
Age <45 years	43
Age 45–64 years	46
Age >64 years	33
KTRs [10, 11]	33–37

DKD, diabetic kidney disease.

Prevalence of obesity in CKD

Obesity is graded in three classes according to the body mass index (BMI) level, Class I: BMI 30–34.9, Class II: BMI 35–39.9 and Class III: BMI >40 kg/m^2; the abnormalities of body composition, however, may be complex and the BMI is inadequate to differentiate between muscle and fat masses and the body fat distribution. The prevalence of obesity in CKD is high throughout the entire spectrum of kidney disease [6]. Furthermore, according to the data from the 2023 report of the United States Renal Data System, the prevalence has increased over time among people with CKD; indeed, 42.4% had obesity in 2005–2008 with increased prevalence (50.2%) after 10 years [7]. Specifically, as evidenced in the 2011–2014 National Health and Nutrition Examination Survey, 21.9% of CKD patients had Class I, 11.1% Class II and 11.1% Class III obesity [8]. In patients with diabetic CKD, 28.4% of type 1 diabetes and 48.8% of type 2 diabetes patients were obese, with a similar distribution across CKD stages [9]. Finally, among end-stage kidney disease patients (ESKD), obesity has 39% prevalence with higher rates in women than men (44% vs 36%) and in young- and middle-age than elderly; among these obese patients, the rate of kidney transplant recipient (KTR) increased from 30.2% in 2008 to 37.4% in 2016 [10]. These data are coherent with the 44% increase in obesity prevalence in KTR over the last decades, with about one-third of patients being now obese [11] (Table 1).

Obesity and risk of CKD progression

Several studies have suggested the role of obesity in the progression of kidney disease in adults and adolescents [12–15]. In addition, unhealthy obesity seems to be related to a higher risk of ESKD [16]. Nonetheless, the role of obesity in the progression to ESKD is incompletely understood. A meta-analysis of four observational studies, enrolling CKD patients stages 3–5, did not find any significant risk of progression to ESKD for obesity Class I and II; in contrast, obesity Class III had a greater risk for ESKD [17]. A study including 3605 Asian CKD patients found a significantly increased risk of CKD progression (renal replacement therapy or 50% GFR decline) for BMI levels ≥27.5 and ≥30 kg/m^2 in CKD stages 1–3, but not stages 4–5 [18]. The role of obesity as independent risk factor for the progression of kidney disease in early CKD was confirmed in a cohort of autosomal dominant polycystic kidney disease patients with GFR >60 mL/min/1.73 m^2 [19]. A much larger meta-analysis including 91 607 participants, showed a J-shaped association between BMI and risk of CKD progression [40% estimated GFR (eGFR) decline, eGFR <10 mL/min/1.73 m^2 or ESKD], with 17% risk increase at BMI 35 kg/m^2 versus BMI 25 kg/m^2 [15].

Obesity and risk of death and cardiovascular disease

Observational studies have reported contradictory findings about the association between obesity and risk of mortality and cardiovascular disease in patients with renal disease. In hemodialysis, some studies have suggested an "obesity paradox," where being obese seems to be protective against mortality [20, 21]. Other studies reported a J-shaped association between obesity and mortality, with a significantly higher risk of death in severe obesity [22].

In non-dialysis CKD 3–5, overweight and obesity Class I were associated with lower mortality, while Classes II–III were not associated with different mortality risks [17]. A systematic review and meta-analysis on 165 cohort studies from non-dialysis CKD, dialysis and kidney transplantation patients, including more than 1.5 million participants, showed that for each 1 kg/m^2 BMI increase, the risk of death decreased by 1% in CKD stages 3–5 and 3% in hemodialysis; no significant relationship was found in peritoneal dialysis and KTR. For the cardiovascular mortality, only in hemodialysis patients was there a significant 4% risk reduction for each 1 kg/m^2 BMI increase [23]; this meta-analysis, however, was limited by the presence of low-quality studies and short follow-up. In opposite, a meta-analysis in CKD found that not only higher BMI but also higher waist circumference heralded higher mortality risk; in particular, the death risk for BMI 35 kg/m^2 was 17% significantly greater than for BMI 25 kg/m^2 and, after excluding the first 3 years of follow-up, this risk became higher (45%) [15]. Data of outcome in obese CKD 1–2 are sparse. A recent cohort study in overweight and mild–moderate CKD, showed that obesity without any components of metabolic syndrome does not increase the risk of cardiovascular complications or progression to ESKD; in contrast, each additional metabolic abnormality, irrespective of BMI, increases the risks [24].

Obesity and risk in ESKD

Observational studies have shown in ESKD patients, the presence of obesity limits the access to kidney transplantation; in a prospective cohort study from a ESRD population, a BMI >30 kg/m^2 at the start of dialysis treatment was associated with lower likelihood of receiving kidney transplant [25]. Notably, in KTRs, two meta-analyses documented that BMI >30 kg/m^2 significantly increases the risk of death, delayed graft function and allograft loss [26, 27].

Summary

Obesity represents a major cause of onset and a key risk factor for progression of CKD as diabetes and hypertension. Similar, obesity acts as a main factor for ESKD, cardiovascular disease and mortality in CKD. The burden of the obesity–CKD association becomes even more severe when considering that the prevalence of is not only high but it is also growing further.

Therefore, it is now mandatory to elevate the awareness and to consider the prevention and treatment on obesity in CKD as an absolute priority; this is emerging a novel pillar in the comprehensive treatment of CKD.

