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CONSENSUS STATEMENT

Nutritional assessment and medical dietary therapy for management of obesity in patients with non-dialysis chronic kidney disease: a practical guide for endocrinologist, nutritionists and nephrologists. A consensus statement from the Italian society of endocrinology (SIE), working group of the club nutrition–hormones and metabolism; the Italian society of nutraceuticals (SINut), club ketodiets and nutraceuticals *"KetoNut-SINut"*; and the Italian society of nephrology (SIN)

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Abstract

Purpose Chronic kidney disease (CKD) is a serious health concern with an estimated prevalence of about 13.4% worldwide. It is cause and consequence of various comorbidities, including cardiovascular diseases. In parallel, common pathological conditions closely related to ageing and unhealthy dietary habits increase the risk of CKD development and progression, including type 2 diabetes and obesity. Among these, obesity is either independent risk factor for new onset kidney disease or accelerates the rate of decline of kidney function by multiple mechanisms. Therefore, the role of diets aimed at attaining weight loss in patients with obesity is clearly essential to prevent CKD as to slow disease progression. Various dietary approaches have been licensed for the medical dietary therapy in CKD, including low-protein diet and Mediterranean diet. Interestingly, emerging evidence also support the use of low-carbohydrate/ketogenic diet (LCD/KD) in these patients. More specifically, LCD/KDs may efficiently promote weight loss, improve metabolic parameters, and reduce inflammation and oxidative stress, resulting in a dietary strategy that act globally in managing collateral conditions that are directly and indirectly related to the kidney function.

Conclusion This consensus statement from the Italian Society of Endocrinology (SIE), working group of the Club Nutrition – Hormones and Metabolism; the Italian Society of Nutraceuticals (SINut), Club Ketodiets and Nutraceuticals *"KetoNut-SINut"*; and the Italian Society of Nephrology (SIN) is intended to be a guide for Endocrinologist, Nutritionists and Nephrologist who deal with the management of patients with obesity with non-dialysis CKD providing a practical guidance on assessing nutritional status and prescribing the optimal diet in order to best manage obesity to prevent CKD and its progression to dialysis.

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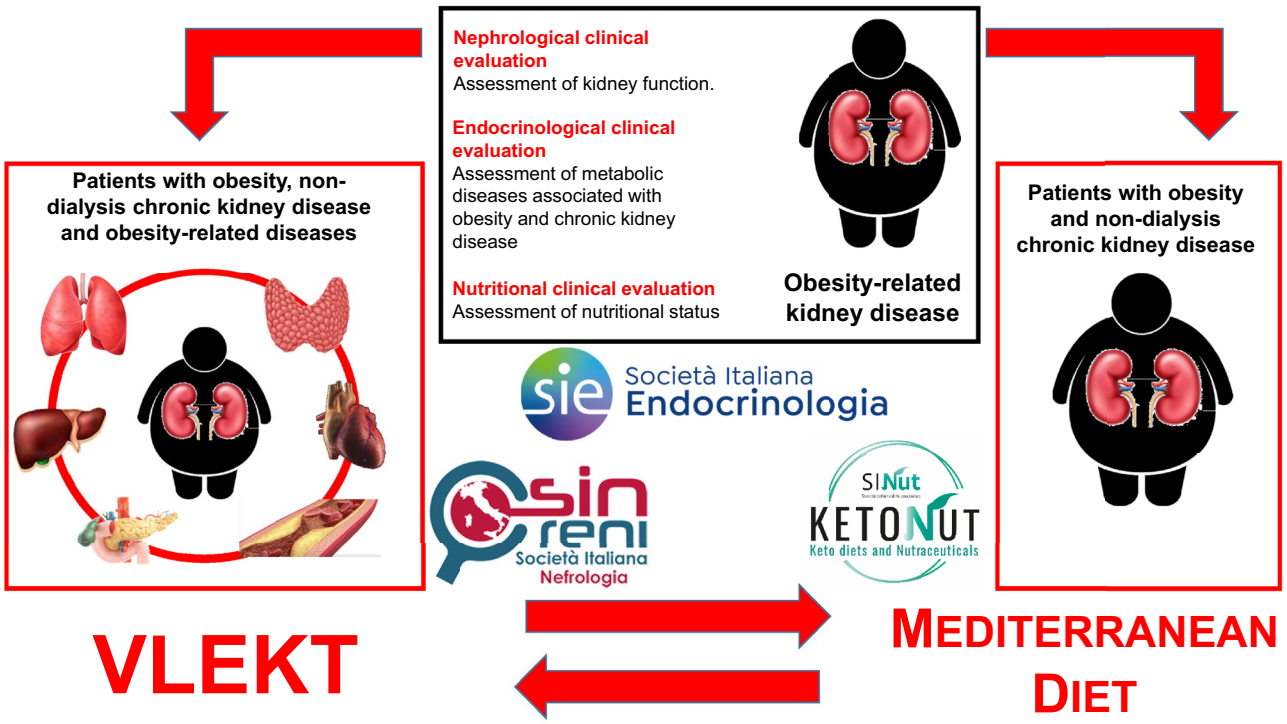
Graphical abstract



Keywords Chronic kidney disease · Obesity · Nutritional management · Bioelectrical impedance analysis · Mediterranean diet · Ketogenic diet · Nutrition · Diet

Abbreviations

AER	Albumin excretion rate
β-HB	β-Hydroxybutyrate
BC	Body composition
BIA	Bioelectrical impedance analysis
BIVA	Bioelectrical impedance vector analysis
BMI	Body mass index
BW	Body weight
CKD	Chronic kidney disease
CRP	C-reactive protein
CVD	Cardiovascular diseases
DXA	Dual-energy x-ray absorptiometry
ECW	Extracellular water
eGFR	Estimated glomerular filtration rate
FA	Fatty acid
FM	Fat mass
FSGS	Focal and segmental glomerulosclerosis
HGS	Handgrip strength
ICKD	Isocaloric ketogenic diet
ICW	Intracellular water
IL	Interleukin
IR	Insulin resistance
K	Potassium
KB	Ketone body
KD	Ketogenic diet
KeNuT	Ketogenic nutritional therapy
LCD	Low-carbohydrate
LCKD	Low-calorie ketogenic diet
MD	Mediterranean Diet
MetS	Metabolic syndrome
Na	Sodium
NKF	Normal kidney function
nPCR	Normalised protein catabolic rate
ORG	Obesity-related glomerulopathy
OxS	Oxidative stress
P	Phosphorus
PBD	Plant-based diet
PEW	Protein-energy wasting
PhA	Phase angle
PUFA	Polyunsaturated fatty acids
R	Resistance
RAAS	Renin–angiotensin–aldosterone system

REE	Resting energy expenditure
SIE	Italian Society of Endocrinology
SIN	Italian Society of Nephrology
SINut	Italian Society of Nutraceuticals
TBW	Total body water
TCI	Total calorie intake
T2DM	Type 2 diabetes mellitus
UACR	Urinary Albumin-to-Creatinine Ratio
VLCKD	Very-low-calorie KD
VLEKT	Very Low-Energy Ketogenic Therapy
VAT	Visceral adipose tissue
WC	Waist circumference
Xc	Reactance

Introduction

Chronic kidney disease (CKD) is a global public health burden, with an estimated prevalence of 13.4% worldwide (CKD stages 1–5) [1], close to 850 million people worldwide [2], although in many cases it is underdiagnosed, and the disease is identified only in its late stages [1]. CKD is also a crucial health concern since it is historically recognised as a cause of associated comorbidities, mainly cardiovascular diseases (CVD), as well as decreased quality of life, and mortality [3–6].

Overweight and obesity represent two main contributors playing a major role in the development of CKD [7], acting through direct and indirect mechanisms [8]. In general, at renal level, obesity leads to a physiological adaptation that results in morpho-functional alterations [9, 10], finally culminating in the development of CKD and faster decline of kidney function [11, 12]. This harmful association needs a "call for action" given that obesity is today a major feature of approximately 50% patients with CKD, with increasing prevalence in the last two decades [13]; even in Italy, the country where Mediterranean Diet (MD) was born, the prevalence of obesity in CKD patients was 39%, approximately 15% higher than in adult population without CKD, at the last national survey on CKD [14].

In this *scenario*, a multidisciplinary management of CKD, in cooperation with Endocrinologists, Nutritionists, and Nephrologists, is important. In particular, a basal in-depth assessment of the nutritional status is needed to evaluate the body weight (BW) and the body composition (BC) before prescribing the optimal dietary intervention, according to the reference guidelines [15]. Various dietary strategies have been studied for the management of CKD patients, including the low-protein diet and MD [16, 17], this latter, however, properly adapted to this class of patients [18]. Interestingly, low-carbohydrate/ketogenic diets (LCD/KDs) have been proposed as potential therapeutic alternative diets in CKD with obesity [9, 19–24]. These diets have been reported to be effective in reducing BW [9], inflammation and oxidative stress (OxS) [25] and improving metabolic parameters [26, 27], resulting in a valid approach for the management the obesity-related CKD. Nevertheless, a potential drawback in patients with obesity and more advanced CKD (estimated glomerular filtration rate -eGFR- less than 45 ml/min/1.73m^2) may be the protein intake relatively higher for the kidney function level [28].

To date, there is a lack of clear scientific consensus and practical guidelines for the clinical-nutritional management of patients with obesity-related CKD. In detail, the nutritional management of these patients is based, to date, only on the clinical practice guidelines for adults with chronic renal failure without taking into account the "obesity" variable which, in itself, is a determining factor in the progression of the CKD, whose mechanisms are complex and include hemodynamic changes, chronic low-grade inflammation, OxS, and activation of the renin-angiotensin-aldosterone system (RAAS).

In order to fill this gap this consensus statement from the Italian Society of Endocrinology (SIE), *working group of the Club Nutrition–Hormones and Metabolism*; the Italian Society of Nutraceuticals (SINut), *Club Ketodiets and Nutraceuticals "KetoNut-SINut"*; and the Italian Society of Nephrology (SIN) is intended to be a guide for Endocrinologist, Nutritionists and Nephrologist who deal with the management of patients with obesity with non-dialysis CKD providing a practical guidance on assessing nutritional status and prescribing the optimal diet in order to best manage obesity to prevent CKD and its progression to dialysis.

The chronic kidney disease: clinical aspects and treatment

CKD is defined as abnormalities of kidney structure or function, present for at least 3 months, and it is classified based on its etiology, eGFR category, and albuminuria category [29]. Five categories of eGFR (Table 1) and three of Albumin Excretion Rate (AER) or urinary Albumin-to-Creatinine Ratio (UACR) (Table 2) are recognized, with their combination used for stratification of adverse outcomes risk in clinical practice where higher albuminuria heralds higher cardiorenal risk even if isolated [29–31].

