Clinical Kidney Journal, 2023, vol. 16, no. 4, 647–661

https://doi.org/10.1093/ckj/sfac267
Advance Access Publication Date: 9 December 2022
CKJ Review

CKJ REVIEW

Plant-based diets for CKD patients: fascinating, trendy, but feasible? A green nephrology perspective

Massimo Torreggiani[1], Antioco Fois[1], Françoise Lippi[1], Rossella Attini[2], Elisa Longhitano[1,3], Ida Matarazzo[1,4], Bianca Masturzo[5], Gianfranca Cabiddu[6], Elisabetta Versino[7] and Giorgina Barbara Piccoli[1]

[1]Néphrologie et Dialyse, Centre Hospitalier Le Mans, 194 Avenue Rubillard, Le Mans, France, [2]Department of Obstetrics and Gynecology, Città della Salute e della Scienza, Ospedale Sant'Anna, Torino, Italy, [3]Department of Clinical and Experimental Medicine, Unit of Nephrology and Dialysis, A.O.U. "G. Martino", University of Messina, Messina, Italy, [4]Unit of Nephrology, Department of Advanced Medical and Surgical Sciences, University of Campania "Luigi Vanvitelli", Naples, Italy, [5]Department of Obstetrics and Gynecology, Ospedale Degli Infermi, Biella, Italy, [6]Nephrology, Azienda Ospedaliera Brotzu, Cagliari, Italy and [7]Department of Clinical and Biological Sciences, University of Torino, Torino, Italy

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

ABSTRACT

Climate change is inducing us to rethink our way of life. There is widespread awareness that we need to adopt environmentally friendly approaches and reduce the amount of waste we generate. In medicine, nephrology was one of the first specialties to adopt a green approach. Plant-based or vegan–vegetarian diets, which are planet-friendly and associated with a reduced carbon footprint, were rapidly acknowledged as a valid method for reducing protein intake in the conservative management of chronic kidney disease (CKD). However, how the transition from an omnivorous to a plant-based diet should be managed is not universally agreed; there is little data in the literature and indications based on randomized trials fail to consider feasibility and patients' preferences. Nonetheless, in some conditions the use of plant-based diets has proved safe and effective. For example, in CKD pregnancies, it has reduced unfavorable maternal and fetal outcomes. This review will present the available evidence on the benefits of plant-based diets in CKD, as well as old and new criticisms of their use, including emerging issues, such as contaminants, additives and pesticides, from a green nephrology perspective.

Keywords: additives, carbon footprint, low-protein diet, pesticides, pregnancy

THE GREEN NEPHROLOGY CONTEXT

We live in a rapidly changing, increasingly globalized, dangerously polluted world.

The concept of sustainability has spread to many fields, from clothing to leisure and even medicine. Nephrology has a tradition of "thinking green," initially on account of the features inherent in dialysis, which consumes large quantities of energy and water and produces enormous amounts of waste, encompassing all the "worst" types: non-recyclable, contaminated and what are called WEEE (Waste Electrical and Electronic Equipment) [1, 2]. The pivotal work done by John Agar

Received: 12.8.2022; Editorial decision: 23.11.2022

and his colleagues in Australia allowed us to rethink dialysis procedures in a more planet-conscious way, suggesting that water could be recycled, solar energy was to be preferred and waste products should be wisely transformed to enable them to be safely reused [3–5]. Subsequent experiments by other groups made it possible to identify additional contextualized approaches to power and water consumption and waste management [6–9].

Although these studies addressed two of the three Rs in the green cycle (reuse and recycle), clinical approaches are crucial in the case of the third R (reduce) [10]. Reducing the burden of disease obviously reduces medical needs, and medical waste, energy and power consumption [10]. While this holds true for all initiatives aiming to prevent disease and promote a healthy lifestyle, nephrology is probably the field that has made the greatest advances, conjugating reductions in energy and water consumption and waste production associated with dialysis from a green perspective, i.e. the wide use of healthy, protein-restricted (either plant-based or, at least, animal-protein restricted) diets to delay dialysis start [11]. More recently, growing interest in incremental dialysis is further extending the potential of green diets [12].

DIET AND SOCIAL CONTEXT

The increase in overall food availability and advances in medicine have increased life expectancy for both rich and poor. At a time when the last famines are being progressively, and possibly too rapidly, forgotten, excessive calorie intake is becoming the world's most important nutritional health challenge [13–15]. Eating in excess is often associated with eating high-calorie, poor quality food, called "junk food" or "empty calories," which often lacks vitamins, trace elements and natural anti-oxidants, is generally highly processed, and contains large quantities of contaminants, taste enhancers and preservatives [16–19]. Globalization has made a wider choice of food available, but this often involved interfering with the physiological food chain, a combination of early harvesting and the use of preservative and conservative agents [20–23].

While disentangling the effects of food habits and lifestyle, or of food contaminants and environmental pollution is not easy, a strong cultural drive towards healthy living has characterized the new millennium, and the effects of the lockdown and the pandemic may have contributed to this reflection [23–31]. In many countries, the principles of a healthy, planet-friendly diet are increasingly being taught in schools, and TV advertising has begun to urge viewers to eat less meat, and more fruit and vegetables [32, 33]. Healthy diets are almost always rich in vegetable sources, and limited in processed and transformed food, thus shifting the target towards a plant-rich, if not necessarily plant-based, diet [33–35].

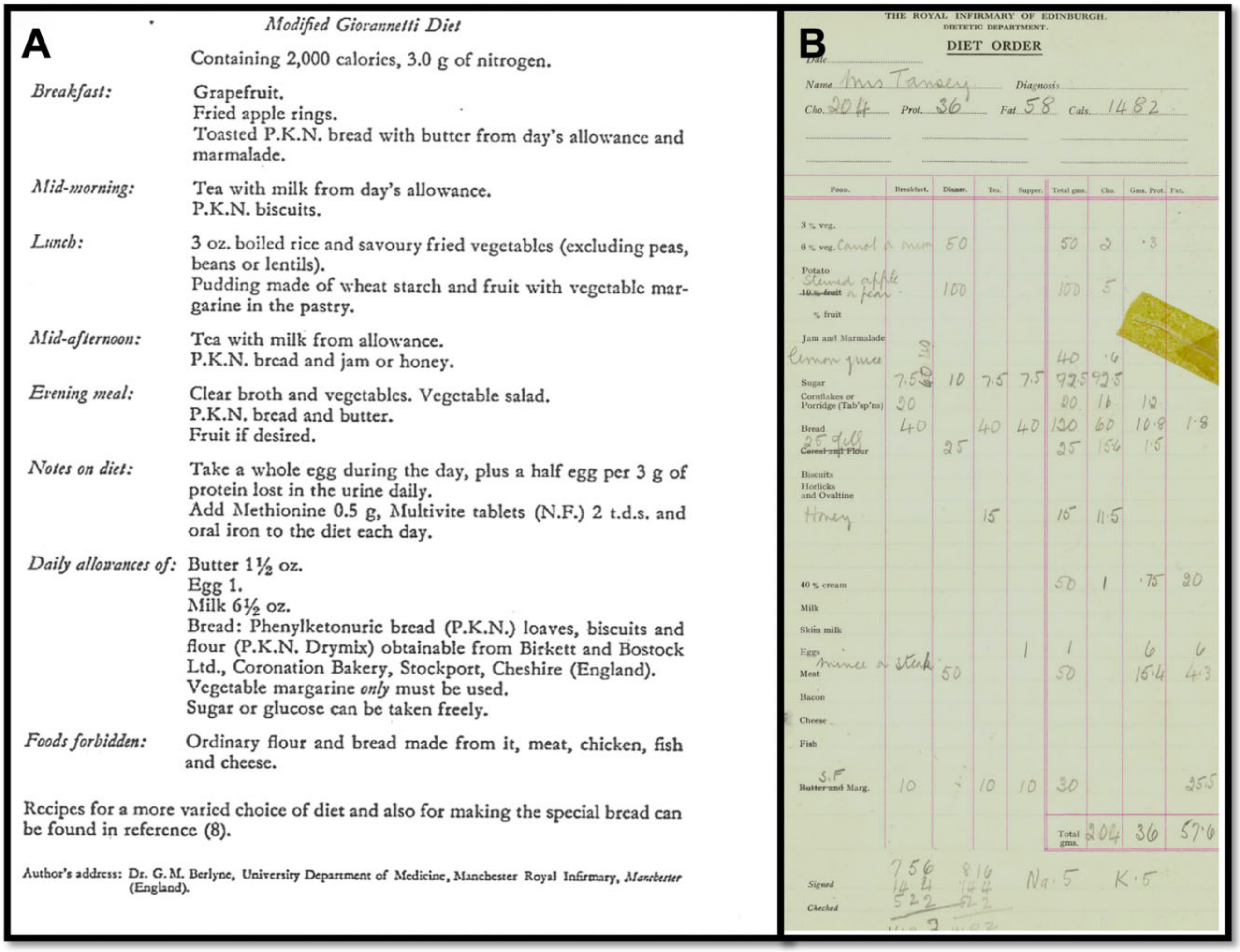
This paradigm shift is important not only for prevention, but also because it creates a favorable cultural background for the nutritional management of a number of chronic diseases, including cardiovascular illnesses, metabolic syndrome, diabetes and obesity, in which a balanced diet is the most important preventive measure, and is pivotal in chronic kidney disease (CKD), in which a reduction in kidney function leads not only to what was once defined as a "state of protein intoxication," but probably also increases susceptibility to reactions to added and toxic substances.