EFFECTS OF WEIGHT REDUCTION IN CKD

Weight loss interventions in CKD aim at increasing insulin sensitivity, ameliorating glucose and lipid metabolism, avoiding ectopic lipid deposition, improving the control of arterial blood pressure, and reducing oxidative stress and inflammation [28]. These effects have potential long-term cardiorenal advantages, mediated by attenuation of glomerular hyperfiltration, corrections of cardiovascular risk factors and reduction of excessive activity of the renin–angiotensin–aldosterone system [29]. On the other hand, according to the "obesity paradox," the higher BMI may be protective in CKD, mainly in ESKD [30]. However, we should be aware that observational studies of obesity and survival violate the consistency of potential outcomes, a necessary condition for meaningful causal inference [31]; first, they do not specify the interventions on BMI that are being compared; second, different methods to modify BMI may lead to different counterfactual mortality outcomes, even if they lead to the same BMI value in a given person. Consistency violations compromise our ability to estimate ill-defined causal effects.

Overall, in the management of obesity in CKD, it is essential to find a good balance between the competing risks related to undernutrition in the short term and overnutrition in the long term [32]; the patient phenotype and the characteristic and intensity of interventions may play a significant role in the effectiveness and safety of weight-losing approaches in CKD. Any strategy in CKD should be, therefore, individualized and closely monitored.

Among the most recent and extensive studies exploring hard outcomes related to any intervention aimed at losing weight in CKD patients, a meta-analysis of 12 randomized controlled trials (RCTs) involving 942 obese patients with type 2 diabetes, 500 on low-carbohydrate or keto-diet (KD) and 442 on a control diet reported no effect of the dietary intervention on changes of creatinine clearance and albuminuria [33]. However, the RCTs were heterogeneous for age, sex, diet composition and duration, and the prevalence of CKD stage was missed.

A retrospective cohort study, including 2004 patients with severe obesity and CKD stage 1–3 who were prescribed a KD, evaluated the predicted changes of eGFR according to the amount of weight reduction (>10%, 5–10%, <5%). Over 1-year observation, the eGFR decreased by 4–6 mL/min in CKD stage 1, with or without type 2 diabetes, and this finding was attributed to the reduction of glomerular hyperfiltration due to weight loss and better metabolic control; in CKD stage 2, the model predicted for all the categories of weight change an eGFR increase by 3–4 mL/min/1.73 m^2 in patients without diabetes, and by 1–3 mL/min/1.73 m^2 in patients with diabetes; this result was explained by the rapid weight loss which leads to better control of blood pressure and glucose levels; in CKD stage 3 without diabetes and adequate adherence to low-carb diet, the eGFR improved by 3 mL/min/1.73 m^2 while in those with diabetes, the eGFR remained unchanged across all categories of weight change [34].

A Mendelian randomization analysis tried to identify the weight reduction 1 year after bariatric surgery, minimizing renal function decline. Investigators studied a Canadian cohort of 5337 non-CKD individuals of young/middle age, predominantly women (>80%), obesity Class III, 50% diabetics [35]. A 30%–40% weight loss was associated with a slower eGFR decline as compared with either lower or higher weight loss in patients with and without diabetes. These findings may be explained by the effects of weight loss on reducing arterial pressure and serum glucose; however, the possible loss of lean body mass dependent on rapid weight loss may be associated with lower creatinine production, leading to an overestimation of eGFR.

A recent study explored the factors associated with health risks while losing weight in CKD [36]. Some 2831 CKD stage 3 patients, 53% males, obesity Class II, age 61 years, underwent interventions to maintain or lose weight. During 6.8 years of follow-up, the subjects with a rapid decline of body weight (irrespective of the intention to lose weight) showed an early decline of serum albumin, an increase in systolic blood pressure and higher mortality; interestingly, a secondary analysis showed that changes in fat-free mass (FFM) modified the association between BMI trajectories and death; the most common profile was characterized by a slow decline in BMI and FFM and was associated with the lowest mortality; meanwhile, the pattern with early substantial BMI decline associated with a steep FFM decline had the highest mortality. Overall, in obese CKD, a steep weight loss with concomitant muscle mass loss implies a high risk of death. It can be therefore argued that in CKD the preservation of lean body mass might be a marker of healthy weight loss. Hence, all weight-loss strategies in CKD should include monitoring and interventions that preserve or even improve muscle mass and function; under this hypothesis, healthy diet and exercise training are essential to enhance health in overweight and obese CKD patients [37].

Altogether, the commonly available information on individual characteristics, such as BMI classes, CKD stages, age and disease, cannot predict health outcomes while losing weight in CKD because they do not allow the identification of a specific phenotype. Conversely, the modality of the intervention seems more important; specifically, a progressive, not steep, body weight decline and the preservation of lean body mass can herald a lower health risk.

NON-PHARMACOLOGICAL TREATMENT OF OBESITY IN CKD

The complexity of the burden of obesity in CKD highlights the importance of considering the treatment of obese patients within a multidisciplinary strategy, a "multimodal approach" with different and complementary methods, increasing in intensity according to the severity of disease (Fig. 1). Lifestyle and dietary treatment represent the first line of intervention and play a central role to prevent the CKD progression and metabolic derangements.

A multidisciplinary approach involving the collaboration of diverse health professionals, including nephrologists, nutritionists and dieticians, must undoubtedly have a "patient-centric" outlook to be effective [38]. At the same time, the nutritional approach, although following the guidelines recommendations, should retain an "obesity-centric" view, that is, considering obesity not merely as a collateral clinical condition but as a determining factor that plays a crucial role in the progression of the disease (Fig. 2).