A precise assessment of GFR is critical in patients with obesity, since they represent a risk group. Measured GFR using urinary or plasma clearance of exogenous filtration markers is the gold standard for the evaluation of kidney function; however due to the invasive nature and complexity of these techniques, endogenous creatinine clearance and

eGFR equations are commonly used. Unfortunately there is no consensus on the best equation (creatinine-based and/or Cystatin C-based) to estimate GFR in the setting of obesity or longitudinally in the setting of weight change [32], given that renal function prediction can be significantly biased in this patient category. A retrospective cohort study in 2011 revealed that the Cockcroft-Gault formula provided the best estimate of kidney function [33]. A later study conducted in CKD patients with obesity concluded that the performance of eGFR CKD-EPI (Epidemiology Collaboration) was valid up to a body mass index (BMI) range of 40 kg/m^2 for GFR ≤ 60 ml/min per 1.73 m^2 [34]. In summary, most but not all studies have found that the Cockcroft-Gault equation (using actual BW) tends to overestimate GFR in individuals with obesity, whereas the CKD-EPI and Modification of Diet in Renal Disease (MDRD) study equations tend to slightly underestimate GFR [35]. Other studies suggest that serum Cystatin C may be less influenced by BC and is more strongly associated with measured GFR than serum creatinine [36]. In a more recent study, Rothberg et al. showed that in subjects with severe obesity undergoing medical weight loss, estimating equations using Cystatin C and indexed to actual body surface area, may provide a more accurate assessment of renal function [37]. Therefore, current limitations of renal function prediction should be carefully considered in patients with obesity.

Among the main risk factors for CKD development and progression are listed non-modifiable factors (ie., genetic, race, age, and sex), nephrotoxic agent exposure [38, 39], as well as modifiable factors including CVDs, hypertension, type 2 diabetes mellitus (T2DM), and obesity [38, 39], this latter extensively discussed in the next section, as focus of the present document. This results in development of diseases comorbidities, such as diabetic nephropathy and hypertensive nephropathy, as a severe complication of T2DM and hypertension, respectively [40, 41], causing end-stage renal disease [40]. Other causes of CKD include glomerulonephritis, autoimmunity, malignancy, infectious disease (i.e., pyelonephritis), renal atherosclerosis, gout, nephrolithiasis and obstructive uropathies, polycystic kidney disease, and other congenital anomalies of the kidney and urinary tract [42–46]. Interestingly, there is emerging evidence on the relationship between altered gut microbiota and CKD [47]. More specifically, local inflammation at gut level, as well as impaired permeability of the intestinal barrier promote the gut-to-blood translocation of uremic toxins (i.e., p-Cresyl sulphate, TMAO, indoxyl sulphate), that cause inflammation and OxS, damaging organs and systems, including kidneys [48].

Clinically, patients with advanced stages of CKD present extracellular volume expansion (salt-sensitive hypertension), altered acid–base balance (metabolic acidosis), electrolyte imbalance (muscle cramps, cardiac arrythmias), and hyperuraemia [49]. General and nonspecific symptoms are appetite loss, fatigue and weakness, dyspnoea, decreased mental acuity, sleep disturbances, vomiting and nausea [50, 51]. Abnormalities in laboratory parameters highlight various complications related to a decline of kidney function, including anaemia, impaired bone metabolism (i.e., altered levels of calcium, phosphate, parathyroid hormone and vitamin D deficiency) [31, 50], and inflammation (increased levels of c-reactive protein (CRP), interleukin 6 (IL-6), tumour necrosis factor-α) [21].

The pharmacological treatment is based on the first-line use of renin-angiotensin-aldosterone pathway modulators and SGLT-2 inhibitors that reduce the intraglomerular pressure, the first acting on the efferent arteriole and the second on the afferent one, thus helping to preserve kidney function by counteracting single nephron hypertension-hyperfiltration [52]. Novel agents used for their anti-inflammatory and antifibrotic effects are the non-steroidal mineralocorticoid receptor antagonists. Other drugs commonly used in the treatment of CKD are loop diuretics, statin or statin/ezetimibe, erythropoietin, calcium, and vitamin D supplements.

Table 1 GFR categories

GFR categories	GFR (ml/min/1.73m^2)	Renal function
G 1	≥ 90	Normal
G 2	89 – 60	Mildly decreased
G 3a	59 – 45	Mildly to moderately decreased
G 3b	44 – 30	Moderately to severely decreased
G 4	29 – 15	Severely decreased
G 5	< 15	Kidney Failure

GFR glomerular filtration rate

Table 2 Albuminuria categories

Albuminuria categories	AER (mg/24 h)	ACR (approximate equivalent)	Description and range
A 1	< 30	< 3 mg/mmol or < 30 mg/g	Normal to mildly increased
A 2	30–300	3–30 mg/mmol or 30–300 mg/g	Moderately increased
A 3	> 300	> 30 mg/mmol or > 300 mg/g	Severely increased

AER albumin excretion rate, *ACR* albumin-to-creatinine ratio

When the patient with end-stage kidney disease (ESKD, eGFR < 15 mL/min/1.73m^2) shows complications no longer responsive to medical (conservative) treatment, dialysis or kidney transplant remain the only possible therapeutic options [30, 31, 50, 53].

Principal mechanisms involved in obesity-related kidney disease

Obesity is an independent risk factor for CKD onset [12], and the prevalence of these two diseases increases in parallel [54]. BMI, indeed, is associated with increasing albuminuria [55], and decreasing eGFR; on the other hand, these two outcomes improve with weight loss [56].

Mechanistically, obesity affects renal function via different mechanisms (summarised in Fig. 1), among which one of the main is related to a physiological kidney adaptation [9]. In obesity states, indeed, kidneys increase renal blood flow, eGFR, and sodium (Na^+) reabsorption, resulting in glomerular hypertension and hyperfiltration [9]. Such alterations of the renal hemodynamic are principally due to afferent arteriole vasodilation and increased expression of Na^+ channels in proximal tubular cells causing water and Na^+ reabsorption [9]. This phenomenon leads to renal hypertrophy and hyperfiltration culminating in glomerulosclerosis, thus resulting in impaired renal function [8]. In this *scenario*, a central role in modulation of vasocontraction is played by the RAAS, which is more active in obesity. RAAS activation, contributing to hypertension, glomerulosclerosis, and endothelial dysfunction, exerts detrimental effects on CKD progression [9]. More specifically, along with the effects of (i) angiotensin II in inducing proteinuria, increasing intra-glomerular pressure, and inflammation, and (ii) aldosterone in inducing insulin and leptin resistance and regulating blood pressure, salt homeostasis, and plasma volume, RAAS activation also promotes the differentiation of adipocytes and the production of adipokines [57], suggesting the existence of an obesity-RAAS activation-CKD vicious cycle.

From a metabolic point of view, obesity is commonly associated with insulin resistance (IR), a further causative factor of kidney dysfunction [58, 59]. IR, indeed, impairing glomerular hemodynamic and inducing the expression of pro-fibrotic and pro-inflammatory genes, contributes to promote onset and progression of CKD [58, 59]. An additional metabolic feature of obesity is represented by the ectopic lipid accumulation [60] that, at renal level, causes glomerular and tubulointerstitial damages and promotes the local inflammation and OxS [9]. Also, lipid accumulation exerts lipotoxicity [60] which, in the kidney, is responsible for morpho-functional changes in podocytes, tubular, and mesangial cells [9].

In addition to the well-known cardiometabolic effects, the adipose tissue distribution plays a role also in renal injury [61, 62]. More specifically, central obesity is associated with several signs of kidney impairment, including albuminuria, increased filtration fraction, reduced renal plasma and blood flow [63]. Interestingly, such negative renal effects seem to be due to a central pattern of fat distribution itself, independently of the BMI [24]. In this sense, a remarkable study on a large number of middle-aged subjects (n.1261) reported that metabolic syndrome (MetS) is an independent risk factor for accelerated GFR (measured not estimated) decline, unlike BMI, waist circumference (WC), or waist-hip ratio. According to the authors, this MetS-measured GFR decline association was mainly governed by triglyceride levels (as a criterion for defining the MetS) which, when elevated, are associated with an increased risk of developing CKD causing renal dysfunction via their atherogenic and proinflammatory effects, as well as acting as a marker of IR [64].

Central obesity is characterised by an enlargement of the visceral adipose tissue (VAT) that is associated with various metabolic aberrations implicated in CKD development and progression, including MetS, IR, and T2DM [65]. Overall, this is mainly mediated and promoted by its pro-inflammatory effect; in subjects with obesity, indeed, VAT presents an altered balance between pro-inflammatory immune cells and anti-inflammatory regulatory cells, with a prevalence of the first ones [66]. This results in the increased production and release of cytokines and adipokines [67], suggesting its role in triggering and exacerbating the chronic low-grade inflammation [25] that, in turn, lead to CKD development [68]. In obesity, indeed, hypertrophic and dysfunctional adipocytes, as well as VAT, due to their endocrine function, promote the expansion of adipose tissue through the release of adipokines (i.e., angiopoietin, vascular endothelial growth factor, and cathepsin) that, in turn, stimulate rearrangements of stroma, neoangiogenesis, and adipogenesis. Angiogenesis and adipogenesis are, thus, closely linked, and circulating adipokines reach the kidney, where they act locally on tubular, mesangial, and Bowman's capsule cells promoting altered and non-physiological responses to cope with glomerular hyperfiltration, resulting in albuminuria, focal and segmental glomerulosclerosis (FSGS), and interstitial fibrosis [69]. Leptin and adiponectin exert pro-inflammatory and anti-inflammatory effects, respectively [9]. Both adipokines are involved in kidney function. In particular, overexpression of leptin stimulates hypertrophy of glomerular mesangial cells via PI3K and ERK1/2 activation, resulting in increased protein and albumin filtration and activating inflammatory pathways. Also, leptin promotes the secretion of transforming growth factor-β1, which causes basement membrane thickening, leading to glomerulosclerosis [70]. On the other hand, lower levels of adiponectin have been associated with impaired

