

## Low-protein diets in CKD: how can we achieve them? A narrative, pragmatic review

Giorgina Barbara Piccoli<sup>1</sup>, Federica Neve Vigotti<sup>1</sup>, Filomena Leone<sup>2</sup>, Irene Capizzi<sup>1</sup>, Germana Daidola<sup>3</sup>, Gianfranca Cabiddu<sup>4</sup> and Paolo Avagnina<sup>5</sup>

<sup>1</sup>Nephrology, Clinical and Biological Sciences Department, S. Luigi Gonzaga Hospital, University of Turin, Italy, <sup>2</sup>Dietetics, Surgical Sciences Department, S. Anna Hospital, University of Torino, Turin, Italy, <sup>3</sup>Nephrology, S. Giovanni Battista Hospital, University of Turin, Italy, <sup>4</sup>Nephrology, Brotzu hospital, Cagliari, Italy and <sup>5</sup>Clinical Nutrition, Clinical and Biological Sciences Department, S. Luigi Gonzaga Hospital, University of Turin, Italy

Correspondence to: Giorgina Barbara Piccoli; E-mail: gbpiccoli@yahoo.it

### Abstract

Low-protein diets (LPDs) have encountered various fortunes, and several questions remain open. No single study, including the famous Modification of Diet in Renal Disease, was conclusive and even if systematic reviews are in favour of protein restriction, at least in non-diabetic adults, implementation is lagging. LPDs are considered difficult, malnutrition is a threat and compliance is poor. LPDs have been reappraised in this era of reconsideration of dialysis indications and timing. The definition of a normal-adequate protein diet has shifted in the overall population from 1 to 1.2 to 0.8 g/kg/day. Vegan-vegetarian diets are increasingly widespread, thus setting the groundwork for easier integration of moderate protein restriction in Chronic Kidney Disease. There are four main moderately restricted LPDs (0.6 g/kg/day). Two of them require careful planning of quantity and quality of food: a 'traditional' one, with mixed proteins that works on the quantity and quality of food and a vegan one, which integrates grains and legumes. Two further options may be seen as a way to simplify LPDs while being on the safe side for malnutrition: adding supplements of essential amino and keto acids (various doses) allows an easier shift from omnivorous to vegan diets, while protein-free food intake allows for an increase in calories. Very-low-protein diets (vLPDs: 0.3 g/kg/day) combine both approaches and usually require higher doses of supplements. Moderately restricted LPDs may be adapted to virtually any cuisine and should be tailored to the patients' preferences, while vLPDs usually require trained, compliant patients; a broader offer of diet options may lead to more widespread use of LPDs, without competition among the various schemas.

**Keywords:** CKD; compliance; keto acids and amino acids; low-protein diets; very-low-protein diets

### Low protein diets: a new garden?

In a wonderful book, 'Cradle to Cradle, Remaking the Way We Make Things', a manifesto of the 'new industrial revolution', a chemist and an architect search for a new production strategy combining abundance, safety and efficacy. One of the many anecdotes concerns the mother of one of the authors, who used to cultivate a wild garden full of diverse flowers and unusual trees. In 1982, the woman was fined by the local administration because her garden was 'too messy'. The lady continued paying a yearly fine for about a decade, until she won an award for creating a habitat for songbirds. The authors concluded that it was not a change in the garden; it was a change in the prevailing aesthetic. It was a change in the society [1].

A similar story may be told for low-protein diets (LPDs). Since the pioneering studies by Thomas Addis, who foresaw

Brenner's theory of 'workload' on the remnant nephrons and systematically used diets in clinical practice, LPDs have encountered alternate fortunes [2–9]. Strong supporters and determined adversaries contributed to the controversy, reflecting changes in the near-world of renal replacement therapies, and the wider-world of nutrition [10–12].

The conflicting interpretation of the largest randomized controlled trial on diet in kidney disease, the Modification of Diet in Renal Disease (MDRD) study, which failed to demonstrate an advantage in the primary intention-to-treat analysis, but supported a positive effect in the secondary per-protocol analyses, further radicalized the positions in favour of or against LPDs [9, 13–17].

The MDRD study highlighted the crucial role of compliance, not yet fully appreciated in chronic diseases, and added two important tools: the MDRD equation for the assessment of GFR and the only dietary satisfaction questionnaire validated in kidney patients [18, 19].