FROM LOW-PROTEIN TO PLANT-BASED DIETS IN CKD

The concept of protein intoxication as the major determinant of the uremic syndrome, and the efforts to counterbalance this intoxication by reducing protein intake, dates back to Thomas Addis, a pioneer of modern nephrology [36, 37]. The initial idea was simple: fewer proteins would produce less intoxication. The fact that this reduction made it possible to limit symptoms and also prolong the lives of patients with severe kidney disease, together with studies in experimental animals, led to the formulation of the renal workload theory: fewer proteins, less hyperfiltration and a lower workload for the remnant nephrons, less severe sclerosis and a longer lifespan [38].

However, the success obtained with a draconian reduction in proteins in prolonging life was counterbalanced by the development of malnutrition, specifically protein wasting. Notwithstanding the role of anemia, acidosis and hyperparathyroidism (that were not corrected at the time), the concept that protein intake, albeit reduced, should be "rich" emerged, leading to the tenet that at least 50% of the proteins in low-protein diets should be of animal origin [39–43]. The difficulty in reaching adequate energy targets, often because of the attempt to correct all nutritional derangements with the same diet (low sodium, low fat, not diabetogenic, etc.), made the first "renal diet" regimens extremely difficult for patients to follow and adaptations of the Giordano–Giovannetti diet, taking tastes and habits in different countries into account, were increasingly introduced [44–47] (Fig. 1). It was found that including protein-free starches in the diet (allowing at least patients in Mediterranean countries to easily increase their calorie intake), and leaving space for animal-derived ingredients and greater variety, made it easier for patients to follow the diet and increased long-term compliance [48]. It was, however, only in the most recent version of the KDOQI guidelines on nutritional management in CKD that the indication that at least 50% of protein intake be of animal origin was no longer retained, opening, as a consequence, room for "plant-based" diets as an alternative option in all CKD stages [49]. At the same time, vegan–vegetarian diets had progressively gained a niche following in the dietary management of advanced CKD, as they are the only way to lower protein content below 0.4 g/kg/day, conventionally set as the upper limit of very-low-protein diets (vLPDs) [49]. These diets were considered to be nutritionally safe only when a mixture of essential amino acids, and more recently and with better results, of amino acids and ketoacids were added [48]. In those early phases, the focus was on the quantity of proteins, and not on their quality or source. However, protein quality may be of pivotal importance, since plant-based regimens are not necessarily synonymous with low-protein intake if not properly designed [50, 51]. However, plant-based diets rarely reach the high protein content typical of diets rich in animal proteins, and their effect on glomerular hyperfiltration is milder [52].

The progressive development of dialysis and transplantation sharply reduced enthusiasm for protein restriction until the rising tide of new dialysis patients, the majority of whom were elderly and had an increased comorbidity burden, as well as the perception of inequalities in dialysis availability worldwide led nephrologists to reconsider the clinical and socio-economic advantages of retarding or avoiding renal replacement therapy. The results of the IDEAL study, showing no advantage of "early," "healthy" dialysis start, led to a paradigm shift, suggesting an intent-to-delay policy with respect to dialysis and,



A

Modified Giovannetti Diet

Containing 2,000 calories, 3.0 g of nitrogen.

Breakfast: Grapefruit.
Fried apple rings.
Toasted P.K.N. bread with butter from day's allowance and marmalade.

Mid-morning: Tea with milk from day's allowance.
P.K.N. biscuits.

Lunch: 3 oz. boiled rice and savoury fried vegetables (excluding peas, beans or lentils).
Pudding made of wheat starch and fruit with vegetable margarine in the pastry.

Mid-afternoon: Tea with milk from allowance.
P.K.N. bread and jam or honey.

Evening meal: Clear broth and vegetables. Vegetable salad.
P.K.N. bread and butter.
Fruit if desired.

Notes on diet: Take a whole egg during the day, plus a half egg per 3 g of protein lost in the urine daily.
Add Methionine 0.5 g, Multivite tablets (N.F.) 2 t.d.s. and oral iron to the diet each day.

Daily allowances of: Butter 1½ oz.
Egg 1.
Milk 6½ oz.
Bread: Phenylketonuric bread (P.K.N.) loaves, biscuits and flour (P.K.N. Drymix) obtainable from Birkett and Bostock Ltd., Coronation Bakery, Stockport, Cheshire (England).
Vegetable margarine *only* must be used.
Sugar or glucose can be taken freely.

Foods forbidden: Ordinary flour and bread made from it, meat, chicken, fish and cheese.

Recipes for a more varied choice of diet and also for making the special bread can be found in reference (8).

Author's address: Dr. G. M. Berlyne, University Department of Medicine, Manchester Royal Infirmary, *Manchester* (England).

Figure 1: Examples of early diets: (**A**) an adaptation of the Giovannetti diet in use at the Royal Infirmary of Manchester in 1965 (from reference [45]); (**B**) a dietary prescription at the Royal Infirmary of Edinburgh in the 1960s (from http://edren.org/ren/unit/history/the-diet-for-patients-on-haemodialysis/?print = print).

as a consequence, once more focused attention on diet as an efficient means for retarding the need for renal replacement therapy [53]. In parallel, changes in western societies, with the emergence of obesity and diabetes epidemics on one hand, and the rise of environmental consciousness on the other, set the stage for large-scale campaigns promoting a healthy lifestyle, reduction of our carbon footprint, the rediscovery of local products and the responsible use of resources, thus, indirectly making the integration of plant-based diets in health and disease easier [54–61].

"HOLY COW! WHAT'S GOOD FOR YOU IS GOOD FOR OUR PLANET"

An interesting article published in the *BMJ* in 1983, reported on the astonishing stabilization of CKD in a small number of Buddhist monks, thus indicating new interest in low-protein diets in advanced kidney disease. Since most Buddhist monks are vegetarian or vegan, even if the details of the dietary regimen were not disclosed in this publication, we can assume that a great proportion of their diet was provided by plant-derived foods [62].

Until the new millennium, very few groups dared to propose vegetarian diets to CKD patients, and even fewer had the courage to publish their data. The diets were often seen as curiosities rather than feasible choices for large numbers of CKD patients [63, 64]. Since vLPDs are almost obligatorily vegan, vegan–vegetarian diets were often considered as synonymous with vLPDs, risky from a nutritional point of view and doomed to failure as a result of low compliance. The impressive results obtained in selected patients in the few well-conducted randomized trials published were largely ignored [64, 65]. Meanwhile, different types of vegetarian diets became popular and veganism gained interest due to its comprehensive lifestyle and planet-friendly approach. Vegan–vegetarian diets in nephrology, previously a niche option for a few selected patients, were increasingly prescribed. The association with essential amino acids but with a lower pill burden in comparison with vLPDs (1 pill/10 kg/day) allowed some groups to propose simplified dietary prescriptions, shifting from complex vegan diets to qualitative diets, added to the moderately protein-restricted diet choice for patients with advanced CKD [66, 67].

As clearly, albeit quite ironically, stated in a brilliant editorial that appeared in the *Archives of Internal Medicine* "Holy cow! What's good for you is good for our planet," reductions in the intake of animal proteins has a wider meaning from an ecological point of view, and the avoidance of processed foods enables us to have healthier nutritional habits [68].

Table 1: Common food additives or preservatives and their effects on health.

Food additive/preservative	*Category*	*Health effects*	*Reference*
E2011 Sodium benzoate (SB)	*Preservative*	*Decreased expression of activation receptors in splenocytes and impaired T and B lymphocyte activity*	[149–152]
		Genotoxic and cytotoxic activity at high concentrations	
		Alteration of cerebellar structure in rats	
E322 Lecithins	*Emulsifiers*	*Increased TMAO production by the intestinal microbiota with potential consequences for arterial stiffness and cardiovascular disease. Increased incidence of Chron's disease*	[153, 154]
E251 Sodium nitrate	*Preservative*	*Associated with all-cause mortality, colorectal, gastric and pancreatic cancers*	[155–159]
E252 Potassium nitrate			
E331 Sodium citrate	*Antioxidant*	*Increased fasting glycemia and impaired glucose tolerance in mice. Potentiate LPS-induced activation of macrophage cell line in vitro*	[160, 161]
E339 Sodium phosphate	*Antioxydants/acidity regulators*	*Endothelial dysfunction and vascular calcification*	[162, 163]
E340 Potassium phosphate			
E341 Calcium phosphate			
E450 Orthophosphoric acid diphosphate salts			
E451 Triphosphore			
E452 Polyphosphate			
E433 Polysorbate-80	*Thickener/emulsifier*	*Low-grade inflammation increased adiposity in mice. Dysbiosis*	[164, 165]
E407 Carrageenan	*Thickener*	*Glucose intolerance in mice, exacerbated glucose intolerance and dyslipidemia induced by a high-fat diet in mice*	[166, 167]
E466 Carboxymethylcellulose	*Thickener/emulsifier*	*Weight gain and impaired glucose tolerance in mice. Dysbiosis, intestinal inflammation, metabolic syndrome*	[164, 165, 168]
E621 Monosodium glutamate	*Flavor enhancer*	*Genotoxicity in human peripheral blood lymphocytes in vitro. Weight gain*	[169–171]
E951 Aspartame	*Sweetener*	*Impaired glucose tolerance in rats. Potential genotoxicity*	[172, 173]
E954 Saccharin	*Sweetener*	*Dysbiosis and impaired glucose tolerance in mice. Potential genotoxicity*	[173, 174]
E955 Sucralose	*Sweetener*	*Dysbiosis in rats and mice, impaired glucose tolerance and liver inflammation in mice. Malignant tumors and hematopoietic neoplasias in male mice*	[174–177]

TMAO, trimethylamine N-oxide.