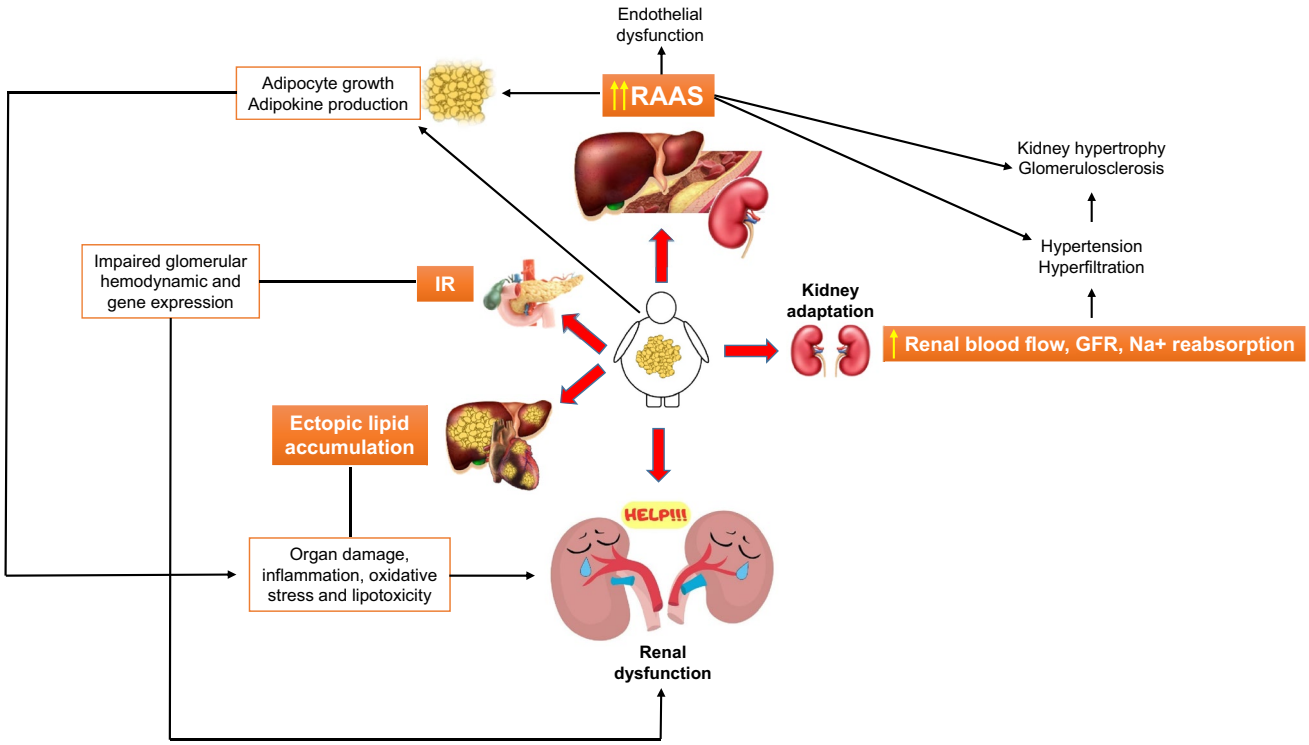


Fig. 1 Main mechanisms involved in obesity-related kidney disease. A kidney adaptation to obesity causes increase in renal blood flow, GFR, and Na^+ reabsorption, resulting in hypertension and hyperfiltration that culminates in kidney hypertrophy and glomerulosclerosis. Moreover, obesity is responsible for an overactivation of RAAS that primarily causes hypertension, glomerulosclerosis, and endothelial dysfunction; also, RAAS induces adipocyte growth and adipokine production. The main metabolic effects of obesity affecting renal function refer to insulin resistance (IR) (impairing glomerular hemodynamic and expression of pro-fibrotic and pro-inflammatory genes), and to ectopic lipid accumulation (causing glomerular and tubulointerstitial damages, inflammation, OxS, and lipotoxicity). Central obesity is directly involved in renal dysfunction, as it causes albuminuria, increased filtration fraction and reduced renal plasma and blood flow. In addition, this type of obesity is responsible for the increased production and release of adipokines that, in general, provoke albuminuria, FSGS, and interstitial fibrosis. More specifically, increased levels of leptin cause mesangial cell hypertrophy (with consequent increased inflammation and albumin and protein filtration) and thickening of basement membranes (resulting in glomerulosclerosis). On the contrary, reduced levels of adiponectin induce albuminuria (via podocyte fusion) and tubular inflammation (via reduced AMPK activation). Finally, increased levels of restin and visfatin also increase the inflammatory status. Overall, such mechanisms are responsible for the development of ORG. *AMPK* 5' adenosine monophosphate-activated protein kinase, *OxS* oxidative stress, *IR* insulin resistance, *FSGS* focal segmental glomerulosclerosis, *GFR* glomerular filtration rate, *RAAS* renin-angiotensin-aldosterone system

kidney function and CKD, since they cause podocyte fusion, resulting in albuminuria. Also, by decreasing AMPK activation, hypoadiponectinemia is responsible for increasing tubular inflammation [70]. Other adipokines, such as resistin and visfatin, whose levels are increased in obesity, have been demonstrated to play a role in renal dysfunction [9, 70], via increased inflammation [70].

Due to these mechanisms, obesity is directly involved in the development of obesity-related glomerulopathy (ORG) [8, 11], a glomerular disease characterized by glomerulomegaly with or without FSGS [69] that presents clinically with albuminuria and kidney dysfunction [71]. Hemodynamic changes, overactivation of RAAS, and ectopic lipid accumulation are the main determinant in ORG pathogenesis [69, 72]. Also, a central role in development of ORG is played by inflammation [69]. In patients with ORG, indeed, an increased expression of inflammatory cytokines, including TNF-α (associated with glomerulonephritis and tubulointerstitial damage) and IL-6 (mediating IR, activation of RAAS, and regulation of the transforming growth factor-β1 pathway) has been observed [9, 73].

Obesity related clinical feature in CKD

Investigations in humans highlighted the association between obesity and CKD [24], including the Coronary Artery Risk Development in Young Adults (CARDIA) study involving 2354 subjects with normal kidney function and reporting a significant association between obesity and microalbuminuria during a 15 year follow-up [74]. Another

large study carried out on 2585 subjects without renal failure reported that BMI increased the odds of CKD development by 23% *per* standard deviation unit [75]. Similarly, in the Physicians' Health Study, involving 11,104 healthy men, the CKD risk increased for each 1-unit increase in BMI, and for subjects with BMI > 26.6 kg/m^2 the OR was 1.45 (95% CI 1.19–1.76; $p < 0.001$) [76]. The role of obesity in the increased risk of kidney disease was also reported by a prospective cohort study (2676 subjects) demonstrating that the odds of stage 3 CKD development increased by 68% in subjects with obesity during 18.5 year follow-up [77], as well as by a retrospective cohort study (320,252 subjects) reporting that end-stage renal disease risk increased in tandem with BMI [78]. Cumulative evidence on this association is provided by a recent meta-analysis reporting that, compared to normal weight, subjects with overweight or obesity have a higher risk of CKD (RR: 1.15, 95% CI 1.08, 1.22 and RR: 1.21, 95% CI 1.10, 1.33, respectively [79].

Assessment of nutritional status in patients with chronic kidney disease

CKD is one of the primary causes of disease-related malnutrition and protein-energy wasting (PEW), especially in older subjects, in whom aging, as well as comorbidities, act synergistically in exacerbating such conditions [80]. Importantly, both disease-related malnutrition and PEW are independent prognostic factors of several clinical outcomes, including mortality. This suggests the remarkable role played by a proper and global nutritional status assessment that, combined with monitoring the inflammatory status, represents a reliable prognostic marker of CKD progression, morbidity, and mortality [80, 81]. This scenario, thus, implies the integration of nutritional and inflammatory biomarkers in prognostic score, rather than their individual use [81]. Nonetheless, the nutritional assessment is poorly applied in the renal clinical practice [82].

A proper assessment of the nutritional status should be performed by qualified nutritionists (or international equivalent) or physician and should follow the medical evaluation of both general health status and stage of renal failure. This is necessary to cover the single competencies of the healthcare personnel who take care of the patient, but also because a clinical evaluation is fundamental to establish the appropriate method and parameter for the nutritional assessment, as well as the dietary intervention. This concept should be applied both at the first visit and during the follow-up, due to the need to carefully monitor the diseases progression, with a network between the healthcare personnel including endocrinologist, nutritionists, and nephrologists.

A complete assessment of the nutritional status in CKD patients should comprise both monitoring of laboratory parameters and the evaluation of the BC. As suggested by the KDOQI guidelines [15], monitoring creatinine kinetics is necessary to estimate muscle mass, in particular in stage 5 patients. However, cautions should be used in its evaluation, including a proper sampling procedure (collecting urine for 24 h), as well as considering the eventual consumption of meat or creatine supplement intake, that may increase the creatine excretion. Other suggested laboratory parameters include serum albumin and pre-albumin, and normalised protein catabolic rate (nPCR) [15]. Albumin is the main circulating protein, and its low levels predict protein malnutrition and mortality, and may indicate pathological conditions, including inflammation, renal and liver diseases, oedema, and infections. The albumin half-life, however, is long (about 20 days), making this parameter not sensitive to a short-term monitoring of the nutritional status. In contrast, the half-life of prealbumin is shorter (about 2–3 days), thus, it is more reliable to monitor rapid changes [83]. However, albuminemia is a good predictor of illness or mortality, thus, its use in nutritional status assessment has been re-evaluated [15]. In non-dialysed CKD patients, nPCR is calculated from urinary urea (after 24 h urine collection) plus non-urinary urea daily excretion. This marker is easily quantifiable and used to estimate the intake of protein. It should be taken into account, however, that these markers are influenced by several conditions, including inflammation, protein loss, illness, body fluids. They, thus, should be integrated and not evaluated singularly to obtain a more comprehensive evaluation [15].

KDOQI guidelines suggest also monitoring BW, BMI, and BC. The use of specific techniques is related to the stage of renal failure, as reported in Table 3. In particular, BW should be monitored periodically, since substantial changes may suggest clinical concerns. As well as BW, BMI should be calculated periodically, using the WHO categories [15] (underweight, BMI < 18.5 kg/m^2; normal weight, BMI = 18.5–24.9 kg/m^2; overweight, BMI = 25.0–29.9 kg/m^2, and obesity, BMI > 30.0 kg/m^2) [84]. The principal limitation of BMI is that it does not provide information on BC, since it does not give any precise discrimination between fat mass (FM) and fat-free mass (FFM). In this sense, the routinely measurement of other reliable anthropometric parameters is suggested, including WC, an indicator of central adiposity, and arm skinfold and circumference to assess muscle mass [81]. Among the various techniques licensed for the BC estimation, skinfold thickness, dual-energy x-ray absorptiometry (DXA), and bioelectrical impedance analysis (BIA) are suggested for CKD patients [15]. In general, skinfold thickness measurement can be used in all CKD patients, including transplanted ones, with periodic evaluations in order to assess accurately eventual changes in body FM.