The issue of the diet was not solved by a Cochrane review in favour of protein restriction in non-diabetic adults, leaving the definition of the optimal protein intake in LPDs up for debate [20, 21].

The present cultural drive favours a lower protein intake in the overall population: several studies have tried to define a healthy diet, i.e. one that is rich in 'healthy foods', such as vegetables, fruits, nuts, olive oil and grains, and poor in red or processed meat [22–24]. Globalization confronts the current European and North American diets with different ones, which are often lower in animal proteins, and this has also led to an in-depth review of recommended daily allowances [25–27]. Rediscovery of the Mediterranean diets, rich in vegetables, legumes and cereals, and demonstration of their association with longer survival, call for attention to traditional diets which are more easily 'transformed' into LPDs [28–30]. Meanwhile, evidence of the increase in all-cause mortality, cardiovascular diseases and cancer related to diets that are rich in red and processed meat calls for attention to the 'too much' [31, 32].

In counter-tendency to the classical food marketing strategy that highlighted the presence of 'valuable' ingredients, a world-wide campaign is being carried out to regulate additives in food [33–35]. Growing attention to the quality rather than the quantity of what we eat activates virtuous cycles of 'zero km' production, with renewed interest in non-preserved, additive-free food.

In this context, vegetarian and vegan diets are becoming increasingly popular, setting the groundwork for easier integration of vegetarian protein-restricted diets in our patients who are no longer seen as 'outliers' in a carnivorous world [36–38].

Vegan-vegetarian diets usually contain between 0.6 and 0.8 g/kg/day of vegetable proteins and may be less effective in enhancing renal hyper-filtration, also since vegetable proteins are less bioavailable than animal proteins [39–42]. Provided that deficits are controlled and corrected (in particular, iron, vitamin B12 and vitamin D), these diets are considered safe by the most eminent associations, including the American Dietary Association, in all phases of life, including growth, pregnancy and lactation [36–38].

This paradigm shift allows 'our' LPDs to be more easily integrated in a society in which 'eating together' is a pivotal moment, with easier access to vegan menus, available on intercontinental flights as well as in most international restaurants.

No alibi: it is possible to reduce protein content and to follow at least a moderately protein-restricted diet almost everywhere. As for the wild garden, our society is moving towards a reappraisal of traditional diets, characterized by lower animal protein content, better quality of food and fewer additives [29–31, 43–47].

### Are we answering the unanswered questions?

Almost 30 years after the provocative paper 'Dietary treatment for chronic renal failure, ten unanswered questions' and its tentative answers, many questions are still unanswered (Does chronic renal failure always progress? How should we assess progression, nutritional status or compliance? Is there a placebo effect in diet trials? When should a low-protein diet start? What are the risks of a low-protein diet? What is the cost of a low-protein diet?) [10, 11]. In this narrative review, we will focus on the most practical one: 'Which low-protein diet?' as a key for implementing the 'right diet' with the 'right patient'.

### What is a diet?

On Wikipedia, 'diet is the sum of food consumed by a person or other organism'. We will employ the word 'diet' in this broad meaning, preferring it for the sake of simplicity to the more elegant, but less practical 'nutritional approach' 'nutritional therapy', however without the restrictive meaning 'diet as reduction of ...'.

Diet is all that we eat. Implicit in this is the opinion that for Chronic Kidney Disease (CKD) patients, being on a diet should consist of changing their habits and not (simply) in restricting the use of some (many-most) foods.

### What is a normal protein diet and what is an LPD?

*From attention to under-nutrition to attention to over-nutrition*

If the definition of diet is simple, the definition of normal protein intake is not. Following the increased availability of food, in the Western world, a 'healthy' diet progressively switched from a diet containing a 'minimum requirement to avoid deficits' to one not surpassing an 'ideal intake' to avoid over-nutrition [48].

The FDA Reference Daily Intake or Recommended Daily Intake (that substitutes the older 'Recommended Daily Allowance') is the daily intake that suffices to meet the requirements of 97–98% of healthy individuals in every demographic in the USA: this is presently identified as 0.8 g/kg/day of proteins, lower than the previous 1.0 g/kg/day, considered the hallmark of 'normal' protein intake [25–27].