Nutritional treatment

Low-energy intake coupled with increased physical activity are the mainstay for losing fat mass while preserving lean body mass. Beyond traditional dietary approaches, the ketogenic diet may be useful in selected obese CKD patients, such as those

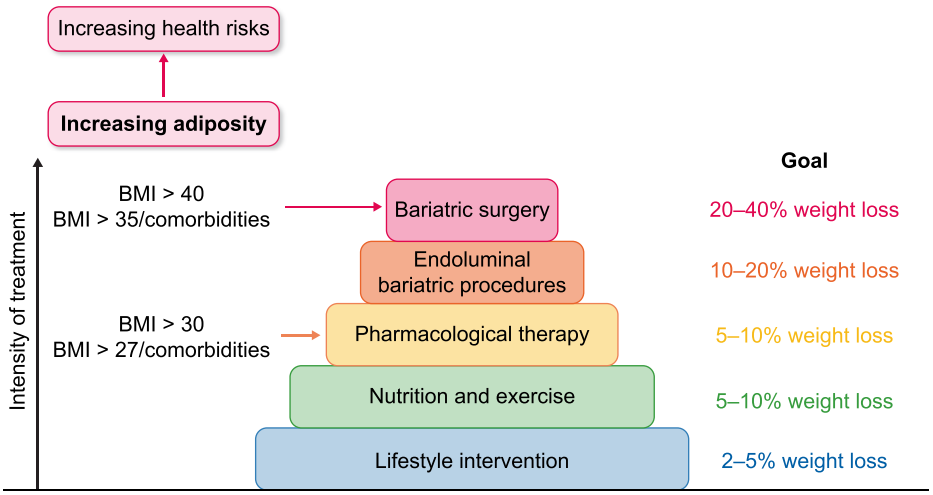

Figure 1: Obesity treatment pyramid.

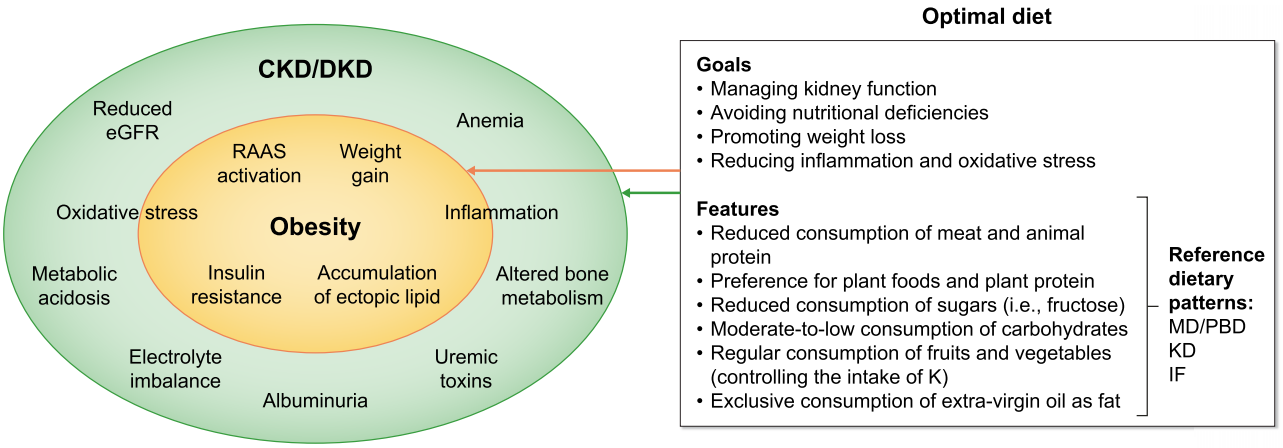

Figure 2: "Obesity-centered" approach as the optimal nutritional strategy for patients with obesity and CKD. RAAS, renin–angiotensin–aldosterone system; K, potassium.

where weight loss is mandatory to be accepted on the kidney transplant list or to improve mobility or when other strategies to lose weight have been unsuccessful.

The "patient-centric" and "obesity-centric" visions (Fig. 2) should guide towards devising the optimal diet for the obese patient with CKD. Diets must be appropriately individualized based on the characteristics and needs of the individual, respecting the recommendations of the guidelines for the management of renal disease and, at the same time, treating obesity as the primary outcome. Overall, such an optimal diet should combine the main features of dietary patterns that have proven effective in the management of this class of patient:

(i) reduction in animal protein intake, preferring vegetable proteins, to avoid glomerular hyperfiltration;
(ii) reduction in simple sugars and moderate–low consumption of carbohydrates to favor weight loss, glycemic control and reduction of oxidative stress and inflammation;
(iii) regular consumption of fruit and vegetables to allow optimal fiber, antioxidants and mineral intake; and
(iv) exclusive use of olive oil as fat, for gaining benefits from the anti-inflammatory properties and avoiding the intake of saturated and trans fatty acids.

Evidence on the nutritional management of patients with obesity and CKD is limited, resulting in a lack of specific practical guidelines. This gap of knowledge implies the need to consider several weight-loss dietary interventions commonly used for the treatment of obesity in the general population and to carefully evaluate the risk–benefit ratio for each of them to establish their safety and, consequently, their potential use in the case of CKD (Fig. 3).

An optimal nutritional intervention for patients with obesity and CKD should consider qualitative and quantitative aspects. Besides calories and optimal protein intake according to the CKD stage, diets should avoid higher consumption of meat and animal protein due to their negative impact on kidney function [39]. This objective justifies the suggestion of plant-based diets (PBDs) in CKD [40]. Among the PBDs, the Mediterranean diet (MD) is a valid nutritional strategy for CKD patients due to its role in preserving renal function [41], and preventing CKD or reducing the disease progression in patients with overt CKD [42, 43]. Of note, MD is effective in promoting weight loss and managing obesity-related comorbidities [44–46], making this dietary pattern suitable for patients with obesity and CKD. Indeed, MD promotes more significant and persistent weight loss than control