Table 3 Main parameters to be monitored and techniques to be used for the assessment of nutritional status in CKD, according to KDOQI Guidelines [15]

Method/parameter	CKD stage	Special recommendation
Laboratory parameters for nutritional assessment		
Creatinine kinetics	S5	Suggested to estimate muscle mass
Serum albumin, serum prealbumin, nPCR	S1-5	To be used as complementary tools for the nutritional status assessment; such measurements, however, should not be used singularly, but interpreted in combination
Serum albumin	S5	To be used a hospitalization and mortality predictor
Parameters for evaluation of BC		
BW/BMI	S1-5	To be assessed at the first visit and monitored periodically
BW/BMI/BC	S1-5	To be monitored at least: • Monthly: MHD and PD • Every three months: S4-5 or post-transplantation • Every six months: S1-3
WC	S5	Suggested to assess abdominal changes, but changes need to be interpreted with caution
Skinfold thickness	S1-5	To be used, in absence of oedema, to assess BF
Technical devices for evaluation of BC		
BIA	S1-5	No sufficient evidence suggesting its use to assess BC
	S5	Use of MF-BIA suggested to assess BC, preferably performed at least 30 min or more after the haemodialysis session
DXA	S1-5	To be used when feasible to assess BC
HGS	S1-5	Suggested as an indicator of protein-energy status, but during the follow-up data should be compared with baseline
Techniques for estimation of the energy requirements		
Indirect calorimetry	S1-5	Suggested to measure REE, when feasible and indicated
REE equations	S5 metabolically stable	Suggested in absence of indirect calorimetry

BC body composition, *BIA* bioelectrical impedance analysis, *BMI* body mass index, *BW* body weight, *DXA* dual-energy x-ray absorptiometry, *HGS* handgrip strength, *MF-BIA* multifrequency bioelectrical impedance analysis, *MHD* maintenance haemodialysis, *nPCR* normalised protein catabolic rate, *PD* peritoneal dialysis, *REE* resting energy expenditure, *S* stage, *WC* waist circumference

However, in subjects with obesity, this technique may be not accurate, since the high subcutaneous adiposity makes difficult the measurement with the callipers. DXA is the reference method of BC assessment [85], able to discriminate bone mineral content, lipids, and lipid-free soft tissues, these latter two referring to FM and FFM, respectively [86]. Although its limitations (i.e., technical expertise, high costs, contraindications) [85], DXA is suggested as a valid method for BC measurement in CKD and transplanted patients, paying the attention to the radiation exposure, thus considering the risk-benefit ratio of such technique [81].

Currently, BIA is recognized as a reliable method for BC estimation. Advantages are the low-cost, the non-invasiveness and low-time consuming. BIA estimates the hydration status, discerning from total, extracellular and intracellular water (TBW, ECW, and ICW, respectively), through the measurement of body tissue electrical properties, namely resistance (R) and reactance (Xc) [85], that, briefly, are related to TBW and to the cell membrane capacitance, respectively [85, 87, 88]. More specifically, low R values are detected in case of elevated TBW [87], while in case of retention of fluids, the alteration of cell membranes reflects in decreased Xc values [88]. It has been reported, indeed, that CKD patients exhibit low R and Xc, suggesting the presence of hyperhydration or, at least, altered hydration status since the early stages [87, 88]. On the other hand, BC estimation is based on the use of predictive equations that, however, are not validated in CKD; although that, the BIA-obtained BC estimation revealed lower body mass cell and FM in mild to moderate CKD compared to controls [87]. Also it suffers the influence of hydration status, suggesting the importance to interpret carefully the results, as well as to use BIA row parameters, in particular in subjects presenting hydration abnormalities [89]. BIA row parameters are R, Xc and their derived phase angle (PhA (°) = arc tangent (Xc/R) x (180/π)) [90]. PhA is the most important BIA-derived parameter, providing information about the intra- and extracellular water distribution, and reflecting the cell membrane integrity, with a linear relationship (low PhA values = reduced cell integrity or cell death) [90]. Interestingly, information on the inflammatory status can be obtained from PhA values

[90]. More specifically, PhA values are inversely correlated to the levels of inflammatory markers, including CRP [91–93]. This correlation is explained considering that chronic and unregulated inflammation, such as the obesity-related chronic low-grade inflammation [94, 95], causes tissue damages [94, 96] that are evidenced by lower PhA values in terms of decreased cell integrity. This suggests, thus, the importance to observe PhA values during the nutritional follow-up also in CKD patients to monitor eventual variations in inflammatory status. Previous studies, indeed, reported lower PhA values in patients with intermediate [88] and mild to severe renal failure (− 22% compared to controls) [87], which are associated with mortality in non-dialysed CKD patients [97]. Also, in such patients, PhA has been found to be an independent factor associated with malnutrition; in particular, PhA values < 4.46° predict a higher risk of PEW (ROC analysis: (AUC = 0.749, sensitivity + specificity = 120.8%) [98].

Since, as aforementioned, CKD patients present alterations in the hydration status, in addition to the conventional BIA, bioelectrical impedance vector analysis (BIVA) is suggested as a valid method to avoid bias in BC and hydration estimation [88]. In BIVA, the single components R and Xc are normalised to height and then plotted in the R-Xc graph [85, 99, 100]. In the R-Xc graph, the vector distribution pattern provides direct information on the hydration status, defining decreases in body hydration (when the vector moves up along the major axis of the ellipse) or fluid retention (when the vector moves in the opposite direction along the same axis) [85]. The distribution patterns are defined as vector length [88]. In these terms, shorten vector lengths indicate overhydration and have been reported to be associated with heart failure in non-dialysed CKD patients [97]. It appears clear, thus, the usefulness of BIVA for a more comprehensive assessment in this class of patients [101].

KDOQI guidelines also suggest handgrip strength (HGS) as simple and valid method to evaluate the muscle function and as a nutritional status indirect measure in CKD patients, both receiving and not receiving dialysis [15]. It has been reported that such patients have a higher odd ratio to the low HGS prevalence, compared to controls (OR 1.896, 95% CI 1.467–2.450 and OR 1.684, 95% CI 1.294–2.191, for men and women, respectively) [102]. Similarly, HGS is directly correlated with eGFR ($R^2 = 0.069$, $F = 633.5$, $p < 0.001$ and $R^2 = 0.045$, $F = 483.1$, $p < 0.001$, for men and women, respectively) [102] and inversely associated with the risk of incident CKD (HR (95% CI) 0.84, 0.76, and 0.72 in quartiles 2, 3, and 4, respectively, compared to quartile 1) [103]. Such results are explained by the progressive muscle wasting, a pathological condition commonly observed in CKD [104, 105]. More specifically, HGS is included within the screening tests for diagnosis of sarcopenia [106–108], an independent predictor of mortality in CKD patients [109–111]. Mechanistically, there is an inverse association between muscle mass and IR [112], which contributes to kidney dysfunction [113]. In addition, it is well-known that muscle exerts antioxidant and anti-inflammatory effects [114, 115] contributing to maintain the kidney health. Overall, such biological functions explain the associations between HGS and clinical outcomes in CKD [103] and suggest the importance to use the method during the nutritional screening and follow-up in this class of patients. Specific precautions in the use of HSG, however, should be taken for T2DM (considering that a reduction in strength should be due to the peripheral neuropathy) [15, 116].

Once assessed the BC, a proper estimation of the resting energy expenditure (REE) is suggested to calculate the nutritional requirements and, thus, elaborate the optimal dietary prescription. In this sense, the guidelines suggest the use of indirect calorimetry, when available and feasible, as the best method to estimate accurately the REE; however, in other cases (i.e., absence of indirect calorimetry or contraindications), predictive equations can be used [15].

Medical dietary therapy in patients with chronic kidney disease

In CKD patients, besides the pharmacological treatment, dietary interventions are necessary to ensure adequate care for kidney preservation and to improve life quality and reduce mortality. Moreover, as the main causes and several risk factors of CKD are strongly influenced by dietary habits, it is essential for these patients to improve their eating behaviours, following health-promoting dietary patterns [15, 29–31, 50, 117]. In particular, for management of obesity, the first-line intervention is advised to be based on lifestyle modifications, including physical activity and nutritional recommendations [26], suggesting the important and primary role played by a proper medical dietary therapy during, and ideally before, the pharmacological treatment.

General dietary requirements in CKD

According to KDOQI Clinical Practice Guideline for Nutrition in CKD, it is recommended an energy intake of 25–35 kcal/kg BW/day to maintain an adequate nutritional status [15]. This recommendation should be adapted considering age, gender, physical activity level, BC, target weight, CKD stage, and presence of concurrent disease or inflammation [15, 18]. However, taking into account the negative nitrogen balance ensured, the total calorie intake (TCI) should be increased by 30–35 kcal/kg/day in order to avoid the risk of malnutrition in this class of patients. To note, in patients with obesity, the daily calorie intake should

be calculated according to adjusted weight or normal weight BMI (23.0 kg/m^2) [18].

With regard to macronutrient intake, there is no recommendations about carbohydrates. Lipids should range from 30–35 to 50–60% of TCI in all CKD stages and in transplanted patients. However, there is no recommendation about polyunsaturated fatty acids (PUFA), one of the main elements of MD. As expected, instead, specific recommendations are provided for protein intake according to the different CKD stages. In particular, the optimal daily needs for protein intake is 0.8 g/kg/day in stages 1–2, 0.55–0.6 g/kg/day in stages 3–5 (without dialysis). Regarding the micronutrient intake, in absence of altered blood biochemistry, there are no specific restrictions. In general, potassium (K) and phosphorus (P) intakes should be individualised, but they should be adapted if their blood values are elevated (K: 1500–2000 mg/day for stages 3–5 and dialysed patients; P: 600–1000 mg/day for stages 3–5 and peritoneal dialysed patients, and 800–1000 mg/day for haemodialyzed ones). Recommendations for NaCl intake is about 5 g/day for all stages [18].

Although the general dietary requirements for CKD patients refer to single nutrients, it should be noted that they are not consumed alone, but as part of a whole dietary pattern. Single nutrient-based recommendations, thus, may be difficult to follow for many patients, due to the multiple and simultaneous restrictions, as well as to the non-personalised approach used that focuses on indicating foods to be avoided, rather than those that can be consumed. In particular, it seems that such strategies have neither conclusive effects nor are able to substantially modify the renal failure degree [23]. Moreover, available evidence on dietary intervention in CKD is of low quality and not sufficient to guide the clinical practice [118]. Of interest, recommendations based on consideration of the global dietary pattern are, in general, associated with improvements in renal outcomes, but also protective against chronic metabolic diseases, such as T2DM and obesity [23].

Medical dietary therapy

Mediterranean diet

MD is a dietary pattern inspired by the traditional eating habits of countries bordering the Mediterranean Sea, mainly characterized by a an abundance of plant-based foods (such as fruits, vegetables, legumes) and non-saturated fats (derived from olive oil, nuts, seeds and fish), and limited consumption of red meat and processed foods [119–121].

Among the well-known beneficial effects of MD, which have earned it the appellation of health-promoting diet, of no little interest is its role in the nutritional treatment of the patient with obesity, both in terms of weight reduction and the management of associated comorbidities [122–124].

In addition to the existence of an inverse relationship between adherence to MD and BMI and weight gain [125, 126], in fact, there is evidence that this dietary pattern is associated with a twofold greater likelihood of maintaining weight loss [127]. In fact, it has been reported that, compared to other control diets, MD is associated with greater weight loss [128] and that this result in subjects with overweight/obesity is greater than that obtained with low-fat diets, but similar to that obtained with LCD [129].

MD, with some modifications, is often recommended for individuals with CKD. As suggested, indeed, the adherence to such a healthy dietary pattern can lead to a lower risk of CKD, delayed progression of CKD, and a reduced risk of kidney disease-related complications [18]. This is thought to be due to the anti-inflammatory and antioxidant properties of this dietary pattern, as well as its beneficial effects on blood pressure and blood lipid levels, glucose control, hyperinsulinemia, IR, and satiety [18, 130].