The link between individual and planetary health has become a matter of general interest and there are now green sites that show the extent to which our carbon footprint is reduced each time we eat a plant-based dish instead of a portion of red-meat [69]. For instance, consuming the equivalent of one typical fast-food hamburger (75 g of beef), once or twice a week, creates 604 kg of greenhouse gas emissions per year. Although one to two servings per week of red meat may not seem to be a great amount, this carbon footprint equals the gas emissions needed to heat an average home in the UK for 95 days. Moreover, this meat consumption requires, on average, 1735 m² of land, equal to the area occupied by six tennis courts [69].

PLANT-BASED DIETS IN CKD PREGNANCIES: A PROOF OF CONCEPT

As a consequence of physiological hyperfiltration, glomerular filtration and proteinuria rates increase in pregnant women [70]. The increase in glomerular filtration may be blunted but is also observed during pregnancy in CKD patients, in whom there may be a significant increase in proteinuria. The need for discontinuation of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers can further contribute to the rise in proteinuria during pregnancy in CKD patients [71].

In this context, a few teams tried to counterbalance pregnancy-induced hyperfiltration and to reduce proteinuria by employing moderately protein-restricted, plant-based diets during pregnancy in patients with either high baseline proteinuria, or in subjects with advanced CKD. While protein restriction is usually milder (with a basis of 0.8 g/kg/day instead of 0.6 g), the plant-based approach is the shared core element in these diets. The results, in keeping with general data recorded in the overall population suggesting that plant-based diets are safe, once controlled for iron and vitamin deficits, are encouraging in terms of safety and almost paradoxically are associated with better intrauterine growth and a lower risk of pre-term delivery, compared with CKD women with unrestricted diets in pregnancy [72, 73]. This particular context also allowed for some interesting observations indirectly supporting the importance of diet quality.

In fact, in two recent cases, one in Italy and the other in Mexico, the start of a plant-based diet was associated not with a relevant reduction in protein intake, but with an improvement in food quality resulting from the avoidance of processed and low-quality junk food. This change was associated not only with a reduction in urea level, which was to be expected in the case of less absorbable proteins, as plant-derived proteins usually are, but also with a rapid reduction in serum creatinine, which suggested avoidance of toxins, and with a renewed, rapid increase in urea and creatinine levels if a patient reverted to her previous eating habits [74, 75].

ADDITIVES, TRACE ELEMENTS AND PESTICIDES: THE DARK SIDE OF PLANT-BASED DIETS

Although the potential toxicity of various food additives is well known, we have fewer data regarding their role in CKD, even if it is logical to suppose that these substances will accumulate when kidney function is impaired. While inorganic phosphate and potassium are the best-known additives, the list is long, and as we await clear data, a wise policy is to advise against the systematic use of canned, prepared, processed and commercially frozen foods [75, 76].

Table 1 reports data on the most common food additives/preservatives, and on their established or presumed effects on health. The list is longer than previously appreciated, at least by nephrologists, and, besides the effects of what is deliberately added to food, the issue of pesticides and trace elements is also relevant, in particular for patients with reduced kidney function [77, 78]. For example, an epidemic of CKD not associated with traditional risk factors has been observed in developing countries including Sri Lanka, Mexico, India, El Salvador, Guatemala, Costa Rica and Egypt [79–81]. Since most of the affected patients were agricultural workers, research has focused on seeing whether there is an association with pesticides, in particular glyphosate [77, 81]. Glyphosate is a widely used herbicide whose chemical structure resembles that of glycine [77, 82]. Due to this similarity, glyphosate is able to replace glycine during protein synthesis leading to increased oxidative stress and apoptosis of renal tubular cells [83]. Although a clear cause–effect relationship has not yet been demonstrated, the potential toxicity of glyphosate in addition to other predisposing factors like dehydration or genetic background, or other pollutants like heavy metals, could contribute to the development of CKD of unknown etiology [80, 84, 85].

It is worth mentioning that, nowadays, "plant-derived" is not synonymous with "healthy." In fact, the increase of subjects following vegan, vegetarian or pesco-vegetarian regimens in the last decades in the Western world has been paralleled by an increased offer of plant-based preparations by the food industry [86, 87]. This has led to the appearance on the market of ultraprocessed foods made of meat substitutes based on vegetable proteins [87, 88]. According to the NOVA classification, ultraprocessed foods are "formulations of ingredients, mostly of exclusive industrial use, typically created by series of industrial techniques and processes" which also contain ingredients of rare culinary use and additives to preserve them or make them more palatable or even hyper-palatable [89]. As discussed above, the effect of additives, or the processing, on human health is still a matter of concern [90] and, as shown by a French paper, the amount of ultraprocessed food eaten by vegetarians, pesco-vegetarians or vegan subjects may be significant [91].

QUALITY VERSUS QUANTITY OR ORIGIN OF FOOD

As discussed above, it is the quality and the origin rather than the quantity of food we eat that makes a difference. But what is a plant-based diet? Plant-based diets are defined as all regimens that are composed for the most part of fruit, vegetables, grains, legumes, nuts, seeds and herbs and generally exclude animal products (meat, fish and seafood, poultry, eggs and dairy products) [11]. Examples of plant-based regimens are the Mediterranean and the Okinawan diets and the Dietary Approaches to Stop Hypertension (DASH) eating plan [34, 92–94]. Table 2 shows the definition of some of the most common plant-based regimens.

Specific studies comparing plant-based and animal-based diets are lacking. Few studies have directly compared the effects of plant-based and animal-based diets. A randomized Israeli crossover study found that a soya-based vegetarian low-protein diet was not inferior to an animal-based one in preserving the nutritional status and kidney function of nine CKD Stage 3 and 4 patients [63]. The benefits of soy for nutritional markers, specifically isoflavones, were demonstrated in another study with

Table 2: Definition of the most common plant-based dietary regimens (adapted from [179]).

Diet (or a person)	Definition
Vegetarian or ovolactovegetarian	A diet composed of dairy and eggs but no meat, fish or other seafood. Some definitions restrict the term ovolactovegetarian to someone who avoids not only flesh from killed animals but also gelatin and cheese curdled with rennet of animal origin
Lactovegetarian	As ovolactovegetarian, consuming dairy but not eggs
Ovovegetarian	As ovolactovegetarian, consuming eggs but not dairy
Pesco-vegetarian	A diet composed of fish and/or seafood but not meat
Vegan	A diet not containing any animal foods and by-products of animal husbandry such as milk and honey
Semivegetarian or flexitarian	A diet predominantly vegetarian but with occasional inclusion of animal products
Macrobiotic	A diet consisting of cereals, pulses and vegetables with small additions of seaweeds, fermented food, nuts and seeds. Most macrobiotic adherents avoid meat, dairy products and fruits. Fish is rarely eaten
Plant-Dominant Low-Protein Diet (PLADO)	A type of low protein diet with a dietary protein intake of 0.6–0.8 g/kg of body weight/day with at least 50% plant-based sources to meet the targeted dietary protein, and which should preferably be whole, unrefined and unprocessed foods [178]

Table 3: Studies showing the benefits of a plant-based diet in the general population and in diabetic patients.

Author, country (year)	Study design	Intervention	Outcomes	Main results
Kim, USA (2019) [106]	Prospective population-based study	None	Incidence of CKD and kidney function decline	14686 middle-aged individuals enrolled in the Atherosclerosis Risk in Communities study. The proportion of plant-based foods in the diet was positively associated with a lower incidence of CKD and a slower decline in eGFR
Chen, The Netherlands (2018) [107]	Observational prospective cohort study	None	Incidence of insulin resistance, prediabetes, type 2 DM	Vegetable consumption was inversely associated with the incidence of type-2 DM in 6770 participants in the Rotterdam study. A plant-based diet was associated with a lower risk of insulin resistance, prediabetes (HR 0.89) and type 2 DM (HR 0.82)
Kahleova, USA (2018) [108]	Randomized controlled trial	Low-fat plant-based diet ($n = 38$) vs no diet changes ($n = 37$) for 16 weeks in subjects without diabetes	Beta-cell function, calculated with a mathematical model comprising C-peptide and HOMA	The vegan diet improved meal-stimulated insulin secretion ($P < .001$) and insulin resistance ($P = .004$) compared with controls
Satija, USA (2016) [109]	Observational prospective cohort study	None	Incidence of type 2 DM	Pooled analysis of three prospective cohort studies including 200727 healthy subjects. The proportion of plant food present in the diet inversely correlated with the incidence of type 2 DM
Lee, Korea (2016) [110]	Randomized controlled trial	Vegan diet ($n = 46$) vs conventional diet recommended by the Korean Diabetes Association, 2011 ($n = 47$) for 12 weeks	Change in HbA1c levels	Both groups showed significant reductions in HbA1C levels but the reductions were larger in the vegan group than in the conventional group (–0.5% vs –0.2%; $P = .017$)
Chiu, Taiwan (2014) [111]	Observational cross-sectional study	None	Association between diet and prevalence of diabetes/IFG	In the study of 4384 Taiwanese Buddhists, a vegetarian diet was negatively associated with diabetes and IFG in men (OR for diabetes: 0.49, 95% CI 0.28–0.89; OR for IFG: 0.66, 95% CI 0.46–0.95); in pre-menopausal women (OR for diabetes: 0.26, 95% CI 0.06–1.21; OR for IFG: 0.60, 95% CI 0.35–1.04); and in menopausal women (OR for diabetes: 0.25, 95% CI 0.15–0.42; OR for IFG: 0.73, 95% CI 0.56–0.95)
Yokoyama, Japan (2014) [112]	Systematic review	None	Differences in HbA1c and fasting blood glucose levels associated with vegetarian diets in type 2 DM	Six out of 477 studies were included in the analysis. A vegetarian diet was associated with lower HbA1c (–0.39%, $P = .001$), while no differences were found in fasting blood glucose levels compared with omnivorous diets in type 2 diabetic patients