As a consequence, what we used to call moderately restricted 'LPDs' (0.8 g/kg/day) now have 'normal protein' content, while diets at 1.0–1.2 g/kg/day should be considered 'high protein'. This is not only semantic: it casts a different light on the classical 0.6 g/kg/day diets, no longer radically different from 'normal' diets (Table 1).

#### *A practical nomenclature: vegan-vegetarian diets*

The systematic distinction between vegan and vegetarian diets is relatively new: the term vegan was coined by Donald Watson in 1944: 'vegan' from the beginning and end of vegetarian 'because veganism starts with vegetarianism and carries it through to its logical conclusion' [49]. The two terms were often used interchangeably in the past, or, most often, vegetarian diets were subdivided into 'strict', corresponding to the current vegan diets, and 'ovo-lacto' vegetarian diets [36–38, 49].

Vegetarian diets are free from fish, meat and poultry, i.e. from living sources of food; there is however, a long list of variants, including ovo-vegetarian (eggs only), lacto-vegetarian (milk and dairy products) and pescetarian (fish is allowed). Honey is excluded by some diets, while others take care in avoiding all animal-derived components which are common in food processing, for example, sugars whitened with bone char, cheeses that use animal rennet or gelatin from animal collagen. Watson, who was registered as 'a conscientious objector' in World War II, expanded his philosophy to object to any harm to living creatures. This latter attitude is extended in the Fruitarianism, based upon fruit, nuts, seeds and food gathered without 'harming the plant' [50].

The cultural roots of vegetarianism are deep: the list of eminent vegetarians includes Buddha, Leonardo Da Vinci,

**Table 1.** Characteristics of the main LPDs, defined according to protein content

Diet definition	Type of proteins	Scheme	Advantages—problems	Supplements protein-free food
Moderate protein restriction: 0.6 g/kg/day 'Traditional' LPD	0.6 g/kg/day, mixed, with at least 50% of animal origin (or 'high biological value')	The diet requires adaptation to the local habits; 30–35 kcal/kg are reached by implementing protein-poor calorie-rich natural food (for example, rice, potatoes, tapioca, fruit, oil and butter)	Advantage: no supplement or special food needed; limits: skilled dietician is needed. The caloric intake may be difficult to reach in particular in 'small' patients	None
Vegan LPD	0.6 g/kg/day, vegetable origin	This diet is strictly vegan; it is based upon a combination of different proteins of vegetable origin, mainly in grains, legumes and soy protein	Advantage: no supplement or special food are needed; limits: the combination of legumes and cereals at each meal is demanding. May not be suited to patients with diverticulosis or intestinal problems	None
Vegan supplemented with keto and amino acids	0.6 g/kg/day, vegetable origin	This diet is strictly vegan; it may be based upon forbidden (all food of animal origin) and allowed food (all food of vegetable origin). Supplements allow integration without need for combining grains and legumes at each meal	Advantage: simplified scheme based upon allowed and forbidden food; may be used in patients who do not like or tolerate legumes. Limits: need for supplementation of many pills (free of charge only in a few countries).	Alpha-keto acids and amino acids, min: 1:10, max 1:5 kg BW
LPD with protein-free food	0.6 g/kg/day, mixed origin	Cereals are all or in part replaced by protein-free food (mainly pasta and bread). This allows moderate quantities of proteins of animal origin	Advantage: no need to drastically change food habits. Problems: easily integrated in Mediterranean diets, less in Northern diets. Limited availability (high cost) of protein-free food in several countries.	Protein-free food
vLPD: 0.3 g/kg/day vLPD-vegan supplemented	0.3 g/kg/day, vegetable origin	This diet is strictly vegan; it may be based upon forbidden (all food of animal origin) and allowed food (all food of vegetable origin). More easily carried out if bread and pasta are substituted with protein-free food.	Advantage: probably more effective in postponing dialysis. Problems: requires separate cooking, is monotonous and requires a high number of pills. Limited availability (high cost) of protein-free food in several countries.	Alpha-keto acids and amino acids, 1:5 kg BW; optional: protein-free food.

In pregnancy: 0.6–0.8 LPD—vegan vegetarian—supplemented: mainly vegetable proteins; small doses of milk and yogurt allowed. Alpha-keto acids and amino acids 1:8–10 kg BW in the first trimester, increased to 1:5–8 kg BW in the last.