In general, the beneficial effects of MD on CKD prevention can be attributed to the main features characterising this dietary pattern. For example, the protein intake in MD is very similar to that recommended for CKD patients [17, 131]. Also, protein intake in MD mainly refers to a low red meat consumption, resulting in a lower Na, P and K intake [17, 131]. Notably, there is a difference in the absorption rate of P from animal and plant sources; in particular, about 40–60% of animal P is absorbed, while that of plant origin is less absorbed by the human gastrointestinal tract [132, 133]. Also, the use of K binders might counterbalance a possible increase in serum K due to higher dietary K intake; however, treatment with the old K binders Na^+ polystyrene sulfonate or calcium polystyrene sulfonate, causes severe gastrointestinal side effects and, to date, evidence on their clinical use is scarce [134]. The novel K binders, patiromer and Na zirconium cyclosilicate, indicated for treatment of CKD patients have no side effects and may favour a more healthy diet with adequate intake of fruits, vegetables, nuts and olive oil that are associated with a reduction in inflammation and OxS [131, 135].

MD adaptation at different CKD stages

Due to its inherent characteristics, MD is classified as a plant-based diet (PBD), as it contemplates the regular consumption of plant foods, with low to moderate consumption of animal foods. This characteristic supports the rationale behind the use of MD in CKD [136]. PBDs, in fact, are suggested as valid and safe dietary approaches for both primary prevention of CKD and delaying disease progression [136], as reported in previous large studies [137, 138]. This appears to be due to several mechanisms. Among

the main ones are (i) the production by the gut microbiota of anti-inflammatory compounds promoted by fibres, with a reduction in the production of uremic toxins promoted by animal food components, (ii) the anti-inflammatory and anti-atherogenic effects exerted by vegetable fats, in particular olive oil, (iii) the reduction of metabolic acidosis due to the low net load of endogenous acids, (iv) the lower bioavailability of vegetable P compared to animal P [136].

Beside a mere qualitative aspect, quantitatively the MD composition should be adapted in function of the stage of CKD [18], as represented in Fig. 2. The recommended daily consumption of cereals and derived foods, and fruit and vegetable is similar to that for the general population (5–6 times daily and 2 times daily, respectively) [18]. The daily consumption of dairy products is considerably reduced in CKD patients compared to that for the general population (1.5 serving daily for all stages). The use of extra virgin olive oil is strongly recommended in CKD patients, with a consumption frequency corresponding to the maximum range limit for the general population (6 servings daily) [18]. Recommendations for the consumption of nuts or seeds (without added salt, sugar, or fat) are available only for stages 1–2 (1 serving daily), while for the other classes of CKD patients their consumption should be individualised [18].

The consumption frequency of protein sources (both animal and vegetal sources) is established weekly and reduced compared to that for the general population. Minimum 4 serving of legumes weekly are recommended for stages 1–5. Fish rich in omega-3 is recommended, paying attention to the P/protein ratio; its consumption frequency is minimum 3 servings/week for all CKD patients, except for stages 3–5 patients, for whom it is reduced by one serving (minimum 2/week). Similarly, P/protein ratio needs to be considered for meat consumption, preferring lean meat such as poultry products; its frequency recommendation is maximum 3 servings weekly for all CKD patients, except for stages 3–5 patients (maximum 2 servings/week). Finally, the recommended weekly consumption of eggs corresponds to the minimum range limit for the general population (maximum 4 servings weekly) for all CKD patients, except for stages 3–5 [18]. Such proposal of adapted MD in CKD is in line with the evidence that within the variants of PBD, the healthy one is significantly associated with lower incidence and slower progression rate of CKD [137, 138].

In developing an MD for patients with CKD, however, the above recommendations regarding food consumption frequencies should inevitably be merged with the general dietary requirements in this clinical setting, paying attention to both the energy intake and the distribution of macronutrients, as recommended by the guidelines. Indeed, in addition to the obvious calculation of protein intake according to the stage of CKD, the qualitative-quantitative intake of carbohydrates should also be monitored, considering the role played by this macronutrient in controlling metabolic parameters and renal function, as profoundly described in the following paragraphs. In this sense, the negative impact of added sugars on renal function is well established [139], leading to the suggestion of carbohydrate-reduced diets for their beneficial effects [16]. However, although to the best of our knowledge there are no studies that have directly investigated the effect of carbohydrate-reduced diets (not KD) in patients with obesity and CKD, nor specific indications to this effect from current guidelines, it should be noted that, as previously reviewed, MD is characterised by a low glycaemic index, mainly due to regular consumption of high quality carbohydrate sources (i.e. whole grains, fruits, vegetables, nuts, not refined sugars) resulting in an optimal daily intake of fibre. This attenuates the postprandial glycaemic and insulinemic response, improving IR and serum lipid profile, ultimately reducing the risk of developing T2DM, with consequent beneficial effects on renal function [17, 130]. In this *scenario*, however, it must be considered that, in addition to the actual role of macronutrients in the progression of CKD, the general health-promoting effects of MD are due to the overall dietary pattern and not to its individual components [17], so the qualitative aspect of the diet should be emphasised or, at least, considered on a par with the quantitative one.

Among the historically known beneficial and health-promoting effects of MD, those on blood pressure, inflammation, lipid profile, and endothelial function may be related to a better-preserved renal function [140]. A meta-analysis of study carried out on the general population, indeed, concluded that MD adherence is associated with a lower risk to develop CKD (10% lower odds for every 1-point greater adherence to MD) [131].

In patients with manifest CKD, MD has been reported to exert beneficial effects [130, 141], including (i) prevention or reduction of disease progression [130, 131, 142], (ii) reduced risk of CVDs [143, 144], in particular lowering blood pressure and, thus, reducing the strain on kidney [143, 145], and (iii) reduced mortality rates [16].

These protective effects on renal function seem to be due to the unique features of MD, as suggested by the CORDIOPREV study reporting that CHD patients following a MD had a 1.58 mL/min/1.72m^2 lower eGFR decline rate compared to those following a low-fat diet, after 5 years of dietary intervention [146]. In this sense, anti-inflammatory and antioxidant properties of MD are undoubtedly the most relevant for prevention and management of CKD. Chronic low-grade inflammation, indeed, has been established as a major underlying cause for CKD, and it is observed that some components of MD, including olive oil, omega-3 fish, fruits or vegetables can decrease the levels of classic inflammatory biomarkers, such as CRP and IL-6, improving renal function [142].

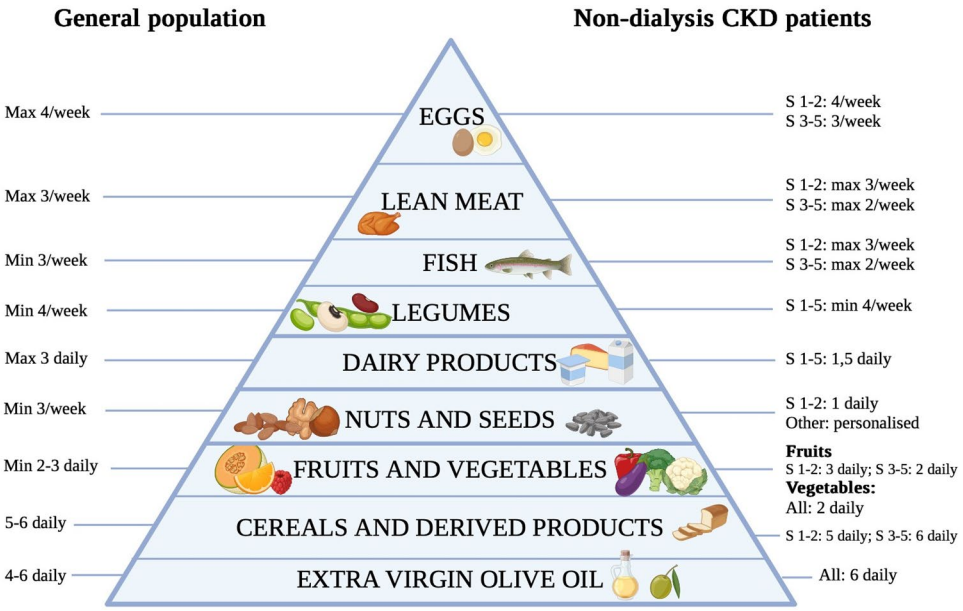


Fig. 2 Recommendations for consumption frequency of Mediterranean diet foods for general population and CDK patients. This graphical representation shows the recommendations for consumption frequencies of typical Mediterranean Diet foods, highlighting the differences between the general population and non-dialysis CKD patients and providing a useful scheme for adapting the dietary pattern to this clinical setting. *S* stages, *CKD* Chronic kidney disease

Ketogenic Diet

As previously reported in both animal and human studies, KD represents a valid strategy to achieve a weight loss [9], as well as to contrast inflammation and OxS [25] and to improve metabolic parameters [26, 27], resulting in a promising dietary approach for management of subjects with obesity and MetS [147].

Actually, the term "ketogenic diet" is generically used to identify various nutritional schemes that share, as main feature, a minimal carbohydrate intake (no more than 30–50 g daily), and thus they belong to the LCD category [9]. Apart from the daily carbohydrate intake, however, LCD/KD may be formulated with different total calories, mainly based on the lipid content rather than protein (though the protein intake may be still higher than recommended for the level of kidney function impairment), since an increased protein intake stimulates gluconeogenesis, thus inhibiting endogenous ketosis. This results in three main kinds of KD, namely isocaloric KD (ICKD), low-calorie KD (LCKD), and very-low-calorie KD (VLCKD) [9, 25–27, 148]. Of interest, very recently, we proposed a change in the nomenclature and acronym of VLCKD [149]. Therefore, we now prefer to use the term Very Low-Energy Ketogenic Therapy with the acronym VLEKT, which is more appropriate and avoids confusion in the definition of the very low carbohydrate diets [149].

In KD, the drastic reduction in carbohydrate intake is used to stimulate a physiological ketogenesis, starting from a glucose level reduction, with consequent decreases in liver glycogen, and promotion of gluconeogenesis and fatty acid (FA) oxidation. In particular, it occurs a lipogenesis-to-lipolysis metabolic shift, resulting in mobilization of triglycerides from adipocytes that are then converted into ketone body (KB) at liver level. In such biochemical *scenario*, the body uses FA-deriving KB as main fuel for brain and other tissues [9, 26, 27]. This mechanism is, thus, operated as a strategy to induce weight loss in management of obesity, since it promotes selectively the loss of FM, preserving lean mass and allowing a better control of the glucose homeostasis, in addition to a KB-deriving increased satiety contributing to enhance the compliance [9].

The proposed use of LCD/KD in CKD is mainly based on the beneficial metabolic effects of this dietary pattern in terms of weight loss, glycaemic control, and normalisation of insulin levels, three outcomes closely linked to improvements in kidney damages [9]. In short term, indeed, LCDs exert a blood glucose and insulin lowering effect [20], resulting in increased diuresis and natriuresis, with consequent blood pressure reduction [20, 150, 151]. Notably, LCDs do not exert negative effects on kidney function, as reported in a meta-analysis of studies on diabetics following this diet [152]; similarly, another meta-analysis reported a greater eGFR-increasing effect of LCD compared to control diet in subjects with overweight/obesity without CKD [153]. It has been observed, indeed, that reducing the percentage of carbohydrate intake results in increase eGFR by 3 ml/min/1.73m^2 [154].