Table 3: Continued

Author, country (year)	Study design	Intervention	Outcomes	Main results
Tonstad, USA (2013) [113]	Observational prospective cohort study	None	Incidence of type 2 DM	Vegetarian diets protected from the incidence of type 2 DM in 41 387 Black and non-Black participants in the Adventist Health Study-2. The benefit, which was maximal for subjects who completely avoided meat, was modulated by the presence of meat in the diet
Tonstad, USA (2009) [114]	Observational prospective cohort study	None	BMI, prevalence of type 2 DM according to type of vegetarian diet	Vegetarians had a lower BMI and prevalence of type 2 DM compared with non-vegetarians. The benefits of a plant-based diet were more evident in completely vegetarian diets and reduced as the proportion of meat included in the diet increased
Vang, USA (2008) [115]	Observational prospective cohort study	None	Incidence of diabetes	Eating meat, at least once weekly, was associated with a 74% increase in odds of developing diabetes compared with vegetarians in 8401 participants in the Adventist Mortality Study and Adventist Health Study over a 17-year follow-up
Barnard, USA (2006) [116]	Randomized controlled trial	Low-fat vegan diet ($n = 49$) vs a diet following the 2003 ADA guidelines ($n = 50$) in type 2 diabetic patients for 22 weeks	Difference in HbA1c	HbA1c decreased significantly in both groups but the reduction was more prominent for the vegan group, without significant differences between groups (0.96% vs 0.56%, $P = .089$). Body weight significantly decreased in the vegan group compared with the comparator diet (delta –6.5 kg vs –3.1 kg, respectively, $P < .001$)
de Mello, Brazil (2006) [117]	Crossover controlled trial	Usual diet (UD) vs red meat replaced by chicken (CD) vs lactovegetarian low-protein diet (LPD) in random order for 4 weeks in type 2 DM	Changes in renal function, UAER and lipid profile	17 type 2 diabetes patients with macroalbuminuria. UAER ($P < .01$) and non-HDL cholesterol ($P = .042$) were lower after CD and LPD than after UD. The increase in total serum polyunsaturated fatty acids was greater in CD and LPD than in UD ($P = .029$). The type of diet did not influence the eGFR ($P = .860$)
Fraser, USA (1999) [118]	Observational prospective cohort study	None	Incidence of chronic diseases	In a cohort of 34 192 California Seventh-day Adventists, male vegetarians had a 37% lifetime lower risk of ischemic heart disease. Colon (RR 1.88), prostate (RR 1.54) and bladder (RR 2.31) cancer were significantly more likely in nonvegetarians. Vegetarians showed a lower risk of DM, hypertension and arthritis compared with non-vegetarians
Jibani, UK (1991) [119]	Intervention trial	Predominantly vegetarian diet vs patient's usual diet in type 1 DM for 8 weeks	Changes in fractional albumin clearance, renal function, glycemic control, blood pressure	8 patients with type 1 DM. A predominantly vegetarian diet for 8 weeks reduced fractional albumin clearance ($P < .05$) but had no effect on eGFR, glycemic control or blood pressure
Snowdon, USA (1985) [120]	Observational prospective cohort study	None	Incidence of diabetes	Vegetarians had a lower risk of having diabetes as an underlying or contributing cause of death in a population of 25 698 adult White Seventh-day Adventists followed up for 21 years

BMI, body mass index; DM, diabetes mellitus; HR, hazard ratio; IFG, impaired fasting glucose; OR, odds ratio; CI, confidence interval; ADA, American Diabetes Association; RR, relative risk; UAER, urinary albumin excretion rate; HDL, high-density lipoprotein; HOMA, Homeostasis Model Assessment index; eGFR, estimated glomerular filtration rate.

hemodialysis patients [95]. However, no differences were shown in inflammatory markers [95]. A randomized controlled trial in 40 peritoneal dialysis patients showed that soy consumption significantly reduces Lp(a) compared with animal-based diets [96].

Controversial data exist about the calcium–phosphorus balance in CKD. In fact, one study did not find an evident influence of type of diet on mineral metabolism in CKD patients not on dialysis [63], while another reported lower blood phosphorus levels for patients on plant-based diets despite similar phosphate urinary excretion [97].

Moreover, as opposed to what is usually thought, soy-based diets did not determine a significant improvement in the lipid profile in CKD, peritoneal or hemodialysis patients [63, 96, 98].

Thus, despite the supposed non-inferiority of plant-based diets, guidelines do not recommend one specific protein type over another because of insufficient definitive evidence [49]. It should be noted, however, that many of these recommendations are based on a pooled analysis of the few available studies, thus mixing different populations with different characteristics, which could prevent the appreciation of the benefits of these diets for CKD rather than dialysis patients.

DIABETIC AND OBESE PATIENTS: THE "FORGOTTEN ONES," AND THE CONUNDRUM OF IDEAL BODY WEIGHT

In spite of the fact that diabetic patients represent one of the major, if not the most common, subset of patients with advanced CKD, very few recent studies have addressed this population, As a result, the old caveats on a higher risk of malnutrition, gathered in older populations mainly composed of type 1, intensively proteinuric diabetic patients, are still reflected in the current guidelines, which warn against an overly strict protein restriction. The recommendations are that these patients follow a "normal" protein diet at 0.8 g/kg/day of ideal body weight [49, 99, 100]. Nevertheless, the most recent KDIGO guidelines on the management of diabetic patients with CKD not on dialysis also suggest to keep a diet rich in plant-based proteins, vegetables and low in processed meats [100].

While observational studies challenge this distinction and show that the population of mainly elderly type 2 diabetic patients would probably benefit from the same approaches proposed for non-diabetic patients, it should be pointed out that the current indications are based on ideal body weight and, due to the fact that type 2 diabetic patients are often overweight, their protein intake is more likely to correspond to 0.6 g/kg/real body weight [101]. The question of ideal versus real body weight is indeed crucial. The prevalence of obesity in the CKD population is presently estimated at between 30% and 50%, and the indications on protein restriction might conflict with the indications for weight loss [102]. Furthermore, while the common indications are based on ideal body weight, it is generally acknowledged that obese patients benefit from a compromise between prescription based on real and ideal body weight [49, 103]. However, probably also on account of the heterogeneity of obesity in terms of severity, sarcopenia and comorbidity, no established formula exists and management remains mainly experience-based. Despite the commonly held belief that obese patients are refractory to changes in diet, in our experience it is often possible to obtain a clinically relevant decrease in protein intake in obese and diabetic patients by means of a flexible approach and strict controls [104, 105].

In such a setting the choice of a qualitative approach privileging quality rather than quantity and choosing plant-based diets is probably both feasible and sound, making an absolute decrease in protein intake possible, but empirically limiting the risk of malnutrition. Regardless of weight loss and the entity of protein restriction, the advantages of plant-based diets can be inferred from the results of some large studies on non-diabetic and diabetic individuals (Table 3) [106–120].

ELDERLY PATIENTS: THE IMPORTANCE OF RESTORING "TRADITIONAL" HABITS

Changing dietary habits is challenging at all ages and elderly patients are usually considered particularly refractory to dietary modifications. Based on some large population studies, it is commonly held that, since protein intake decreases with age and is overall lower in advanced CKD, reducing protein intake in the elderly CKD population is a sterile and useless exercise [121, 122]. While this may be true in those cases that are already stabilized with a spontaneous reduction in protein intake, data from our group in Central France suggest that protein intake exceeds 1.2 g/kg/day in about 20% of CKD patients (Stages 3–5 not on dialysis) aged 90 years or above, and is over the 0.6 target in about 60% of CKD patients aged over 80 years [123].