Gandhi, Tolstoy, George Bernard Shaw (who foresaw the participation at his funeral of all the animals he had not devoured), Isaac Bashevic Singer (I did not become a vegetarian for my health, I did it for the health of the chickens), but also music stars, such as Paul McCartney (If slaughterhouses had glass walls, everyone would be a vegetarian).

Even if the demonstration of the possibility to combine public success and vegetarian diet is reassuring, the motivations of a 'vegetarian by choice', be it for the sake of the chickens or for the sake of the soul, may be different from those of a 'vegetarian for health', in whom the motivation is sustaining health, or avoiding dialysis. We need different strategies, while learning from the 'vegans-vegetarians' by choice.

#### LPDs in CKD: learning from the beginning

Tracking the development of LPDs is fascinating: the first attempts to counterbalance the hyper-azotaemia of advanced kidney disease date to the first half of the Twentieth Century [3, 51–53]. However, most of the approaches that proved to be effective in clinical practice were developed in the 50–60s; our current diets are the result of the strategies to overcome the difficulties identified in these early studies.

The first problem was combining LPDs with a sufficient caloric intake, because a hyper-catabolic state leads to an increase in blood urea [54–57]. Different sources of calories were tested, and the cultural differences were highlighted: surrogates of pasta and bread were compatible

only with Italian diets, while in Anglo-Saxon countries mixtures of lipids and carbohydrates were tested, overall with poor success [54–58].

These first diets were very hard: the effort of having to keep all foods under control made them exceedingly complex: this is, for example, a typical dinner published in the late '60s with a low-protein mixed diet: 120 g carrots (cooked weight); 100 g runner beans; 100 g potatoes (raw weight); 15 g salt-free butter; 135 g tinned peaches (100 g peach, 35 g juice); 15 g single cream and 10 g white bread. The modified Giovannetti diet was no easier: this is a 'supper' from a 1970 paper: '50 g egg; 15 g lettuce; 55 g tomato; 30 g beetroot (cooked weight); 50 g low-protein bread; 15 g unsalted butter; 100 g mandarins (tinned) (80 g fruit + 20 g juice); 15 g single cream' [57].

The definition of the protein target was a crucial issue. The underlying idea was simple: protein intake should be 'the lowest the best', provided that hyper-catabolism was avoided [3, 52–62].

Different levels of protein restriction were tested, initially defined according to total protein content (the 40 g versus the 20–19–18 g diets [54–57]) and later according to body weight, finally leading to a pragmatic subdivision into LPDs at 0.8–0.6–0.3 g of protein per kg/body weight (Tables 1 and 2, Figure 1).

Early studies attempted to assess the minimum protein intake requirement. 'Very-low-protein diets' (vLPDs) derive from data suggesting that 0.3 g/kg/day is the lowest, safely achievable protein intake, provided supplementation with essential amino and/or keto acids is included.

**Table 2.** Energy, minerals and vitamins in the different LPDs

	'Traditional' LPD	LPD with protein-free food	Vegan LPD	Vegan supplemented with keto and amino acids	VLPD-vegan supplemented
Calories	30–35 kg body weight: this is the most crucial point to avoid protein malnutrition, in particular in elderly patients with cardiovascular disease (MIA syndrome); this is a basic prescription for all LPD; the risk of hyper-catabolism may increase in 'very low' protein diets				
Calcium	Calcium is usually added				
Phosphate	Phosphate content strictly depends upon the quota of animal proteins. It may be increased if canned, preserved or frozen foods are employed	Phosphate content is usually low in vegan diets, in particular if only fresh food is used. Bioavailability of vegetable phosphate may be different. Readily bioavailable phosphate may be remarkably increased if canned or frozen food is routinely consumed (usually frozen vegetables and canned legumes)			
Vit D	Supplementation is commonly needed; however the quota of animal proteins may protect from severe deficits	Vitamin D is commonly needed; bioavailable vit D is less represented in vegetable-based products			
Folate	Supplementation may be needed if the patient eats low quantities of fresh fruits and vegetables				
B12	Supplementation may be needed; however, the quota of animal proteins usually protects from severe deficits	Supplementation is commonly needed; B12 deficit is particularly prevalent and may lead to severe problems in vegan-vegetarian pregnancy			
Iron	Supplementation is commonly needed; however, the quota of animal proteins may protect from severe deficits	Supplementation is usually needed; the bioavailability of vegetable iron is usually lower, even if well-designed vegan diets are not necessarily associated with a deficit in iron			

We did not consider in this review the intake of two main nutrients: sodium and potassium, on the account of their dependence from several other elements, including, for the former the type of disease (interstitial versus vascular or glomerular nephropathy), the blood pressure level and the anti-hypertensive therapy, and for the latter the acidosis status, the use of diuretics and the eventual potassium-containing food additives.