Apart from the relative higher protein intake, a general concern with KDs that may limit their use in CKD is the possible blood acidification due to the excessive KB production. It should be note, however, that ketosis induced by KDs is physiological and different from the pathological diabetic ketoacidosis, since excessive circulating KBs stimulate the secretion of insulin, resulting in reduced FA release from adipocytes [25, 155].

Main putative mechanisms of KDs in improving renal function

Over the years, an extensive literature profoundly described and discussed that KDs exert marked metabolic (i.e., weight loss, glucose/insulin/lipid control) [26] and extra-metabolic effects (i.e., anti-inflammatory and antioxidant properties) [25]. Such effects of KDs support their use also in CKD, where this diet should be considered as a nutritional strategy to manage collateral conditions that can worsen the progression of renal failure. In this context, the main actor are the KBs, which production is endogenously stimulated by KDs [24]. KBs, indeed, have been suggested as a therapy for kidney disease [24, 156], due to their multiple effects, such as acting as signalling molecules [157], protecting of kidneys against stress, aging and diseases, and contrasting inflammation, OxS, apoptosis, and fibrosis [25, 156, 157]. In general, ketosis seems to increase the circulating levels of fibroblast growth factor-21, a hepatokine exerting anti-inflammatory effects [25]. More specifically, β-hydroxybutyrate (β-HB), the principal KD-produced KB, directly inhibits both assemblage and activation of NLRP3 inflammasome (involved in regulation of innate immune system linked to inflammation related to obesity), and decreases interferon-γ and TNFα in human PBMCs [25]. In addition, β-HB is an endogenous agonist of the hydroxycarboxylic acid receptor 2 (GRP190A), which exerts, among other, anti-inflammatory effects. Similarly, via increasing adenosine levels, β-HB attenuates the inflammation induced by HIF-1α, that mediates the cellular response to hypoxia [25]. Notably, KBs have been demonstrated to act as epigenetic factors able to increase the histone acetylation via inhibiting the class I histone deacetylases, with consequent regulation of both chromatin architecture and gene transcription, and mainly resulting in up-regulation of genes encoding for OxS resistance factors [25]. Moreover, KBs regulate the gene expression, including down-regulation of mTOR, PKA, insulin, and IGF-1 (involved in anabolic pathways), and up-regulation of AMPK (involved in catabolic/autophagy mechanisms); also, KBs contribute to reduce inflammation and OxS via activation of antioxidant and anti-inflammatory pathways [9].

Beyond the effects of KBs, KDs have been reported to decrease OxS and prevent OxS-mediated mitochondrial dysfunction via up-regulation of Nrf2 transcription [25], resulting in stimulation of antioxidant defences (i.e., SOD1/2 and NQO1) [158], with consequent regulation of the reactive oxygen species concentrations [21]. Being OxS closely related to flogosis, the anti-inflammatory potential of KDs is easily understood. However, KDs exert a direct effect on inflammation, mainly via various mechanisms [25], among which the main is undoubtedly the suppression of the NF-κB pathway, resulting in down-regulation of pro-inflammatory cytokines [21].

As described in previous sections, certain types of KDs (LCKD and VLEKT) provide a caloric restriction that itself exerts anti-inflammatory effects via modulating the expression of several inflammation-related genes (i.e., TIMP-3, NFKBIA, PPARs) and reducing the levels of pro-inflammatory factors (i.e., TNFα, IL-6, ICAM-1, VCAM-1, COX-2, iNOS) [25]. Again, regarding the main features of this dietary pattern, KDs are characterised by increased lipid intake. This results in elevated circulating levels of FAs (including long-chain PUFAs) that bind and activate PPAR-γ, exerting anti-inflammatory effects [25].

Another interesting mechanism by which KDs reduce inflammation is a gut microbiota modulation, in particular, increasing *Bacteroidetes* and reducing *Firmicutes* and *Bifidobacteria*, in this last case with consequent reduction of Th-17 cells, involved in inflammatory response. In addition, such KD-induced shift of gut microbiota come forth from a decrease in *Ruminoccocus, Eubacterium, Clostridium,* and *Bifidobacterium* and an increase in *Eggerthella, Streptococcus,* and *Lactococcus*. This two last strain produce folate, thus their increase is associated with increased levels of such vitamin, resulting in improved lipid metabolism, as well as reduced OxS and inflammation [25].

Of no less importance, KDs exert a plethora of metabolic effects that could also contribute to manage CKD as well as slow disease progression. First among all is their effect in reducing rapidly the BW and selectively FM [26], which role in renal function has been extensively discussed in previous sections. The weight loss obtained following KDs (in particular VLEKT) seems to be marked and constant during the intervention (− 7.48 kg at 1 month follow-up, − 15.04 kg at 2 month follow-up; − 16.76 kg at 4–6 month follow-up; − 21.48 kg at 12 month follow-up) [26]. The mechanisms behind the KD-induced weight loss are multifactorial and mainly include the general calorie restriction as well as the reduction of FM due to the ketosis-induced FA mobilization. These effects are easily maintained in long-term by a KB-induced appetite suppression that, in turn, ensures a greater dietary compliance. This aspect is of relevant importance considering that, in general, subjects with obesity are prone to dropout classical calorie restriction diets due to constant sense of hunger [25].

The weight loss achieved with this type of diet reflects a favourable BC, in terms of FM reduction (− 11.12 kg from baseline) and minimal loss of fat-free mass (− 2.96 kg from baseline) that, however, is not statistically significant from that obtained with other weight loss-dietary intervention. Interestingly, it can be speculated that VLEKT mainly acts on central obesity, thus decreasing abdominal FM, as suggested by the marked reduction in WC (− 16.53 cm from baseline [26].

The metabolic benefits of KDs (in particular VLEKT) have been extensively described by a meta-analysis included into the European Guidelines for the use of VLEKT in subjects with obesity, suggesting significant reductions in fasting glycaemia (− 8.85 mg/dl), HbA1c (− 0.43%), HOMA-IR index (− 2.30), total cholesterol (− 7.12 mg/dl), LDL-cholesterol (− 9.04 mg/dl), and triglycerides (− 49.68 mg/dl), while no changes are observed for HDL-cholesterol [26].

The effects of KDs on both BC and circulating lipids are closely linked by the low carbohydrate intake that induces reductions in hepatic glycogen stores and FA de novo synthesis in adipocytes, resulting in stimulation of body fat catabolism, that culminates in reduced blood and liver lipids [148].

Another important metabolic effect of KDs that could contribute to preserve and/or manage the renal function is reduction of insulin levels [25]. Such insulin-reducing effect is exerted by various mechanisms, including reduction of visceral adipose tissue depots and improvement in mitochondrial capacity and efficiency of skeletal muscle [148], acting with an "exercise-type" mechanism [159]. At liver level, KDs reduce rapidly and markedly the fat content, improving the IR and reducing the excessive gluconeogenesis and compensatory hyperinsulinemia. This KD-induced reduction in hepatic fat seems to improve insulin sensitivity also via amelioration of the mitochondrial efficiency, as well as reduction in both local OxS and inflammation [148]. In addition to these molecular mechanisms, the intrinsic features of KDs contribute to reduce insulinemia. The reduced intake of carbohydrates, indeed, reduces postprandial glycaemia, with consequent decrease in insulin requirements [148].

Studies

The main concern that LCDs, due to the relative higher protein intake, could impair kidney function was investigated in a study on subjects with abdominal obesity without pre-existing renal failure randomised into two intervention groups, LCD and high-carbohydrate diet. Authors observed that, in addition to weight loss, there were no significant changes in serum creatinine, eGFR, and urinary albumin excretion. The same results were observed in subjects following an high-carbohydrate diet, suggesting that LCDs does not exert adverse effect at renal level [160]. Similarly, in 2013, Tirosh and colleagues compared the effects of MD, LCD, and low-fat diet on renal function in subjects with overweight/obesity with or without T2DM, and pre-existing mild to moderate kidney dysfunction. Authors observed that all the three dietary strategies improved eGFR and urinary albumin-creatinine ratio with similar magnitude across diets, suggesting that LCDs, beyond weight loss do not impact negatively on renal function [161]. Similar results were obtained in a study on patients with T2DM and mild-to-moderate kidney disease showing that LCD, in addition to significant reduction of weight, WC, IL-6 and total daily insulin dose, did not worsen serum creatinine, despite a minimal decrease in eGFR, compared to a standard low-protein diet. Also, both diets resulted in significant reductions in fasting glucose and HbA1c, and no adverse events were reported [19].

The absence of apparent organ damages, but potential benefits at renal level following LCD/KDs was confirmed by a large retrospective study involving 2000 CKD patients (stages 1–3). LCD/KD promoted weight loss and amelioration of eGFR in stages 2–3; however, in stage 1 an eGFR worsening was observed, suggesting that in CKD intermediate stages the benefits related to rapid and significant weight loss outweigh the risk of early renal function decline, probably through improvements in blood pressure and glucose homeostasis [20].

Although no long-term studies are available to evaluate a risk/benefit ratio of LCD in CKD [9], a consensus suggests that in such patients with early CKD, in particular T2DM ones, an elevated carbohydrate intake is associated with a 15% increased odd of incident or progression of CKD, while the same probability associated with the relative increased protein intake provided by LCD is less than 14% [162]. In this sense, in subjects with eGFR > 80 ml/min/1.73m^2 a high intake of protein is not associated with eGFR decline [162].

Among the LCD/KDs, VLEKT is suggested as an attractive and valid nutritional strategy for management of obesity, in particular to achieve weight loss in subjects who failed previous dietary and/or pharmacological interventions. Although this is a very restrictive diet (in terms of TCI and distribution of macronutrients), VLEKT have been demonstrated to be effective and safe. As reported in a recent study conducted on 106 non-CKD subjects with obesity underwent VLEKT, indeed, no serious side effects were recorded during the entire duration of the protocol. Also, no signs of kidney dysfunction were recorded, as suggested by no significant changes in eGFR (94.13 ± 19.00 *vs* 89.00 ± 20.83 ml/min/1.73m^2, baseline *vs* end of VLEKT; $p = 0.123$) [163]. A safety study was also carried out to evaluate the feasibility of VLEKT in patients with T2DM. In addition to greater weight loss, WC reduction, and HbA1c decline in VLEKT group compared to standard low-calorie diet one; no significant differences were recorded in safety parameters between the groups; as well, no serious side effects were reported. With regard to the kidney function, authors did not observe significant changes in UCRA, BUN, creatinine, and eGFR,

suggesting that VLEKT does not impair renal function in this class of patients [164].