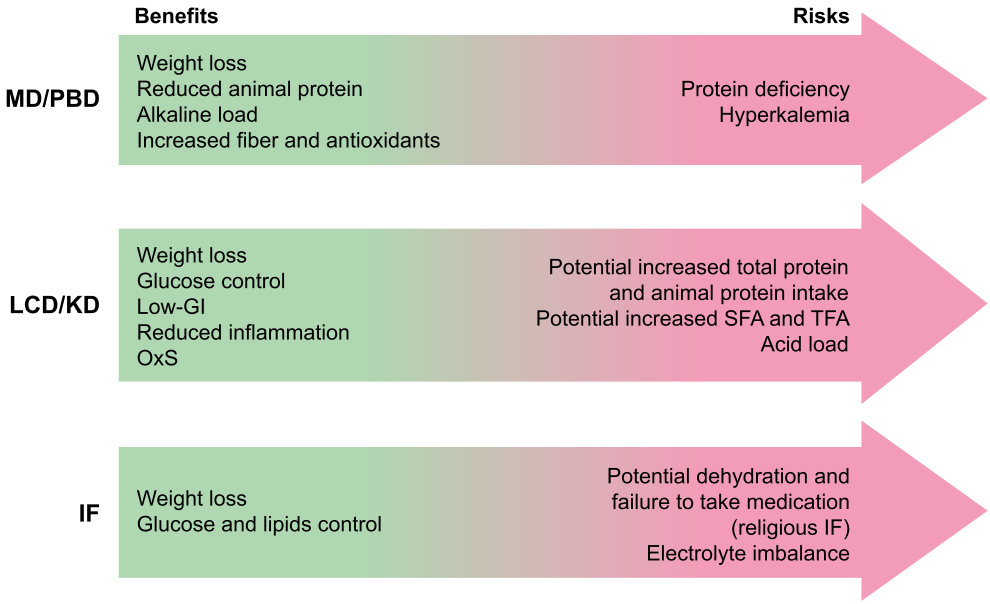

Figure 3: Main risks and benefits of various dietary patterns considered for the management of patients with obesity and CKD. LCD, low-carbohydrates diet; SFA, saturated fatty acids; TFA, trans fatty acids.

diets, including low-fat diets [47–49]. It is necessary, however, that MD be appropriately designed according to each patient's individual needs to avoid the occurrence of some common risks associated with PBDs, such as hyperkaliemia or protein deficiency [39, 50].

The role of carbohydrates is a crucial issue to be considered in prescribing the optimal diet for patients with obesity and CKD. Apart from the well-established negative effect of added sugars on renal function [51], the potential benefit of reduced carbohydrate intake is generally accepted [39]. This paved the way for the use of KD in these patients. KDs, characterized by a standardized carbohydrate intake <30–50 g daily and a lipid intake that can reach 70%–80% of calories, have been reported to promote significant beneficial effects, including weight loss [51–53]. However, one of the main concerns with these diets in CKD is the relatively higher protein intake that may impair kidney function. Nonetheless, the protein content of KDs is 0.8–1.2 g of high-biological value protein per kg of ideal body weight [54, 55], resulting in a normal-protein diet that can be easily adapted for CKD stages 1–2 patients, but not for stages 3–5, for whom a protein restriction is recommended and a KD is contraindicated [56, 57]. Hence, in CKD stages 1–2, at least for proteins, KDs are not contraindicated. Interestingly, RCTs on CKD patients have not reported alteration of the kidney function following KDs [58, 59], suggesting that this nutritional approach can be considered a safe and valid tool for obtaining weight loss [39], at least in the early phases of CKD [60]. Notably, worsening of hyperfiltration dependent on the higher protein intake can be counteracted at least in part by concomitant therapy with gliflozins [61]. Concerns remain on the impact of the high lipid content on the control of dyslipidemia related to CKD; few preliminary data do not evidence such complication, nonetheless, a close lipid monitoring is suggested and this issue has to be addressed in the future.

Other possible nutritional approaches include intermittent fasting (IF), which has been recognized as a strategy to achieve weight loss and possibly improvement in metabolic parameters by improving dietary compliance in a specific class of subjects [62]. It should be noted, however, that the impact of IF on renal function in patients with CKD is controversial due to the lack of controlled studies; evidences on religious fasting (Ramadan) have shown that abstaining from water and drug intake can result in volume depletion and acute renal damage [39].

The effects of dietary and lifestyle interventions in obese CKD subjects are reported in Table 2 [63–74]. Most studies are of small sample size, the CKD stage is not reported or limited to stage 1–3, the obesity class is mainly unknown or different within the single study, dietary interventions are different, length of intervention variable from few months to 1–2 years, and the primary aim is generally only the weight reduction. The obtained weight/BMI reduction and the achieved reduction of proteinuria were variable as the trajectories of renal function, mostly improving, sometimes reducing, mainly in early CKD. Data are too heterogeneous to conclude the best approach to the individual patient phenotype.

Surgical treatment

In recent decades, many studies have compared the surgical and medical treatment for obesity in inducing and maintaining weight loss, improving obesity-related comorbidities in the long term and reducing mortality [75–79]. Accordingly, eligibility criteria for bariatric surgery (BS) were established [80–82]. Patients with obesity Class II–III are the ideal candidates to bariatric surgery when other interventions have failed (Table 3).

Different bariatric procedures have been proposed (Fig. 4). Laparoscopic sleeve gastrectomy (LSG) and laparoscopic Roux en Y gastric bypass (LRYGB) are the most commonly performed worldwide due to their safety, metabolic efficacy and activity on hunger and satiety driven in part by the impact on gut hormones rather than pure nutrient restriction. LSG consists of the tubulation of the stomach by resection; LRYGB consists of creating a small gastric pouch connected to the small bowel, with an alimentary limb of 100–120 cm and a bilio-pancreatic limb of 100 cm. These procedures allow a 50%–60% loss of excess weight at 5 years and variable remission rates or improved

Table 2: Most relevant studies on the effects of dietary and lifestyle interventions in subjects with obesity and CKD.