Conversely, the other 'magic number' of 0.6 g/kg/day was believed to identify the upper level of protein restriction exerting a measurable effect on CKD progression [3, 52–62].

The concept of malnutrition came later, when the availability of dialysis allowed to carry out a long-term analysis of the diet and of its carry-over effect after the start of renal replacement therapy [61–64].

Interestingly, these early studies calculated that LPDs allowed life span to be prolonged by about 1 year (in the absence of dialysis) and slowed progression when started earlier [55, 61]. These results are remarkably similar to more recently reported ones, with different, more palatable, LPDs, in a context of widespread dialysis availability [8, 16, 20, 21, 62–71].

### Why is the evidence on LPDs in CKD inconclusive: personalized medicine, or RCTs?

The controversy over LPDs in CKD is indirect proof of the lack of conclusive data [7–11, 14–16, 63, 64]. After the MDRD study, several well-conducted Randomized Controlled Trials (RCTs) and one Cochrane review on non-diabetic adults were in favour of protein restriction [14, 65–67, 71–73]. However, no study is devoid of biases and none represented a paradigm shift towards a systematic acceptance of LPDs in CKD.

There are many reasons why studies may be non-conclusive or biased. Diet, for which compliance is key to success, is highly intrusive in a patient's life, as demonstrated by the attrition bias according to which patients tend to switch to their preferred diets despite the original prescriptions [14, 74–78].

Personalized, patient-centred medicine is an emerging clinical model, that is hardly compatible with the rigidity of RCTs [79–82]. Following the lesson of the complementary medicines, the focus may shift from the demonstration of the superiority of a treatment to an observational multidimensional 'whole system' approach [83].

In fact, to cite a *BMJ* educational report, 'when the effectiveness of the intervention depends on the subject's active participation', a reflection of the patient's preferences, 'a randomized trial may be inappropriate because the very act of random allocation may reduce the effectiveness of the intervention' [84]. Thus, while RCTs are best for studying short-term efficacy, observational studies may be more appropriate for analysing their implementation and highlighting the interactions with patients' preferences and compliance [76, 84–86]. RCTs and observational studies have complementary roles: 'high quality observational studies may extend evidence over a wider population and are likely to be dominant in the identification of harms and when RCTs would be unethical or impractical' [87].

The methodological drawbacks of studies on diets in CKD are similar to those of dialysis: randomization of peritoneal dialysis versus haemodialysis is considered 'unethical and unpractical'. The endless search for the best dialysis treatment shows that the main reason for supporting treatment choice is the demonstration of its equivalence in terms of hard end points [88]. The diet is probably as intrusive as dialysis is in daily life. The price of an appealing randomized study design not involving 'indifferent' therapies is a low enrolment rate or an important attrition bias: indeed how many of us would accept being randomized to a restricted versus an unrestricted diet? [14, 15, 65, 66, 71].