In this population, dialysis may be particularly challenging and the desire not to impose dietary restrictions needs to be counterbalanced by the much higher intrusiveness of dialysis and by the importance of avoiding, whenever possible, the difficult clinical and ethical choice between dialysis and "palliative CKD care" [124]. Interestingly, low-protein diets are normally a component of this palliative or conservative care, thus suggesting that early proposal may not be devoid of interest [125–127]. These choices are even more challenging in settings, such as some medium–low income countries, in which dialysis coverage is not universal. An interesting pragmatic approach comes from Mexico, a country where less than half of the population has free access to chronic dialysis and where the burden of CKD is particularly high. Based on the consideration that protein intake has only recently increased in this country, a team of experienced dieticians studied the eating habits of a large number of ethnic groups, basing their dietary prescriptions on traditional cuisine, considering that this approach would be both reassuring and easier to integrate in daily life, in particular for elderly patients [128].

Similar considerations apply to elderly patients in many European countries. Italy's Mediterranean diet can be considered plant-based, even though the consumption of meat, fish and dairy products has increased since the end of the Second World War [11]. In Central France, as well as in Romania and other Eastern European countries, the evening meal often consists of vegetable soup, while van Gogh's painting "The Potato Eaters" reminds us that in the late nineteenth century, the main source of calories in many northern countries was plant-based [129].

Once more, although one size may not fit all, the policy of restoring old habits can play an important role in transforming a protein-rich into a plant-based diet. Furthermore, rethinking traditional dishes that can easily be adapted and become vegan–vegetarian delicacies shows patients that protein-restricted, plant-based food can actually be very tasty. In addition, this option will tend to be environmentally friendly, as traditional diets are usually based on local products which do not need long-distance transportation, thereby reducing our carbon footprint.

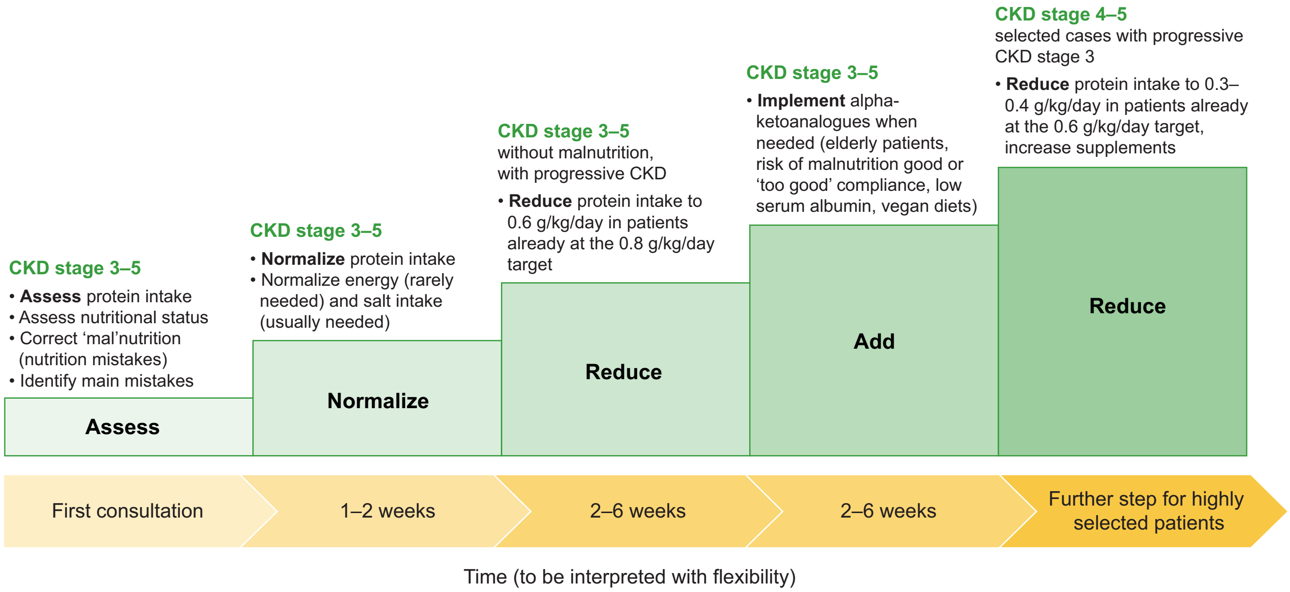


Figure 2: Stepwise dietary approach. Modified from reference [105].

INCREMENTAL DIALYSIS AND THE FALL OF THE WALL SEPARATING PRE-DIALYSIS AND DIALYSIS

Incremental dialysis refers to once- or twice-weekly dialysis schedules [130]. A "softer" start of hemodialysis is associated with better preservation of residual kidney function and is not inferior to thrice-weekly schedules in terms of morbidity and mortality [131, 132]. The recent renewed interest in dialysis schedules other than thrice-weekly has led us to reconsider the use of low-protein diets for patients on incremental dialysis [133, 134]. The combination of a low-protein diet with less frequent dialysis was first proposed in the 1980s [135, 136]. More recently, a controlled trial in Italy showed that in selected individuals the combination of a dietary program with once-weekly hemodialysis was not inferior to thrice-weekly hemodialysis in terms of patients' wellbeing and the maintenance of a good metabolic balance, and was effective in preserving residual renal function [137]. Moreover, patients on the combined program were less frequently hospitalized and less in need of erythropoietin-stimulating agents or drugs to control CKD-associated mineral and bone disorders [137]. A subsequent analysis of the same cohort after a longer follow-up demonstrated a survival advantage of the combined program over conventional hemodialysis [134]. This combined approach could, on one hand, smooth the transition from conservative therapy to hemodialysis, tempering so-called "dialysis shock," from a patient's perspective and, on the other hand, overcome physicians' traditional concerns about inadequate clearance [132]. Experiments with vLPDs are encouraging [135, 136, 138].

In this context, plant-based, ketoanalogue-supplemented diets can make it possible to decrease daily protein intake to 0.3–0.4 g/kg of body weight, while preserving calorie intake, and represent a promising option for patients starting once- or twice-weekly dialysis.

Besides being patient-friendly, the incremental dialysis approach helps conserve precious natural resources and has a lower environmental impact. Reduced dialysis frequency is associated with reduced energy and water consumption and generates less organic and plastic waste. In-center hemodialysis, in fact, uses about 500 l of water per patient per session and has a carbon footprint of about 3.8 tons of CO_2-eq per patient per year [4, 139]. Moreover, it has been estimated that each hemodialysis session produces between 1.5 and 8 kg of waste, in addition to the water consumed in their original production and the carbon footprint associated with their disposal [1]. Usually, less than one-third of these waste products can be recycled [1].

ADHERENCE, COMPLIANCE AND CONCORDANCE: FROM THEORY TO PRACTICE

According to the most recent guidelines and sound evidence, the best diet for a patient with advanced CKD without contra-indications is vLPD, vegan and supplemented [49]. However, in the largest, best designed trials from Brunori and Garneata only a minority of the patients screened had actually been enrolled, as these better diets require better adherence, which is not easy to obtain from all patients [126, 140]. If following a well-designed vLPD is not easy but the reduction in protein intake (and probably, more importantly, the reduction in animal protein intake) is associated with better preservation of the kidney function, there are at least two complementary strategies that could increase patient's adherence to prescription. The first, more conventional one consists in trying to get as close as possible to prescription and is meant to gently push patients to follow it. The advantage of this approach is that it does not lose sight of the "ideal" prescription, while the principal drawback involved in its use is the often frustrating distance between prescription and compliance [141–143]. In a way, the success of this approach is quantifiable in the distance to the ideal target.

The second strategy is based on an analysis of the individual patient's habits and preferences and adapts dietary prescriptions in order to achieve a gradual decrease in protein intake and a progressive shift from an omnivorous (or animal-based) to a plant-based diet. This softer strategy, that can profit from adopting some of the options described above, aims to adapt the prescription to the patient, and find a quantitative, qualitative or

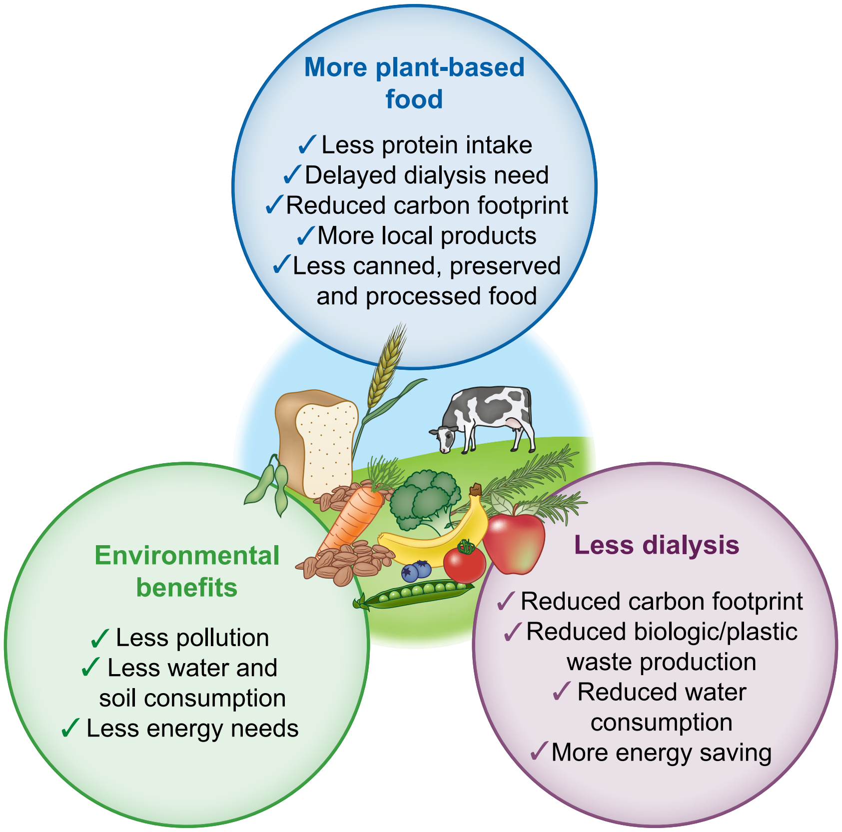


Figure 3: Benefits of plant-based diets.

mixed strategy to mediate between “best diet” and what is feasible [66, 105, 144]. The success of this strategy is measured by the concordance between the prescribed and actual diet.