Type of study	No. of subjects	CKD stage	BMI (kg/m^2)	Intervention (diet)	Outcomes/ endpoints	Main results and comments	Ref.
				Hypocaloric diet			
P	37	n.d.	36.1 ± 3.2 (no-DM, $n = 7$); 47.6 ± 4.8 (GI, $n = 6$); 39.1 ± 1.7 (DM, $n = 24$)	4-week very hypocaloric diet (500 kcal/day, 50 g carbohydrate/day)	Body weight Proteinuria Albuminuria	Significant reduction BW: no-DM = 14.7%; GI = 18.2%, DM = 13.7% Significant reduction proteinuria (62%) and albuminuria (56%) only in DM The CKD stage was not defined The sample size by group is disproportionate Large difference in BMI by group Large range BMI, no stratification for BMI classes	[63]
P	24	DKD (CKD stage n.d.)	33.0 ± 1.6	1-year hypocaloric diet (1400 kcal/day)	eGFR Albuminuria Proteinuria	Significant reduction BMI (21.2%), proteinuria (51.3%), albuminuria (32.0%) Significant increase in eGFR (22.7%) Dietary intervention, baseline characteristics of participants, BW variations, CKD stage are missing	[64]
P	22	DKD (CKD stage n.d.)	30.4 ± 5.3	4-week very hypocaloric (740 or 970 kcal/day; 11–19 kcal/kg), normal-protein (0.9–1.2 g/kg/day) diet, partly supplemented with formula diet	Body weight sCreatinine proteinuria	Significant reduction BW (7.3%), sCreatinine (24.1%), proteinuria (54.1%) CKD stage not defined Visceral and subcutaneous fat area significantly reduced by 18.1% and 11.7%, respectively	[65]
R	9	Proteinuria (CKD stage n.d.)	37.1 ± 3.1	12-month hypocaloric diet (1000–1400 kcal/day), no protein restriction	BMI Proteinuria	Significant reduction BMI (12.1%), proteinuria (86.2%) CKD stage, dietary characteristics, body composition are missing	[66]
				Low-carbohydrate diet			
R	2004	1–3	40 (35–47)	Low carbohydrate (<20 g/day), high fat, relatively high-protein diet	Body weight eGFR	BW loss: ≥10% = 16%; 5 to <10% = 14%; 0 to <5% = 17% subjects BW loss by CKD stage: stage 1: ≥10% = 12%, 5 to <10% = 13%, 0 to <5% = 18% stage 2: ≥10%=18%, 5 to <10% = 15%, 0 to <5% = 16% stage 3: ≥10% = 22%, 5 to <10% = 16%, 0 to <5% = 16% eGFR: stage 1: decreased by 4–6 mL/min/1.73 m^2 stage 2–3: unchanged or improved not reported: - characteristics and duration of dietary intervention - adherence to diet - time to achieve weight loss - variations of body composition	[34]
P, Ob, NR	38	Stage-2	33.8 ± 5.8	5-step VLCKD with replacement meals Diet protocol: 450–800 kcal/day; 20–50 g carbohydrate/day; 1–1.4 g protein/kg IBW/day; 15–30 g lipids/day Duration: 14.9 ± 8.5 weeks (steps 1–2, steps 3–5: half/half time)	Body weight Body composition Blood pressure Metabolisms Liver function kidney function	Significant reductions body weight (16.3%), fat mass (32.5%), muscle mass (8.4%), SBP (4%), DBP (5%), sCreatinine (5.4%) Significant increase eGFR (7.7%) Sodium, potassium, total protein, albumin and urinary protein, unchanged Real-life study No control group and/or randomization	[59]

Table 2: Continued

Type of study	No. of subjects	CKD stage	BMI (kg/m^2)	Intervention (diet)	Outcomes/ endpoints	Main results and comments	Ref.
P	6	DKD (eGFR = 21 [17–35])	38.6 (32.8–43.7)	12-week VLCKD with replacement meals Diet protocol: 800 kcal/day; <50 g carbohydrate/day; at least 75 g protein/day	Body weight Proteinuria Albuminuria eGFR	Significant reduction body weight (12%) Significant increase eGFR (4.7%) Not significant reduction albuminuria and proteinuria Very small sample size does (not conclusive)	[67]
Comparison of different dietary interventions							
R, C	318	Stages 1–3	30.9 ± 3.17 (stages 1–2, *n* = 219); 30.9 ± 3.4 (stage 3, *n* = 99)	2-year calorie-restricted low-fat diet, calorie-restricted MD or non-calorie-restricted low-carbohydrate diet	Microalbuminuria eGFR	Significant increase eGFR: +5.3% low-carbohydrate diet, +5.2% MD, +4% low-fat diet Significant decrease microalbuminuria: -24.8 ± 51.6 mg/mL Characteristics dietary interventions not reported Men prevalence: CKD 1–2 = 80%; CKD 3 = 99% Variation BW and body composition not reported	[68]
R	30	Proteinuric diseases	33 ± 3.5, diet group (*n* = 20); 34.3 ± 5.7, control group (*n* = 10)	5-month calorie-restriction diet (–500 kcal/day) vs standard diet Nutritional characteristics of calorie-restriction diet: carbohydrate = 55–60%; fat = 25%–30%; protein = 1–1.2 g/kg/day Nutritional characteristics of standard diet: no modification usual diet, except to provide 1–1.2 g/kg/day protein intake	Proteinuria Serum creatinine Body weight	Significant reduction BMI (4.2%) and proteinuria (32.14%) in experimental group No significant change sCreatinine in experimental group Significant increase BMI (2%), sCreatinine (12.5%), proteinuria (16.7%) in control group CKD stage not defined, no stratification BMI Body composition not evaluated	[69]
R	45	n.d.	36.7, diet group (*n* = 21); 35.4, control group (*n* = 24)	12-month moderate-protein vs standard-protein dietary intervention Nutritional characteristics of moderate-protein diet: protein = 30%; fat = 30%; carbohydrate = 40% (protein intake: 90–120 g/day) Nutritional characteristics of standard-protein diet: protein = 20%; fat = 30%; carbohydrate = 50% (protein intake: 55–70 g/day)	Weight loss eGFR Proteinuria	No different weight loss (–9.7 ± 13.4 kg vs –6.6 ± 7.1 kg) and proteinuria between intervention and controls Significant improvement eGFR (4 mL/min) in 1–3 CKD Weight loss *per se* improves renal function independently of protein intake Heterogeneous population: wide ranges BMI and eGFR; small sample size; short duration; inconclusive	[70]
Lifestyle intervention (diet + exercise)							
OL, P, NR	32	3–5	35.7 ± 4.5	24-month program: low-fat calorie-reduced renal diet + regular exercise + behaviour therapy + orlistat (120 mg, thrice daily) Nutritional characteristics of dietary intervention: fat intake <70 g/day; protein intake adapted to CKD: stage 2–4 = 1.0 g/kg IBW/day; stage CKD 5D = 1.2 g/kg IBW/day	Body weight Kidney transplant wait listing	Controls were subjects on usual-care Significant weight loss (8%) and less reduced eGFR in intervention vs control group 35% of CKD 5D patients were accepted for kidney transplant list No randomization, no definition contribution of each treatment (diet, exercise, behavioural, drug) Inflammation markers, body composition, nutritional status not monitored Small sample size No stratification for CKD stage and/or obesity grade	[71]