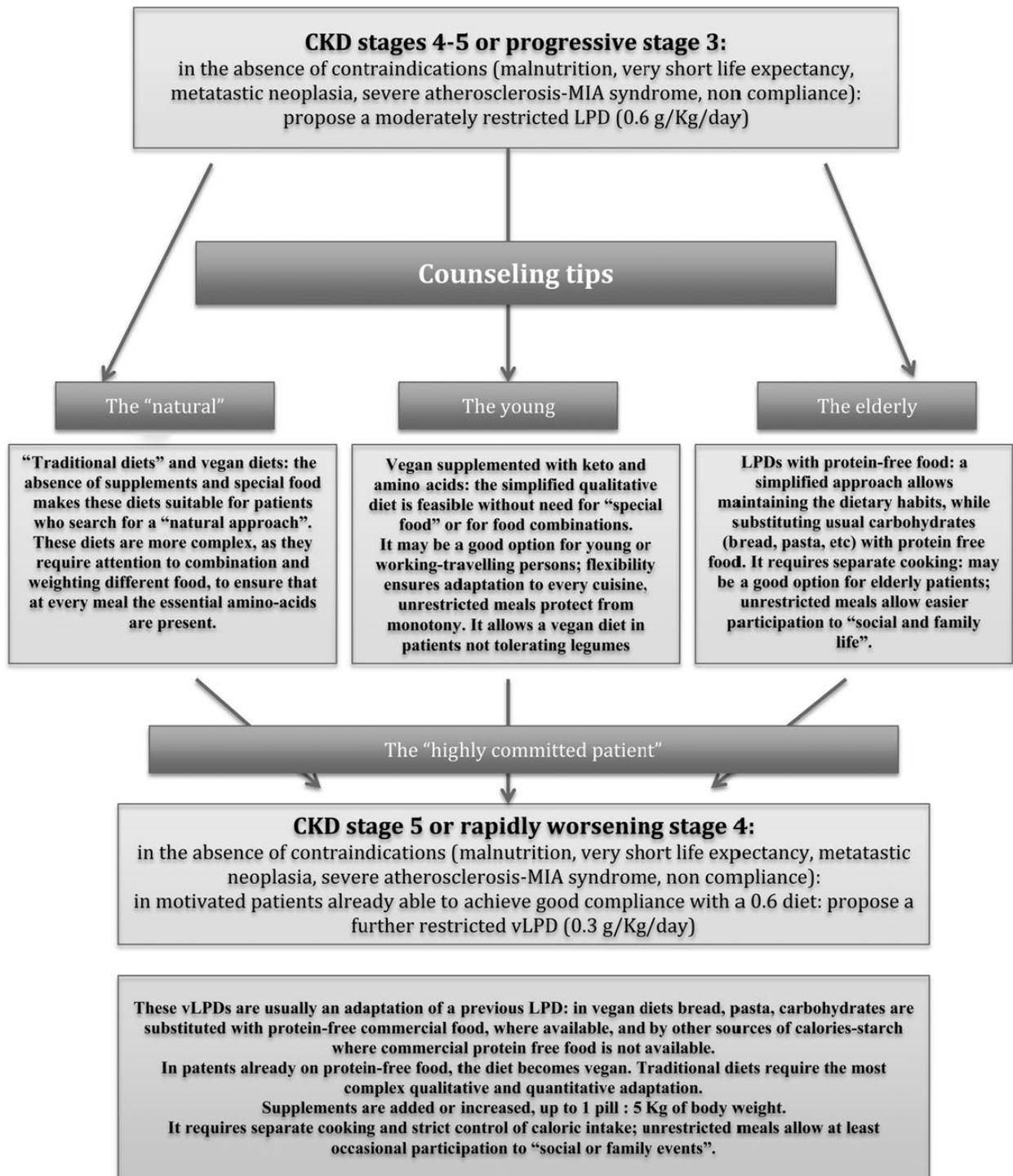


Fig. 1. A diet flowchart and counseling tips.

**A practical nomenclature: moderate protein restriction: low-protein ‘0.6-diets’: ‘traditional’, vegan, vegan-supplemented and with protein-free food**

The approaches to ‘moderate protein restriction’ which is synonymous with a diet having a protein intake of 0.6 g/kg/day encompass various combinations of protein content,

prevalence of vegetable proteins, use of dietary supplements and protein-free food (Tables 1 and 2, and Figure 1).

There are four main policies for achieving a balanced ‘0.6 diet’: we will call them ‘traditional’, vegan, vegan-supplemented and with protein-free food.

Although all protein-restricted diets share the risk for malnutrition, which is obviously enhanced by baseline malnutrition, severe atherosclerotic disease and inflammation (the Malnutrition-Inflammation-Atherosclerosis (MIA)

syndrome), the risks are low in moderately restricted diets and may be more frequent in the case of stricter protein restriction. A 'hidden' but crucial point in the management of all types of LPDs is indeed the exclusion of the cases with baseline malnutrition, long-term steroid therapy, very advanced age, with or without MIA [89, 90]. Differences in exclusion policy may account for the different results obtained in various studies, in particular as for the safety issues.

#### 'Traditional' 0.6-diets

There is substantial agreement that moderate protein restriction is feasible without the need for supplements or protein-free food [12, 72, 73, 75, 91].