While, for obvious reasons, randomized controlled trials follow the first strategy, mediating between needs and preferences may be a very good option for helping patients reduce their protein intake and choose plant-based foods. A recent randomized trial, once again, reported the real-life difficulties in following dietary prescription, noting a low compliance resulting in a difference of 0.23 g/kg/day of protein intake between the prescription and the actual intake. The same article, however, found that a supplemented vLPD was safe, did not associate with malnutrition, and had an additional favorable effect on phosphate levels, urea, mineral metabolism, blood pressure and proteinuria [145]. It is worth noting that, in this publication, dietary regimens employed different source of proteins (animal or vegetables) and a combined prescription approach: the original standard diets developed by expert dieticians were adapted to patients’ preferences and habits [145].

The stepwise, multiple-choice options developed in our setting are examples of this policy (Fig. 2) [105].

CONCLUDING REMARKS AND FUTURE DIRECTIONS

Plant-based diets are safe and allow a greater reduction in protein intake in CKD patients than omnivorous diets. Moreover, they can contribute to reducing the environmental impact of CKD (Fig. 3). As most of the available evidence comes from the general population and not CKD patients the benefits of plant-based diets needs to be further assessed in dedicated trials. However, due to the difficulties in performing randomized controlled trials on this subject, other forms of research should be explored. In this respect, patient preference trials or trial emulation could be valid alternatives [146–148]. Nevertheless, given the encouraging results of discrete experiments, and as demonstrated by their use in pregnancy, plant-based diets should be widely promoted for the benefit of our patients and our planet.

AUTHORS’ CONTRIBUTIONS

Conceptualization, G.B.P.; data curation, A.F., F.L, R.A., E.L, I.M., B.M., G.C. and E.V.; writing—original draft preparation, G.B.P. and M.T. All the authors have read and agreed to the published version of the manuscript.

FUNDING

This research received no external funding.

DATA AVAILABILITY STATEMENT

No new data were created or analyzed in this study. Data sharing is not applicable to this article.

ACKNOWLEDGEMENTS

We thank Susan Finnel for her careful language editing.

CONFLICT OF INTEREST STATEMENT

G.B.P. received a research grant and consultant fees from Fresenius Kabi. She is also member of the *CKJ* Editorial Board. All the other authors declare there are no conflicts of interest.

REFERENCES

1. Piccoli GB, Nazha M, Ferraresi M *et al*. Eco-dialysis: the financial and ecological costs of dialysis waste products: is a ‘cradle-to-cradle’ model feasible for planet-friendly haemodialysis waste management? *Nephrol Dial Transplant* 2015;**30**:1018–27.
2. Ramesh Babu B, Parande AK, Ahmed Basha C. Electrical and electronic waste: a global environmental problem. *Waste Manag Res* 2007;**25**:307–18.
3. Agar JW. Reusing and recycling dialysis reverse osmosis system reject water. *Kidney Int* 2015;**88**:653–7.
4. Barraclough KA, Agar JWM. Green nephrology. *Nat Rev Nephrol* 2020;**16**:257–68.
5. Agar JW, Perkins A, Tjipto A. Solar-assisted hemodialysis. *Clini J Am Soc Nephrol* 2012;**7**:310–4.
6. Chang E, Lim JA, Low CL *et al*. Reuse of dialysis reverse osmosis reject water for aquaponics and horticulture. *J Nephrol* 2021;**34**:97–104.
7. Bendine G, Autin F, Fabre B *et al*. Haemodialysis therapy and sustainable growth: a corporate experience in France. *Nephrol Dial Transplant* 2020;**35**:2154–60.
8. Molano-Trivino A, Wancjer B, Neri MM *et al*. Blue Planet dialysis: novel water-sparing strategies for reducing dialysate flow. *Int J Artif Organs* 2017. doi: 10.5301/ijao.5000660
9. Mtioui N, Zamd M, Ait Taleb A *et al*. Carbon footprint of a hemodialysis unit in Morocco. *Ther Apher Dial* 2021;**25**:613–20.
10. Piccoli GB, Cupisti A, Aucella F *et al*. Green nephrology and eco-dialysis: a position statement by the Italian Society of Nephrology. *J Nephrol* 2020;**33**:681–98.
11. Carrero JJ, Gonzalez-Ortiz A, Avesani CM *et al*. Plant-based diets to manage the risks and complications of chronic kidney disease. *Nat Rev Nephrol* 2020;**16**:525–42.
12. Torreggiani M, Fois A, Chatrenet A *et al*. Incremental and personalized hemodialysis start: a new standard of care. *Kidney Int Rep* 2022;**7**:1049–61.
13. Bray GA, Bouchard C. The biology of human overfeeding: a systematic review. *Obes Rev* 2020;**21**: e13040.
14. Conway B, Rene A. Obesity as a disease: no lightweight matter. *Obes Rev* 2004;**5**:145–51.
15. Caballero B. Humans against obesity: who will win? *Adv Nutr* 2019;**10**:S4–9.
16. Gracey M. Junk food or ‘junk eating’? *Nestle Nutr Workshop Ser Pediatr Program* 2005;**56**:143–50; discussion 150–45.
17. Hemmingsson E. Early childhood obesity risk factors: socioeconomic adversity, family dysfunction, offspring distress, and junk food self-medication. *Curr Obes Rep* 2018;**7**:204–9.
18. Cooksey-Stowers K, Schwartz MB, Brownell KD. Food swamps predict obesity rates better than food deserts in the United States. *Int J Environ Res Public Health* 2017;**14**:1366.
19. Milani GP, Silano M, Pietrobelli A *et al*. Junk food concept: seconds out. *Int J Obes* 2017;**41**:669–71.
20. Monteiro CA, Moubarac JC, Cannon G *et al*. Ultra-processed products are becoming dominant in the global food system. *Obes Rev* 2013;**14**:21–8.
21. Popkin BM, Reardon T. Obesity and the food system transformation in Latin America. *Obes Rev* 2018;**19**:1028–64.
22. Cooksey Stowers K, Jiang Q, Atoloye A *et al*. Racial differences in perceived food swamp and food desert exposure and disparities in self-reported dietary habits. *Int J Environ Res Public Health* 2020;**17**:7143.
23. Schultz S, Cameron AJ, Grigsby-Duffy L *et al*. Availability and placement of healthy and discretionary food in Australian supermarkets by chain and level of socio-economic disadvantage. *Public Health Nutr* 2021;**24**:203–14.
24. Diez J, Bilal U, Cebrecos A *et al*. Understanding differences in the local food environment across countries: a case study in Madrid (Spain) and Baltimore (USA). *Prev Med* 2016;**89**:237–44.
25. Gonzalez N, Marques M, Nadal M *et al*. Occurrence of environmental pollutants in foodstuffs: a review of organic vs. conventional food. *Food Chem Toxicol* 2019;**125**: 370–5.
26. Silano M, Silano V. Food and feed chemical contaminants in the European Union: regulatory, scientific, and technical issues concerning chemical contaminants occurrence, risk assessment, and risk management in the European Union. *Crit Rev Food Sci Nutr* 2017;**57**:2162–217.
27. Poelman MP, Gillebaart M, Schlinkert C *et al*. Eating behavior and food purchases during the COVID-19 lockdown: a cross-sectional study among adults in the Netherlands. *Appetite* 2021;**157**:105002.
28. Ruiz-Roso MB, de Carvalho Padilha P, Matilla-Escalante DC *et al*. Changes of physical activity and ultra-processed food consumption in adolescents from different countries during Covid-19 pandemic: an observational study. *Nutrients* 2020;**12**:2289.
29. Lamarche B, Brassard D, Lapointe A *et al*. Changes in diet quality and food security among adults during the COVID-19-related early lockdown: results from NutriQuebec. *Am J Clin Nutr* 2021;**113**:984–92.
30. Cancello R, Soranna D, Zambra G *et al*. Determinants of the lifestyle changes during COVID-19 pandemic in the residents of Northern Italy. *Int J Environ Res Public Health* 2020;**17**:6287.
31. Lopez-Moreno M, Lopez MTI, Miguel M *et al*. Physical and psychological effects related to food habits and lifestyle changes derived from Covid-19 home confinement in the Spanish population. *Nutrients* 2020;**12**:3445.
32. Dudley DA, Cotton WG, Peralta LR. Teaching approaches and strategies that promote healthy eating in primary school children: a systematic review and meta-analysis. *Int J Behav Nutr Phys Act* 2015;**12**:28.
33. Locke A, Schneiderhan J, Zick SM. Diets for Health: goals and guidelines. *Am Fam Physician* 2018;**97**:721–8.
34. Cena H, Calder PC. Defining a healthy diet: evidence for the role of contemporary dietary patterns in health and disease. *Nutrients* 2020;**12**:334.
35. Fischer NM, Pallazola VA, Xun H *et al*. The evolution of the heart-healthy diet for vascular health: a walk through time. *Vasc Med* 2020;**25**:184–93.
36. Addis T, Lew W. Diet and death in acute uremia. *J Clin Invest* 1939;**18**:773–5.
37. Piccoli GB. Patient-based continuum of care in nephrology: why read Thomas Addis’ “Glomerular Nephritis” in 2010? *J Nephrol* 2010;**23**:164–7.