Table 2: Continued

Type of study	No. of subjects	CKD stage	BMI (kg/m^2)	Intervention (diet)	Outcomes/ endpoints	Main results and comments	Ref.
P, NR	44	2–4	35.7 ± 4.5	12-month program: hypocaloric diet (–500 kcal/day) + exercise + orlistat (120 mg thrice daily)	Body weight Waist circumference eGFR	Controls were subjects on standard-care Significant reduction body weight (6.9%), waist circumference (11.4%), eGFR (20%–8%) with intervention Same limitations of the study [71]	[72]
P	63	ORG	30.8 ± 2.9	24-month calorie restriction diet (–500 kcal/day) + exercise Diet characteristics: 500 kcal daily reduction respect to usual diet; 55%–60% carbohydrate; 20%–30% fat; 15% protein Exercise characteristics: at least 60 min aerobic exercise at least thrice weekly	BMI Proteinuria	Significant reduction BMI (9.2%) and proteinuria (51.3%) in 43% of participants The protein intake of dietary intervention not reported	[73]
R	122	3–4	31–36	4-month/4 groups: calorie-restriction diet + aerobic exercise (n = 30); calorie-restriction + usual activity (n = 28); usual diet + aerobic exercise (n = 27); usual diet + usual activity (n = 26) Nutritional characteristics of the dietary intervention: 10%–15% calorie-restriction	Body weight Body composition eGFR	Hypocaloric diet + exercise and hypocaloric diet alone statistically significant reduction body weight and body fat No effect of aerobic exercise alone No significant change of eGFR in all groups	[74]

DM, diabetes mellitus; GI, glucose intolerance; DKD, diabetic kidney disease; BW, body weight; BP, blood pressure; C, controlled; DBP, diastolic blood pressure; IBW, ideal body weight; MC, multi-centric; NR, non-randomized; n.d., not-defined; ORG, obesity-related glomerulopathy; Ob, observational; OL, open label; P, prospective; R, randomized; SBP, systolic blood pressure; VLCKD, very low-carbohydrate keto diet.

obesity-related comorbidities. Further options are the "endoluminal bariatric procedures" which are performed by entero-endoscopy and include gastric occupying devices (intragastric balloons), endoscopic sutures, gastroplasties (endo-sleeves) and endoscopic "bypass" [83]. Usually, endoluminal bariatric procedures are offered to obesity Class I in addition to pharmacological therapy, in case of failure of non-surgical interventions, in patients not eligible for conventional bariatric surgery (extreme ages, surgical risk, patients who refuse surgical treatment).

Given the negative impact of obesity on kidney function and outcomes and the limited efficacy and feasibility of lifestyle modifications alone or drug treatment in CKD patients with obesity Classes II–III, bariatric surgery could be an option also in these patients. The objective of bariatric surgery in the CKD population (when the other approaches are ineffective or not practicable) should be:

(i) preserve the kidney function decline;
(ii) prevent the CKD related complications and progression to ESKD;
(iii) reduce the mortality;
(iv) facilitate the access to kidney transplant programs in advanced CKD.

Preserve kidney function

A recent meta-analysis, including 49 studies and 8515 patients, has summarized the impact of bariatric surgery on renal function; BS significantly increased eGFR in patients with CKD over the 6–12 months following surgery [84]. A further meta-analysis—24 studies in CKD stage 2–3, 2126 patients with Class III obesity—evaluated albuminuria and proteinuria after BS; the pooled risk ratio versus baseline was reduced for albuminuria by 42% and proteinuria by 31%, allowing to hypothesize that in CKD the BS may prevent decline in renal function over the long term [85]. A later meta-analysis in 2145 type 2 diabetes mellitus patients who underwent BS compared the change in albuminuria with the changes in BMI; the study did not disclose any correlation, concluding that metabolic surgery can improve diabetic kidney disease independently of weight loss [86]. Finally, an RCT compared the effect of LRYGB versus medical treatment on proteinuria in patients with CKD stage 1, diabetes mellitus type 2 and obesity Class I; the remission of albuminuria occurred in 55% of patients on the best medical treatment against 82% of patients after LRYGB, concluding that BS is more effective than the best medical treatment for remission of albuminuria in early CKD with type 2 diabetes and obesity [87].

Prevent CKD-related complications and progression to ESKD

A recent observational, controlled, long-term study comprehensively evaluated benefits and risks of BS (two-thirds LSG, one-third LRYGB) in 19 patients with CKD stage 3–4 and obesity Class III versus 38 matched controls with normal renal function [88]. During 5-year follow-up, the excess weight loss was far above 50% for all subjects and was comparable among groups at 1 and 5 years, the eGFR improved significantly at 1 year, diabetes disappeared in 42% of CKD and 50% of controls, while hypertension remained unchanged in either group even though the number of antihypertensive drugs decreased. Overall, in CKD stage 3–4 patients with obesity Class III, the bariatric surgery was effective and safe in the long term.