Achieving this goal may be easier where the traditional cuisine is mainly based upon vegetable proteins, such as in India or in Mediterranean countries, and is integrated with small quantities of animal proteins, but may be difficult in Anglo-Saxon or Northern European countries [28–32, 43–46].

Designing LPDs with mixed protein content may start from an adaptation of local diets: for example, Mediterranean diets integrate legumes and cereals, and the addition of a very small amount of dairy products or meat-fish supplies the essential amino acids that are needed; on the other side of the world, in the 'Okinawa diet', very small amounts of animal protein were added to a diet that is rich in fruit and vegetables [23, 29, 30, 92]. Adaptation may be more difficult in other contexts where the baseline diet is less rich in vegetables and cereals, however protein content has only recently risen in the Western world, and most traditional cuisines have a lower protein intake in 'everyday food' [28–31].

#### Vegan 0.6–0.8 diets

As already mentioned, non-restricted vegan diets usually provide a protein intake of 0.6–0.8 g/kg/day and are nutritionally adequate if carried out with attention to the integration of essential amino acids [36–38]. As a rule, legumes and cereals and/or soy should be combined at every meal, and a high variety of legumes and cereals ensures integration of essential amino acids. Some interesting schemas are available from different parts of the world, such as the Italian Barsotti scheme, or the Israel approach by Soroka. Both Barsotti and Soroka employed dietary regimens at 0.7–0.8 g/kg/day on the account of the lower bioavailability of vegetable proteins [40, 41, 93].

#### Supplemented, vegan 0.6-diets

Supplementation with amino and keto acids and substitution with protein-free commercial food represent two strategies to 'be on the safe side' as for malnutrition. The first strategy provides supplementation of essential amino acids (in the form of amino and keto acids, metabolized *in vitro* with an additional urea-sparing effect), the second one adds calories in the form of protein-free food [89, 94].

In the past, various mixtures/combinations of amino acids and keto acids were used; presently only two of them, both of which are marketed by the same company, are available: Alfa Kappa (in Italy) or Ketosteril (all over the world) [94, 95]. Their composition is identical but for the presence of 23 mg per pill of L-tryptophan in Ketosteril. The Italian formula is tryptophan free due to its possible role as a precursor of pro-fibrotic cytokines and indoles [96, 97]. In the absence of a clear demonstration of any clinical difference, they are usually considered equivalent

and have been used interchangeably in some studies, also on account of manufacturing changes that have taken place over time [69, 70].

According to a consensus statement, supplements are not strictly needed in vegan diets at 0.6 g/kg/day of proteins [89]. However, they may be useful when omnivorous patients are 'forced' into a vegan regimen, or when a patient does not like or cannot tolerate legumes. Supplementation allows a simplified quantitative approach that excludes animal-derived food, but leaves a free choice of vegetables, fruits, legumes and cereals [69, 70]. On the basis of our group's experience, this is also a good strategy in fragile patients, including diabetics, pregnant women or patients recovering renal function [69, 70, 89, 98–101].

The dose of supplements with the 0.6 diets is not standardized; our group indicates 1 pill every 10 kg of body weight, as a compromise between 'too many pills' and risk of malnutrition [69, 70, 98–101].

#### 0.6-Diets with protein-free food

The issue of protein-free foods is complex [102]. The idea was born in the era of limited dialysis availability: natural protein-free foods (tapioca, butter, sugar, fruits and vegetables) resulted in very monotonous diets. Following the English example of starch-containing food for coeliac patients, the first protein-free pasta was produced in 1966, followed in the late '70s by an industrial production of pasta, flour, biscuits, bread and crispbread. More recently, protein-free drinks, snacks, and partially cooked foods have become commercially available [102]. However, to the best of our knowledge, protein-free food is available free of charge to CKD patients only in Italy, thus limiting the systematic diffusion of this approach [70].

Replacing the usual cereals with protein-free food allows the patient to achieve a high caloric intake, thus giving him/her more freedom to plan the rest of the diet. This is especially favourable in Mediterranean countries where up to half of the proteins derive from bread and pasta (12 g of proteins per 100 g), and replacing them allows the patients to reach the target protein intake without substantially changing their dietary habits. Hence, in our experience, these diets are preferred by elderly patients, while younger ones tend to prefer vegan supplemented diets [70, 71].