38. Brenner BM, Meyer TW, Hostetter TH. Dietary protein intake and the progressive nature of kidney disease: the role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. *N Engl J Med* 1982;**307**:652–9.
39. Kolff WJ. Forced high caloric, low protein diet and the treatment of uremia. *Am J Med* 1952;**12**:667–79.
40. Monasterio G, Giovannetti S, Maggiore Q. The place of the low protein diet in the treatment of chronic uraemia. *Panminerva Med* 1965;**7**:479–84.
41. Salteri F, Pittaluga F. Dietetic products, treatment of chronic uremia, and the Giordano-Giovannetti low protein diet. *Am J Clin Nutr* 1968;**21**:590–1.
42. Sorensen MK, Kopple JD. Assessment of adherence to protein-restricted diets during conservative management of uremia. *Am J Clin Nutr* 1968;**21**:631–7.
43. Rosman JB, Langer K, Brandl M *et al*. Protein-restricted diets in chronic renal failure: a four year follow-up shows limited indications. *Kidney Int Suppl* 1989;**27**:S96–102.
44. Protein restriction and the progress of renal insufficiency. *Nutr Rev* 1990;**48**:320–3.
45. Shaw AB, Bazzard FJ, Booth EM *et al*. The treatment of chronic renal failure by a modified giovannetti diet. *Q J Med* 1965;**34**:237–53.
46. Giovannetti S, Maggiore Q. A low-nitrogen diet with proteins of high biological value for severe chronic uraemia. *Lancet North Am Ed* 1964;**283**:1000–3.
47. Giordano C. Use of exogenous and endogenous urea for protein synthesis in normal and uremic subjects. *J Lab Clin Med* 1963;**62**:231–46.
48. Wasserstein AG. Changing patterns of medical practice: protein restriction for chronic renal failure. *Ann Intern Med* 1993;**119**:79–85.
49. Ikizler TA, Burrowes JD, Byham-Gray LD *et al*. KDOQI Clinical Practice Guideline for Nutrition in CKD: 2020 Update. *Am J Kidney Dis* 2020;**76**:S1–107.
50. Huang CJ, Fan YC, Liu JF *et al*. Characteristics and nutrient intake of Taiwanese elderly vegetarians: evidence from a national survey. *Br J Nutr* 2011;**106**:451–60.
51. Rizzo NS, Jaceldo-Siegl K, Sabate J *et al*. Nutrient profiles of vegetarian and nonvegetarian dietary patterns. *J Acad Nutr Diet* 2013;**113**:1610–9.
52. Cases A, Cigarran-Guldris S, Mas S *et al*. Vegetable-based diets for chronic kidney disease? It is time to reconsider. *Nutrients* 2019;**11**:1263.
53. Cooper BA, Branley P, Bulfone L *et al*. A randomized, controlled trial of early versus late initiation of dialysis. *N Engl J Med* 2010;**363**:609–19.
54. Singer ME, Dorrance KA, Oxenreiter MM *et al*. The type 2 diabetes 'modern preventable pandemic' and replicable lessons from the COVID-19 crisis. *Prev Med Rep* 2022;**25**:101636.
55. World Health Organization. *Controlling the global obesity epidemic*. https://www.who.int/activities/controlling-the-global-obesity-epidemic (17 May 2022, date last accessed).
56. Mitchell NS, Catenacci VA, Wyatt HR *et al*. Obesity: overview of an epidemic. *Psychiatr Clin North Am* 2011;**34**:717–32.
57. Haththotuwa RN, Wijeyaratne CN, Senarath U. Chapter 1 - Worldwide epidemic of obesity. In: Mahmood TA, Arulkumaran S Chervenak FA (eds), *Obesity and Obstetrics (Second Edition)*. Amsterdam, The Netherlands: Elsevier, 2020;3–8.
58. Commission of European Communities. *Green Paper. Promoting healthy diets and physical activity: a European dimension for the prevention of overweight, obesity and chronic diseases*. https://ec.europa.eu/health/ph_determinants/life_style/nutrition/documents/nutrition_gp_en.pdf (17 May 2022, date last accessed).
59. Turner-McGrievy G, Mandes T, Crimarco A. A plant-based diet for overweight and obesity prevention and treatment. *J Geriatr Cardiol* 2017;**14**:369–74.
60. McMacken M, Shah S. A plant-based diet for the prevention and treatment of type 2 diabetes. *J Geriatr Cardiol* 2017;**14**:342–54.
61. Jardine MA, Kahleova H, Levin SM *et al*. Perspective: plant-based eating pattern for type 2 diabetes prevention and treatment: efficacy, mechanisms, and practical considerations. *Adv Nutr* 2021;**12**:2045–55.
62. Sitprija V, Suvanpha R. Low protein diet and chronic renal failure in Buddhist monks. *BMJ* 1983;**287**:469–71.
63. Soroka N, Silverberg DS, Greemland M *et al*. Comparison of a vegetable-based (soya) and an animal-based low-protein diet in predialysis chronic renal failure patients. *Nephron* 1998;**79**:173–80.
64. Barsotti G, Morelli E, Cupisti A *et al*. A low-nitrogen low-phosphorus vegan diet for patients with chronic renal failure. *Nephron* 1996;**74**:390–4.
65. Barsotti G, Navalesi R, Giampietro O *et al*. Effects of a vegetarian, supplemented diet on renal function, proteinuria, and glucose metabolism in patients with 'overt' diabetic nephropathy and renal insufficiency. *Contrib Nephrol* 1988;**65**:87–94.
66. Piccoli GB, Nazha M, Capizzi I *et al*. Diet as a system: an observational study investigating a multi-choice system of moderately restricted low-protein diets. *BMC Nephrol* 2016;**17**:197.
67. Piccoli GB, Vigotti FN, Leone F *et al*. Low-protein diets in CKD: how can we achieve them? A narrative, pragmatic review. *Clin Kidney J* 2015;**8**:61–70.
68. Ornish D. Holy Cow! What's good for you is good for our planet: comment on "Red Meat Consumption and Mortality". *Arch Intern Med* 2012;**172**:563–4.
69. *Climate change food calculator: What's your diet's carbon footprint?* https://www.bbc.com/news/science-environment-46459714 (13 May 2022, date last accessed).
70. Cheung KL, Lafayette RA. Renal physiology of pregnancy. *Adv Chronic Kidney Dis* 2013;**20**:209–14.
71. Williams D, Davison J. Chronic kidney disease in pregnancy. *BMJ* 2008;**336**:211–5.
72. Pistollato F, Sumalla Cano S, Elio I *et al*. Plant-based and plant-rich diet patterns during gestation: beneficial effects and possible shortcomings. *Adv Nutr* 2015;**6**:581–91.
73. Attini R, Leone F, Parisi S *et al*. Vegan-vegetarian low-protein supplemented diets in pregnant CKD patients: fifteen years of experience. *BMC Nephrol* 2016;**17**:132.
74. Attini R, Montersino B, Leone F *et al*. Dialysis or a plant-based diet in advanced ckd in pregnancy? A case report and critical appraisal of the literature. *J Clin Med* 2019;**8**:123.
75. Orozco-Guillien AO, Munoz-Manrique C, Reyes-Lopez MA *et al*. Quality or quantity of proteins in the diet for CKD patients: does "junk food" make a difference? Lessons from a high-risk pregnancy. *Kidney Blood Press Res* 2021;**46**:1–10.
76. Banderali G, Carmine V, Rossi S *et al*. Food additives: effects on pregnancy and lactation. *Acta Biomed Ateneo Parmense* 2000;**71**:589–92.
77. Gunatilake S, Seneff S, Orlando L. Glyphosate's synergistic toxicity in combination with other factors as a cause of chronic kidney disease of unknown origin. *Int J Environ Res*