Table 3: Therapeutical approach for obesity according to severity of disease.

	Lifestyle intervention	Pharmacologic therapy	Endoluminal bariatric procedures	Bariatric surgery
Class I obesity	x	x	x	
Class II obesity	x			x
Class III obesity	x			x

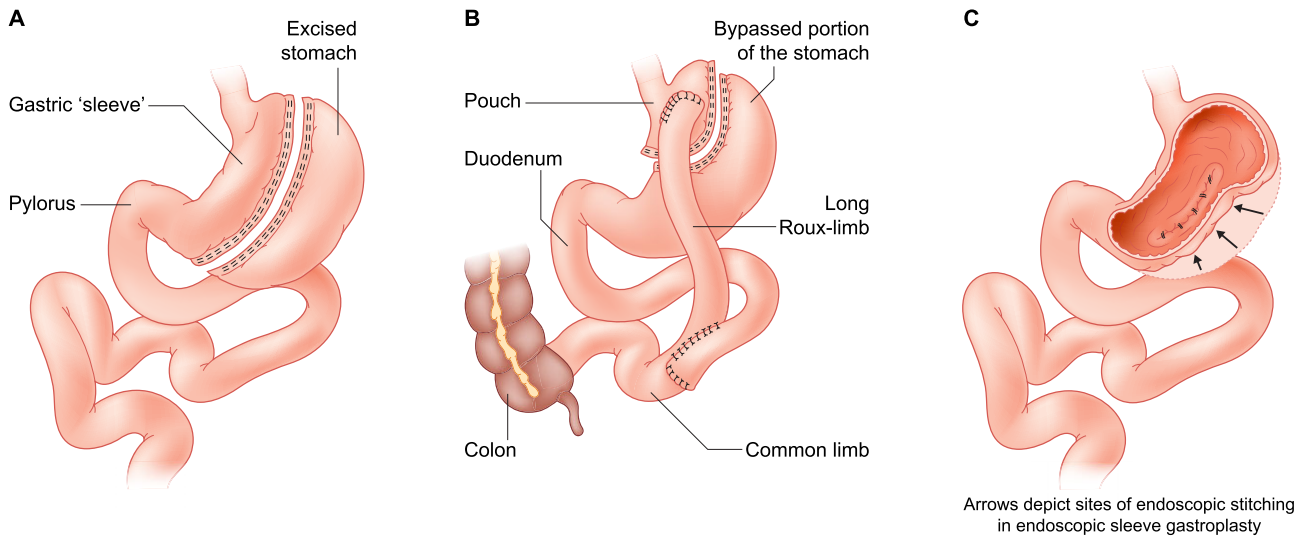

Figure 4: Laparoscopic bariatric surgery: (**A**) LSG; (**B**) LRYGB. Endoluminal bariatric: (**C**) endoscopic gastroplasty "endo-sleeve" (arrows depict sites of endoscopic stitching in endoscopic sleeve gastroplasty).

Reduce mortality

Recent studies in CKD patients (stages 3–5 or dialysis) have focused on safety and hard outcomes. A retrospective cohort study based on the USRDS registry 2006–2015 reported that the adjusted all-cause mortality in dialysis patients with obesity Class II–III treated with BS ($n = 1597$) was 31% lower compared with matched non-surgical controls on usual care ($n = 4750$) [89]. At 5 years, all-cause mortality was 25.6% for BS and 39.8% for controls with 31% risk reduction; cardiovascular deaths were 8.4% versus 17.2% with 49% risk reduction; conversely, a higher rate of kidney transplant rate was observed in BS group (33.0 vs 20.4%). The surgical techniques were LSG in 45.1%, LRYGB in 41.6%, laparoscopic gastric banding in 12.8% and duodenal switch in 0.4%.

In non-dialysis CKD stage 3–5 patients who underwent BS, the risk of death at 5 years was 79% lower than matched controls. Additionally, in the sub-setting of patients who underwent BS and reached ESKD, the early mortality rates at 30 and 90 days were low and similar to those of matched BS patients without CKD; furthermore, BS patients who reached ESKD were more likely to receive a kidney transplant [90].

Kidney transplant programs

A major obesity-related issue in advanced CKD is the access to transplant programs that are limited due to the increased risk of graft loss and delayed graft function. The BMI cut-off to access the kidney transplant list differs by transplant center; usually, patients with BMI >35 kg/m^2 are excluded, and many of these subjects try to achieve the target BMI by lifestyle modification and pharmacological therapy. Available data on the effects of pre-transplantation bariatric surgery are derived from low-quality and short-term studies; though limited, results show a lower rate of graft loss and mortality along 5 years in patients who underwent BS before kidney transplantation, but these data have to be confirmed [91].

An additional important issue linking obesity and kidney transplant is represented by the obese living kidney donors. BS may be a valid option to facilitate the admission of donors to the transplant program. A recent systematic review showed that obesity increases the risk of ESKD among living donors [92]. In these conditions, weight loss can allow obese living kidney donors to be suitable candidates and protect their residual kidney. The candidate is re-evaluated 6–12 months after surgery, and admitted to the transplant program once stable body weight persists for at least 3 months.

Surgical technique in CKD

There is no recommendation about the preferred modality of bariatric procedure in CKD; each bariatric center offers different procedures according to its own expertise. Sleeve gastrectomy could be a prime option for CKD patients [93]. Evidences on endoluminal bariatric procedures in CKD lack; nonetheless, endoluminal techniques are appealing for their low invasiveness, operative risk and reversibility and endo-sleeve may represent a first-choice option for CKD patients not eligible for bariatric surgery or with Class I obesity [83, 94].