Remarkable insights on the use of KDs in CKD are provided by a study investigating the effects of VLEKT in this class of patients [22]. In particular, a replacement meal-based VLEKT was prescribed to 38 mild chronic kidney disease (MCKD, eGFR: 60–89 ml/min/1.73m^2) patients and 54 subjects with normal kidney function (NKF) (eGFR: ≥ 90 ml/min/1.73m^2). The VLEKT protocol consisted of five steps. In the first two steps (ketosis steps), the diet provided daily 450–800 kcal, 20–50 g of carbohydrates, 1–1.4 g/kg of ideal BW of proteins, and 15–30 g of lipids. In the following steps (3–5, carbohydrate reintroduction steps), a gradual increase in total energy and carbohydrate intakes was carried out [22]. Overall, the entire duration of the protocol was about 14 weeks (about 7 weeks covered by steps 1–2, and the same duration for steps 3–5). In both NKF and MCKD, it was observed a significant weight loss, mainly represent by FM reduction (assessed by BIA). In addition, reductions in TBW, ECW, ICW, and blood pressure (both systolic and diastolic) were observed, mainly due to the diuretic effect of KD. Similarly, all study participants experienced improvements in fasting glycaemia, HbA1c, cholesterol, and triglyceride levels. No significant changes were observed for liver and kidney function markers; only an increase in blood urea nitrogen was found, that, according to the authors, might be due to the significant dehydration [22]. Finally, P only increased significantly in NKF, remaining unchanged in MCKD, while no changes were observed in both groups for Na^+ and K^+ levels. Noteworthy, in MCKD creatinine and uric acid significantly reduced (from 0.93 ± 0.16 to 0.88 ± 0.17 mg/dl, $p = 0.002$ and from 5.49 ± 1.10 to 4.96 ± 0.94 mg/dl, $p = 0.008$, respectively), eGFR significantly increased (from 76.32 ± 10.44 to 82.21 ± 15.14 ml/min/1.73m^2, $p = 0.002$), while total protein, albumin and urinary protein levels remained unchanged. Among these, however, the most remarkable result was a full recovery of kidney function at the end of the VLEKT protocol observed in a significant number of MCKD patients (27.7%) that reported an eGFR ≥ 90 ml/min/1.73m^2. Overall, thus, this study suggests that VLEKT is an effective and safe tool to achieve weight loss in patients with MCKD and obesity, but also this dietary strategy is able to ameliorate renal function [22]. Table 4 summarises the main studies investigating the effects of LCD/KDs on kidney function.

Adaptation of LCD/KDs in CKD

In previous section, we referred to the increased protein intake provided by LCD/KDs defining it as "relative". This is due by the fact that, actually, compared to other dietary approaches (i.e. the classical MD), in LCD/KDs the percentage of protein (on the total calories) is higher than that of carbohydrates, but this does not imply an effective high amount of protein consumed daily. In the context of LCD/KDs, indeed, the protein intake generally ranged between 0.8 and 1.2 g of high-biological-value protein *per* kg of ideal BW [26, 27, 148], resulting in a normoprotein (and not hyperprotein) diet. It is plausible to speculate, thus, the use of properly adapted LCD/KDs for CKD patients, except for stages 3—5 ones, for whom a protein restriction (0.55–0.6 g/kg without T2DM, 0.6–0.8 g/kg with T2DM) is recommended to retard the progression of renal failure [15] (Fig. 3). Such adaptations refer to (i) the TCI, established on the basis of the nutritional outcome to achieve (weight maintenance = ICKD, weight loss = LCKD or VLEKT), (ii) the protein intake, established on the basis of the CKD stage, and (iii) the overall diet quality, in terms of choice of food, and in particular the source of dietary fats and protein. In this sense, beneficial metabolic effects would be obtained replacing animal-based food with unprocessed plant food by reducing saturated fatty acid and trans fats and increasing mono-unsaturated fatty acids and PUFA content. A higher consumption of red meat seems to be deleterious for kidney function, while other animal-based protein sources (i.e., fish, eggs, poultry, and dairies) do not show the same negative effects [165]. Differently, although no general consensus are available to establish the effective benefits of a PBD in CKD [16], evidence suggests a possible nephroprotective role of plant proteins [136–138, 166, 167]. In this context, non-meal replacement LCD/KDs for CKD patients should be properly formulated proving a balanced distribution between animal and plant protein sources. On the other hand, VLEKT is generally based on meal replacements formulated with both plant (i.e., soy and peas) and/or animal (i.e., whey, eggs) proteins, thus resulting in a suitable approach for CKD patients in terms of protein source choice [22, 26, 163]. Moreover, further cautions have been suggested to be adopted: (i) prescribing no more than 1.4 g protein *per* kg of ideal BW during all the VLEKT phases, preferring as much as possible plant-based proteins (> 50%) and choosing as much as possible low Phosphate/Protein food, (ii) monitoring carefully the protein intake during the carbohydrate reintroduction phases, (iii) avoiding red meat consumption during the reintroduction phases, (iv) recommending optimal water intake (at least 2 l daily), and (v) recommending supplementation with minerals and vitamins during the protocol to avoid micronutrient deficiencies [22], according to the current guidelines [26, 155]. Of note, plant-derived proteins differently from animal proteins, are well known to be not associated with the detrimental effects of hyperfiltration on kidney function [168].

Table 4 Effects of LCD/KDs on kidney function

LCD/KDs	Population	Main results	Reference
LCD	Subjects with obesity without pre-existing renal dysfunction	• Weight loss • Unchanged creatinine and eGFR	[160]
LCD	Subjects with overweight/obesity and with or without type 2 diabetes, and pre-existing mild to moderate kidney dysfunction	• Improved eGFR • Improved UACR	[161]
LCD	Subjects with overweight/obesity with normal or high (E1), mildly reduced (E2) or moderately to severely reduced (E3) kidney function	• Weight loss • Unchanged or improved eGFR in E2 and E3 patients • Decreased eGFR in E1 patient	[20]
LCD	Subjects with type 2 diabetes with mild to moderate kidney diseases	• Weight loss and reduced WC • No changes in creatinine levels • Reduced eGFR • Decreased HbA1c, fasting glycaemia, and IL-6 levels	[19]
VLEKT	Subjects with obesity and type 2 diabetes	• Weight loss and reduced WC • Reduced HbA1c and glycaemia • No significant changes in UACR, BUN, creatinine, and eGFR	[164]
VLEKT	Subjects with obesity, NKF and MCKD	• Weight loss • Reduced FM • Reduced TBW, ECW, and ICW • Reduced systolic and diastolic BP • Improved fasting glucose, HbA1c, cholesterol, and TG • Increased BUN • Increased P in NKF • Unchanged Na and K • Reduced creatinine and uric acid in MCKD • Increased eGFR in MCKD • Unchanged T-Pr, albumin, and U-Pr	[22]
VLEKT	Subjects with obesity without renal failure	• Weight loss and reduction in WC • Unchanged eGFR • Minimal increase in creatinine, azotemia, uricemia, Ca, and Na • Unchanged K	[163]

BP blood pressure, *BUN* blood urea nitrogen, *Ca* calcium, *ECW* extracellular water, *FM* fat mass, *ICW* intracellular water, *IL-6* Interleukin-6, *K* potassium, *LCD/KD* low-carb diet/ketogenic diet, *MCKD* mild chronic kidney disease, *Na* sodium, *NKF* normal kidney function, *P* phosphorus, *PTH* parathyroid hormone, *TBW* total body water, *TG* triglyceride, *T-Pr* total protein, *UACR* urinary albumin-creatinine ratio, *U-Pr* urinary protein, *VLEKT* very-low energy ketogenic therapy, *WC* waist circumference

General indication and contraindication of KD

Although it is a dietary intervention, it should be emphasised that KD represents a medicalised therapeutic approach, also referred to as ketogenic nutritional therapy (KeNuT) [147]. Therefore, it is crucial to consider the main indications for which this therapy may be prescribed, among which overweight, obesity and related comorbidities stand out in the first place. Similarly, however, in the context of a medical nutritional therapy appropriately tailored to the patient's characteristics, KeNuT also has the following contraindications: pregnancy, lactation, childhood, type 1 diabetes, T2DM with beta-cellular insufficiency or being treated with glyphozines, rare metabolic disorders, organ failure, heart attack and stroke, severe psychiatric disorders, eating disorders, alcohol and substance abuse. The indications and contraindications of KeNuT, and supporting studies, are detailed in a consensus statement from the working group of the Club of SIE [147].

Conclusion

This is a consensus statement from the Italian Society of Endocrinology (SIE), the Italian Society of Nutraceuticals (SINut), and the Italian Society of Nephrology (SIN).

Due to its specific features (decline in kidney function), as well as the associated pathological conditions (such as inflammation, OxS, fibrosis, and autophagy), CKD requires profound lifestyle modifications, including a proper dietary program [21]. This becomes even more important when considering that obesity and T2DM (two diseases strongly linked to diet) contribute to the development of renal failure and adversely affect the progression of kidney disease [9, 20]. Treatment and management of these two conditions