Adding calorie-rich food to avoid malnutrition was also attempted by other supplements (for example, maltodextrin and oil creamer), once more in keeping with the local dietary habits [103, 104].

#### vLPDs: a combination of vegan, supplemented diets and protein-free food

A supplemented LPD is not synonymous with a vLPD [89]. However, vLPDs (usually at 0.3 g/kg/day) require integration to avoid malnutrition [14–16, 66–68, 71, 72, 90, 104]. The amount of amino and keto acid supplements, conventionally measured in pills per kg/day, is 1 pill/5 kg of body weight [89].

The combination of a vegan diet, requiring many pills, possibly together with commercial protein-free food, makes these 'artificial diets' extremely complex and an option for only a small number of patients. The Bucharest group, which to date has probably achieved the best compliance with vLPDs, enrolled about 10% of the initially screened patients into their trial [71, 105]. Similar difficulties were

encountered in the Brunori trial [65–67]. Interestingly, in our observational study, which allowed patients to freely choose their own diet, the prevalence vLPDs was also about 10% with respect to all LPDs [70]. Despite the difficulties, vLPDs are usually considered more effective in postponing dialysis in compliant patients [71–75]. A ‘missing point’ in the literature is the actual menu of these diets.

In Italy, the availability of protein-free food makes it easier to reach the ideal caloric intake, however, when protein-free food is not available, the diet may be even more demanding [16, 66–68, 71, 72, 105].

While this review was focussed on the ‘classical’ indications for CKD; however, it may be worth mentioning that vLPDs may have a specific indication in the ‘rescue treatment’ of nephrotic syndrome resistant to the therapies specifically addressed at the pathophysiologic mechanisms [106, 107].

### **Quality matters, but compliance matters more; different proteins may have different effects, and what about ‘unrestricted meals’?**

The quality of the protein matters: some studies suggest there is a favourable effect of soy proteins in kidney transplant patients, diabetic patients or experimental animals [108–111]. However, the evidence is limited and shares the same methodological drawbacks as trials on LPDs: compliance is crucial in the long term and it is difficult to achieve if the diet is too rigid.

Various policies have been employed to improve compliance: one option is to alternate different LPDs in order to increase the variety of food [112].

The approach followed by our group is a qualitative simplification of the diet, based upon forbidden and allowed food for the vegan diets, or upon substitution of carbohydrates with protein-free food, without otherwise changing the diet [69, 70, 98–101]. An occasional unrestricted meal (one to three times per week) or one day a week off-diet is another strategy for ensuring compliance. At least two groups have systematically reported inclusion of free meals, thus leading to good compliance [69, 70, 75, 98–101, 113].

### **A warning: an LPD is not synonymous with a healthy diet**

A decrease in kidney function is associated with an increased risk in adverse drug reactions. Less is known about the toxic effect of food additives, preserving agents or taste enhancers. Recent studies highlighted the importance of added polyphosphates and warned about sodium and potassium content [114–117]. The list of potentially toxic additives is long and the effect in the context of reduced kidney function has not yet been investigated. While waiting for further studies to be carried out, attention should be paid to all food components and not only to the quantity of proteins, and should be a warning to patients and manufacturers alike.

This review did not consider other important elements, including sodium and potassium, on account of their highly complex inter-dependence with other issues, including type of disease, blood pressure level and anti-hypertensive therapy, acidosis balance and food additives. While each of these issues may be worth a specific review, reminding them may underline the complexity of a comprehensive dietary approach to CKD patients [118, 119].

### **Working conclusions: which diet for which patient?**

If we extend the approach that has been developed for dialysis, i.e. allowing each patient to choose the most acceptable treatment and encouraging empowerment and self-care, we may design a multiple choice diet system with easy access to different options so that each patient may find the best diet (or at least the least intrusive one).

A stepwise option, starting from moderate protein restriction, could be proposed to all patients with progressive or advanced CKD in an attempt to allocate each patient to the simplest and most feasible diet option (such as vegan simplified diets for younger patients, traditional and with protein-free food for elderly patients), while strict 0.3 diets will probably play a role in highly motivated, well-trained patients, or in selected patients for whom postponing dialysis may be of particular relevance (Figure 1).

In such a setting, there may be no competition among different diets, and the availability of more schemas may allow a greater number of patients to follow an LPD for a longer period, with potential benefits for the overall CKD population.

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