CONCLUSIONS

Several therapeutic options may be effective and safe to treat obesity in patients with CKD, even though the optimal approach remains unclear. The strategy may differ according to the stage

Table 4: Obesity and CKD: from epidemiology to therapeutical approaches.

Epidemiology facts
- Obesity Class II–III in any CKD stage are at high risk of progressive CKD, mortality and limited access to kidney transplantation
- Effective reduction of body weight for early to moderate CKD improves proteinuria and does not impair renal function
- Excessively rapid body weight loss may impair lean body mass (body composition must be closely monitored during any intervention for weight loss)

Intervention strategies
- Lifestyle intervention: recommended for all overweight and obesity patients
- Diets: hypocaloric, healthy and ketogenic can be chosen according to the patient's preference and adapted for better metabolic control
- Anti-obesity drugs: can precede surgery or be associated with endosurgery in patients with BMI >27 kg/m^2 and comorbidities as in patients with obesity Class I
- Bariatric surgery: safe, reduces mortality, favors access to kidney transplant in CKD stages 3–5 and obesity Classes II–III within a multidisciplinary approach
- Endoluminal bariatric procedures: promising techniques in terms of safety and efficacy (endoscopic gastroplasty "endosleeve") in the following conditions:
  - obesity Class I in addition to medical therapy or in the case of therapy failure
  - candidates to bariatric procedures not eligible for surgery
  - patients refusing surgical strategies

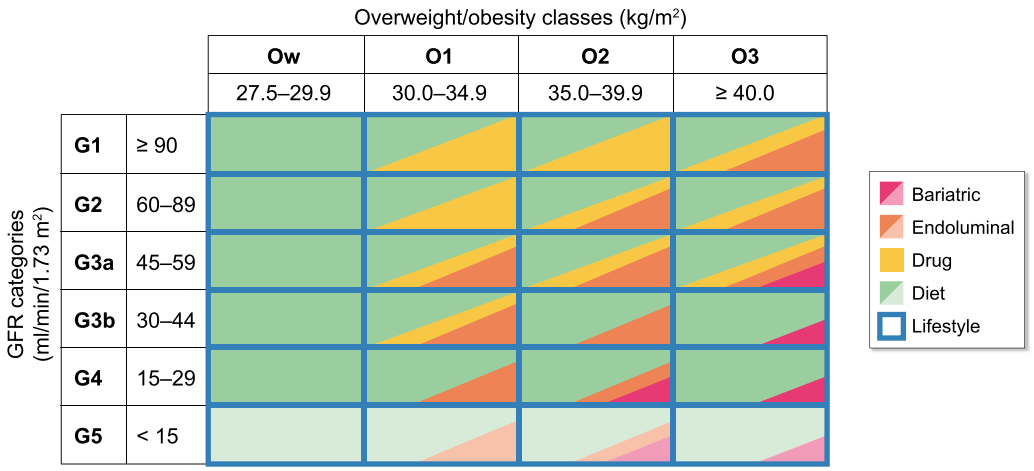

Figure 5: Integrated approach to manage weight losing in patients with overweight (OW) and obesity and CKD according to disease stage (G) and degree of obesity (O) (light colors of interventions in G5 means need of case-by-case evaluation).

of kidney disease, the Class of obesity, the desired target weight and whether the patient is a candidate for a kidney transplant. Due to the intrinsic nature of CKD, most patients are in dynamic conditions, moving across stages and changing the degree of comorbidities. Therefore, a "one-size-fits-all" recommendation to lose weight in this population cannot be drawn. Nonetheless, evidence collected to date in terms of epidemiology and intervention allow to suggest the best individual strategy (Table 4).

PERSPECTIVES

Evidence on interventions to lose weight in non-dialysis CKD overweight/obese patients are not yet conclusive; meanwhile all the available approaches are improving. Any singular, specific approach (physical activity, diet, drugs, surgery) induces some weight loss with respect to usual care, usually of small entity, except surgery [95]. Recently, the glucagon-like peptide 1 (GLP-1) receptor antagonists have been approved for obesity and semaglutide have been demonstrated effective and safe in type 2 diabetes with moderate CKD (eGFR 47 mL/min, on average) and mild obesity (BMI 32 kg/m^2) [96]; nonetheless, it has been achieved only 5% weight reduction in 2 years of treatment, high gastrointestinal (GI) adverse effects and high drug discontinuation (13%). The effects in advanced CKD and severe obesity are unknown. The optimal treatment for obesity in CKD remains to be determined and should necessarily be a precision treatment including all the available options.

We should be aware that two major issues impact on weight loss in obese CKD and must be considered to achieve efficient treatments. First, the individual and disease conditions: according to the degree of obesity, in fact, the weight reduction program should be of different duration. In contrast, in advanced CKD and transplant candidates, the duration of the program could not be too long because of the incoming ESKD; moreover, in moderate–advanced CKD some treatments could negatively impact on CKD metabolic derangements (i.e. diets vs malnutrition) or CKD symptoms (i.e. GLP-1i vs GI disturbances). Second, the strength and weakness of treatments: lifestyle + diet approach is healthy, affordable, highly adaptable, though burdened by low adherence, and it is slow and provides only limited results. Pharmacological approach is effective, and improves renal and patient outcomes; however, it is costly, and burdened by GI adverse

effects, by discontinuation and by rebound of body weight [97]. Bariatric surgery is highly effective, fast, effective in severe obesity and safe in terms of renal function; however, it is also not exempt of rebound.

Overall, the precision combination of different technique according to the individual aim and the actual clinical conditions should be the key to success (Fig. 5). All individuals should be prescribed healthy lifestyle; diet intervention is mandatory at least up to CKD stage 3; drugs could be prescribed for any obesity class, and early during the disease because of the slow action; more advanced CKD stages, that requires larger weight reduction and eventually faster action, should benefit of surgery; CKD stage 5 requires more cautious interventions and even more personalization.

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DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

C.Z. is member of the *CKJ* Editorial Board.

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