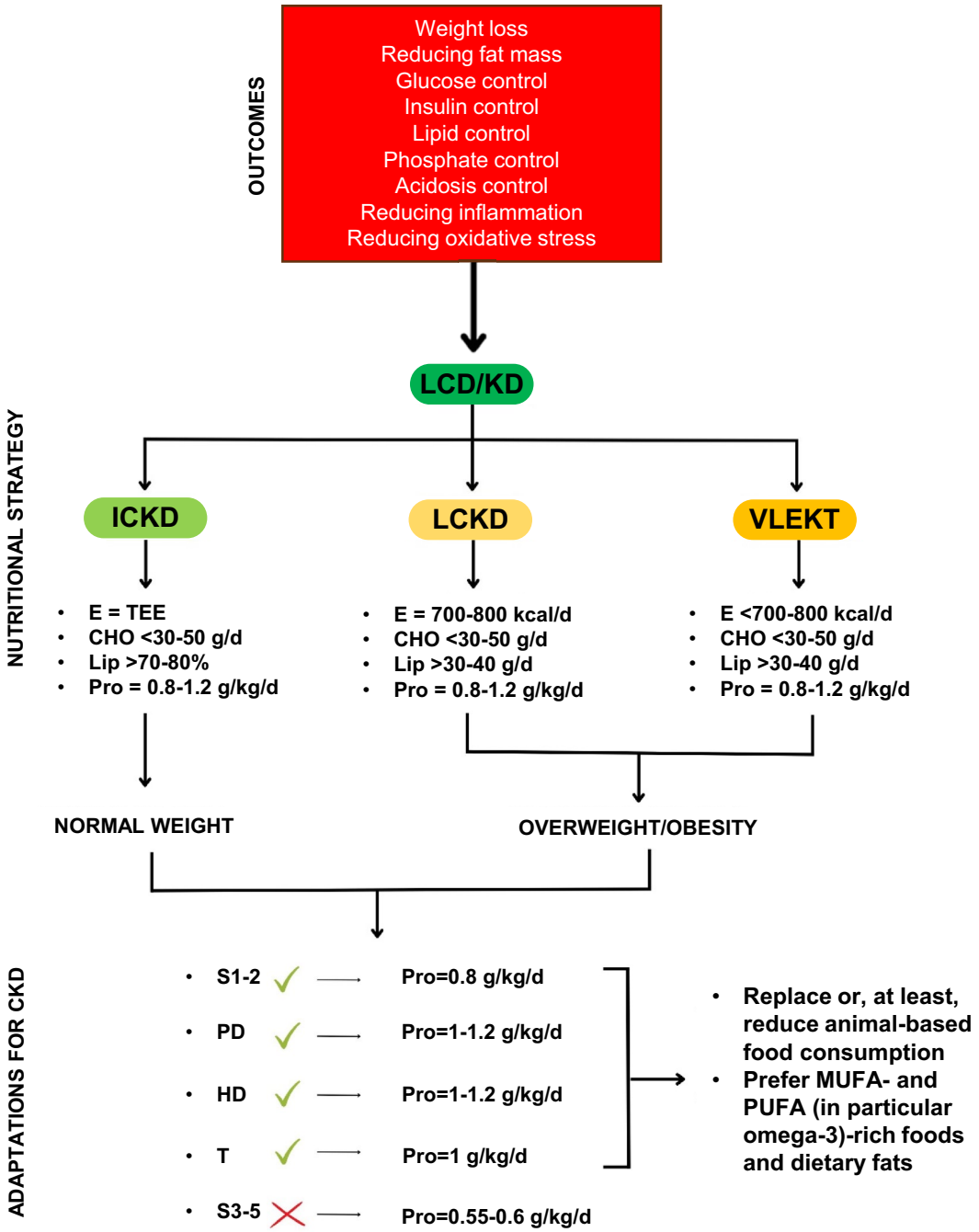


Fig. 3 Prescription of LCD/KDs in CKD and relative adaptations for the various stages according to KDOQI guidelines [15], EASO guidelines [26], Barrea et al.,2022 [25], and Paoli et al.2023 [148]. Obesity with the presence of related metabolic complications is an indication for the prescription of KD, which, in particular, should include a hypocaloric approach (LCKD, VLEKT). However, it should be emphasised that, with the appropriate adjustments in terms of energy intake and macronutrient distribution (ICKD), it is also possible to develop this type of diet in subjects in whom it is not necessary to achieve weight loss, but still utilise the benefits of ketosis for therapeutic purposes. However, in both cases, and irrespective of the type of KD prescribed (ICKD, LCKD or VLEKT), the nutritional intervention must always be adapted by establishing the optimal protein intake according to the degree of CKD. Green checkmark and red-cross indicate whether KDs can be prescribed or not, respectively. *LCD/KD* low-carb/ketogenic diet, *ICKD* isocaloric ketogenic diet, *LCKD* low-calorie ketogenic diet, *VLEKT* very low-energy ketogenic therapy, *E* energy, *CHO* carbohydrates, *Lip* lipid, *Pro* proteins, *g* grams, *kg* kilograms, *d* day, *S* stages, *PD* peritoneal dialysis, *HD* haemodialysis, *T* transplant, *TEE* total energy expenditure, *MUFA* monounsaturated fatty acids, *PUFA* polyunsaturated fatty acids

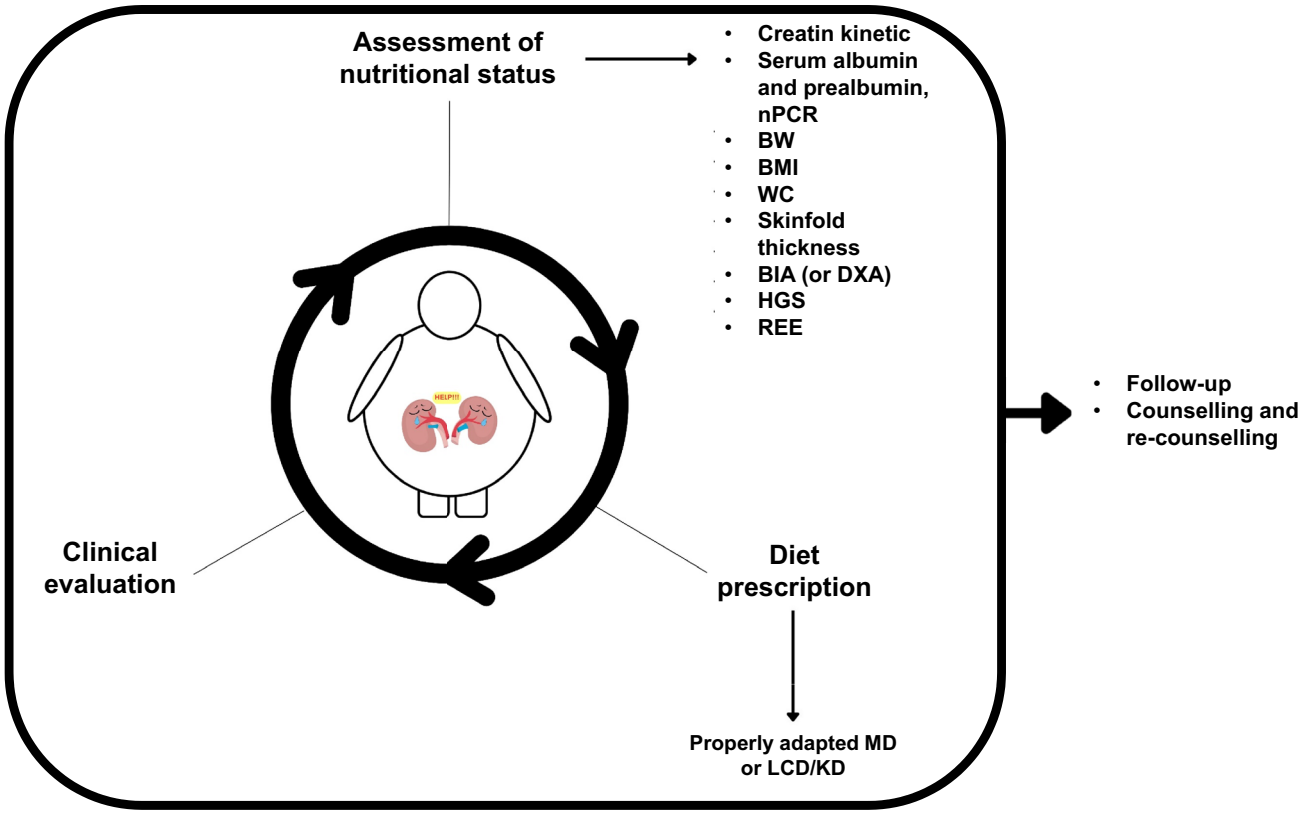


Fig. 4 The complete evaluation of the CKD patients. After the clinical evaluation (performed by Endocrinologist and Nephrologist), qualified Nutritionists (or international equivalent) or physicians perform a deep assessment of the nutritional status comprising laboratory parameters, measurements, and use of technical devices. Such assessment is, then, followed by the estimation of the required energy that is necessary for the dietary intervention. Finally, after evaluating the risk/benefit ratio, the proper diet is prescribed. *nPCR* normalised protein catabolic rate, *BW* body weight, *BMI* body mass index, *WC* waist circumference, *BIA* bioelectrical impedance analysis, *DXA* dual-energy X-ray absorptiometry, *HGS* handgrip strength, *REE* resting energy expenditure, *MD* mediterranean diet, *LCD/KD* low-carbohydrate/ketogenic diet

with dietary interventions aimed at weight loss, thus, is necessary in CKD [20]. In general, the initiation of a dietary intervention in a critical clinical setting (as in the case of CKD) can sometimes be challenging, especially due to psychological/motivational concerns that sometimes complicate the pre-existing clinical condition. In this sense, therefore, it is important that all nutritional interventions, in general, and those for CKD, in particular, are finely tuned to the patient's needs, condition and, above all, approval. If the patient does not approve of a particular dietary intervention, physicians and nutritionists must work to find other possible and more compliant strategies to achieve the same clinical results. However, although the patient's wishes must always be taken into account in a patient-centred disease management perspective, the decision on the optimal strategy to be adopted always remains at the physician's discretion after careful clinical evaluation. In this context, KD will certainly be suggested in cases of obesity with coexisting metabolic complications, in the absence of which MD may be opted for. Likewise, it will be at the physician's discretion to determine when to start a dietary intervention, which, in any case, should be undertaken as soon as possible to slow down the progression of the disease.

Besides the mere caloric aspect, different dietary patterns have been suggested to be suitable and effective in management of obesity, also in patients with CKD. Among these, MD/PBD and LCD/KDs emerge as the main studied and investigated. Although presenting intrinsic and marked differences, these two dietary patterns exert beneficial effects in reducing BW, inflammation and OxS, and improving metabolic parameters and insulin sensitivity [16], with understandable differences in terms of the extent of improvement and the timing to achieve the results. Properly adapted (Figs. 2 and 3), thus, MD and LCD/KDs can be prescribed to CKD patients. For the MD, such adaptations mainly refer to the amount and consumption frequencies of Mediterranean foods [18]. For LCD/KDs, instead, the protein intake needs to be adapted according to the guideline recommendations for the single CKD stages [16], while carbohydrate intake remains below the 50 g threshold to allow

the ketosis, and fats are included compensatively to reach the total daily calorie intake, resulting in ICKD (energy = total energy expenditure), LCKD (energy = 700–800 kcal/day), or VLEKT (energy < 700–800 kcal/day) [25, 26, 148]. This allows obtaining a dietary pattern that effectively and contextually contributes to manage the obesity and improves the renal outcomes. Overall, the evidence reported in previous sections tears down the wall of preconceptions about the use of LCD/KDs in CKD patients, due to the mistaken belief that they were high-protein diets. Such diets, thus, should not be a priori refused, but considered as a potential alternative (an opportunity), after a careful clinical screening followed by a detailed assessment of the nutritional status (Fig. 4), and should be used for a limited time, necessary to obtain the target weight loss and metabolic improvement. However, since many patients with CKD and obesity also have T2DM, it is mandatory to recall that the use of KDs is contraindicated in all patients treated with SGLT2 inhibitors, due to the risk of normoglycemic ketoacidosis, as reported in several case reports [169]. In consideration of the proven cardiorenal long-term benefits demonstrated in clinical trials and real-world studies with SGLT-2 inhibitors, it is therefore preferable to use alternative dietary approaches in these patients, where the mild nutritional ketosis induced by the diet could become harmful, in consideration of the glycosuric effect of the drug. In these cases, a balanced hypocaloric nutritional regimen should be considered, according to the weight loss target and patient features. A complete evaluation of the CKD patient operated by the different qualified healthcare personnel, according to their single competencies, allows finding the best therapeutic approach and creating a dense network and cooperation among patients, endocrinologist, nutritionists, and nephrologists with, in the middle, the health of the patients [117].

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Declarations

Conflict of interests All authors declare neither financial nor non-financial interests that may be relevant to the submitted work.

Research involving human participants and/or animals Not applicable.

Informed consent Not applicable.

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