Public Health 2019;**16**:2734.
78. Chan-Hon-Tong A, Charles MA, Forhan A *et al*. Exposure to food contaminants during pregnancy. *Sci Total Environ* 2013;**458–460**:27–35.
79. Rajapakse S, Shivanthan MC, Selvarajah M. Chronic kidney disease of unknown etiology in Sri Lanka. *Int J Occup Environ Health* 2016;**22**:259–64.
80. Almaguer M, Herrera R, Orantes CM. Chronic kidney disease of unknown etiology in agricultural communities. *MEDICC Rev* 2014;**16**:9–15.
81. Sene S, Orlando LF. Is glyphosate a key factor in Mesoamerican nephropathy? *J Environ Anal Toxicol* 2018;**7**:542.
82. Soares D, Silva L, Duarte S *et al*. Glyphosate use, toxicity and occurrence in food. *Foods* 2021;**10**:2785.
83. Gao H, Chen J, Ding F *et al*. Activation of the N-methyl-d-aspartate receptor is involved in glyphosate-induced renal proximal tubule cell apoptosis. *J Appl Toxicol* 2019;**39**:1096–107.
84. Valcke M, Levasseur ME, Soares da Silva A *et al*. Pesticide exposures and chronic kidney disease of unknown etiology: an epidemiologic review. *Environ Health* 2017;**16**:49.
85. Perez-Gomez MV, Martin-Cleary C, Fernandez-Fernandez B *et al*. Meso-American nephropathy: what we have learned about the potential genetic influence on chronic kidney disease development. *Clin Kidney J* 2018;**11**:491–5.
86. Leitzmann C. Vegetarian nutrition: past, present, future. *Am J Clin Nutr* 2014;**100**:496S–502S.
87. Kumar P, Chatli MK, Mehta N *et al*. Meat analogues: health promising sustainable meat substitutes. *Crit Rev Food Sci Nutr* 2017;**57**:923–32.
88. Macdiarmid JI. The food system and climate change: are plant-based diets becoming unhealthy and less environmentally sustainable? *Proc Nutr Soc* 2022;**81**:162–7.
89. Monteiro CA, Cannon G, Lawrence M *et al*. 2019; *Ultra-processed foods, diet quality, and health using the NOVA classification system*. Rome: FAO.
90. Gibney MJ. Food technology and plant-based diets. *J Nutr* 2021;**151**:1–2.
91. Gehring J, Touvier M, Baudry J *et al*. Consumption of ultra-processed foods by pesco-vegetarians, vegetarians, and vegans: associations with duration and age at diet initiation. *J Nutr* 2021;**151**:120–31.
92. Davis C, Bryan J, Hodgson J *et al*. Definition of the Mediterranean diet; a literature review. *Nutrients* 2015;**7**:9139–53.
93. Appel LJ, Moore TJ, Obarzanek E *et al*. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *N Engl J Med* 1997;**336**:1117–24.
94. Sho H. History and characteristics of Okinawan longevity food. *Asia Pac J Clin Nutr* 2001;**10**:159–64.
95. Fanti P, Asmis R, Stephenson TJ *et al*. Positive effect of dietary soy in ESRD patients with systemic inflammation—correlation between blood levels of the soy isoflavones and the acute-phase reactants. *Nephrol Dial Transplant* 2006;**21**:2239–46.
96. Tabibi H, Imani H, Hedayati M *et al*. Effects of soy consumption on serum lipids and apoproteins in peritoneal dialysis patients: a randomized controlled trial. *Perit Dial Int* 2010;**30**:611–8.
97. Moe SM, Zidehsarai MP, Chambers MA *et al*. Vegetarian compared with meat dietary protein source and phosphorus homeostasis in chronic kidney disease. *Clin J Am Soc Nephrol* 2011;**6**:257–64.
98. Chen W, Liu Y, Yang Q *et al*. The effect of protein-enriched meal replacement on waist circumference reduction among overweight and obese Chinese with hyperlipidemia. *J Am Coll Nutr* 2016;**35**:236–44.
99. Yamada S. First, do no harm: critical appraisal of protein restriction for diabetic kidney disease. *Diabetology* 2021;**2**:51–64.
100. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. *Kidney Int* 2022;**102**:S1–127.
101. Bellizzi V, Calella P, Hernandez JN *et al*. Safety and effectiveness of low-protein diet supplemented with ketoacids in diabetic patients with chronic kidney disease. *BMC Nephrol* 2018;**19**:110.
102. Friedman AN, Kaplan LM, le Roux CW *et al*. Management of obesity in adults with CKD. *J Am Soc Nephrol* 2021;**32**:777–90. CrossRef]
103. Lambert K, Beer J, Dumont R *et al*. Weight management strategies for those with chronic kidney disease: a consensus report from the Asia Pacific Society of Nephrology and Australia and New Zealand Society of Nephrology 2016 renal dietitians meeting. *Nephrology* 2018;**23**:912–20.
104. Fois A, Torreggiani M, Trabace T *et al*. Quality of life in CKD patients on low-protein diets in a multiple-choice diet system. Comparison between a French and an Italian experience. *Nutrients* 2021;**13**:1354.
105. Fois A, Chatrenet A, Cataldo E *et al*. Moderate protein restriction in advanced CKD: a feasible option in an elderly, high-comorbidity population. A stepwise multiple-choice system approach. *Nutrients* 2018;**11**:36.
106. Kim H, Caulfield LE, Garcia-Larsen V *et al*. Plant-based diets and incident CKD and kidney function. *Clin J Am Soc Nephrol* 2019;**14**:682–91.
107. Chen Z, Zuurmond MG, van der Schaft N *et al*. Plant versus animal based diets and insulin resistance, prediabetes and type 2 diabetes: the Rotterdam Study. *Eur J Epidemiol* 2018;**33**:883–93.
108. Kahleova H, Tura A, Hill M *et al*. A plant-based dietary intervention improves beta-cell function and insulin resistance in overweight adults: a 16-week randomized clinical trial. *Nutrients* 2018;**10**:189.
109. Satija A, Bhupathiraju SN, Rimm EB *et al*. Plant-based dietary patterns and incidence of type 2 diabetes in US men and women: results from three prospective cohort studies. *PLoS Med* 2016;**13**:e1002039.
110. Lee YM, Kim SA, Lee IK *et al*. Effect of a brown rice based vegan diet and conventional diabetic diet on glycemic control of patients with type 2 diabetes: a 12-week randomized clinical trial. *PLoS One* 2016;**11**:e0155918.
111. Chiu TH, Huang HY, Chiu YF *et al*. Taiwanese vegetarians and omnivores: dietary composition, prevalence of diabetes and IFG. *PLoS One* 2014;**9**:e88547.
112. Yokoyama Y, Barnard ND, Levin SM *et al*. Vegetarian diets and glycemic control in diabetes: a systematic review and meta-analysis. *Cardiovasc Diagn Ther* 2014;**4**:373–82.
113. Tonstad S, Stewart K, Oda K *et al*. Vegetarian diets and incidence of diabetes in the Adventist Health Study-2. *Nutr Metab Cardiovasc Dis* 2013;**23**:292–9.
114. Tonstad S, Butler T, Yan R *et al*. Type of vegetarian diet, body weight, and prevalence of type 2 diabetes. *Diabetes Care* 2009;**32**:791–6.
115. Vang A, Singh PN, Lee JW *et al*. Meats, processed meats, obesity, weight gain and occurrence of diabetes among adults: findings from Adventist Health Studies. *Ann Nutr Metab* 2008;**52**:96–104.

116. Barnard ND, Cohen J, Jenkins DJ *et al*. A low-fat vegan diet improves glycemic control and cardiovascular risk factors in a randomized clinical trial in individuals with type 2 diabetes. *Diabetes Care* 2006;**29**:1777–83.
117. de Mello VD, Zelmanovitz T, Perassolo MS *et al*. Withdrawal of red meat from the usual diet reduces albuminuria and improves serum fatty acid profile in type 2 diabetes patients with macroalbuminuria. *Am J Clin Nutr* 2006;**83**:1032–8.
118. Fraser GE. Associations between diet and cancer, ischemic heart disease, and all-cause mortality in non-Hispanic white California Seventh-day Adventists. *Am J Clin Nutr* 1999;**70**:532s–8s.
119. Jibani MM, Bloodworth LL, Foden E *et al*. Predominantly vegetarian diet in patients with incipient and early clinical diabetic nephropathy: effects on albumin excretion rate and nutritional status. *Diabet Med* 1991;**8**:949–53.
120. Snowdon DA, Phillips RL. Does a vegetarian diet reduce the occurrence of diabetes? *Am J Public Health* 1985;**75**:507–12.
121. Drewnowski A, Shultz JM. Impact of aging on eating behaviors, food choices, nutrition, and health status. *J Nutr Health Aging* 2001;**5**:75–9.
122. Krok-Schoen JL, Archdeacon Price A, Luo M *et al*. Low dietary protein intakes and associated dietary patterns and functional limitations in an aging population: a NHANES analysis. *J Nutr Health Aging* 2019;**23**:338–47.
123. Torreggiani M, Fois A, Moio MR *et al*. Spontaneously low protein intake in elderly CKD patients: myth or reality? Analysis of baseline protein intake in a large cohort of patients with advanced CKD. *Nutrients* 2021;**13**:4371.
124. Piccoli GB, Sofronie AC, Coindre JP. The strange case of Mr. H. starting dialysis at 90 years of age: clinical choices impact on ethical decisions. *BMC Med Ethics* 2017;**18**:61.
125. Fassett RG, Robertson IK, Mace R *et al*. Palliative care in end-stage kidney disease. *Nephrology* 2011;**16**:4–12.
126. Brunori G, Viola BF, Parrinello G *et al*. Efficacy and safety of a very-low-protein diet when postponing dialysis in the elderly: a prospective randomized multicenter controlled study. *Am J Kidney Dis* 2007;**49**:569–80.
127. Brunori G, Viola BF, Maiorca P *et al*. How to manage elderly patients with chronic renal failure: conservative management versus dialysis. *Blood Purif* 2008;**26**:36–40.
128. Nava J, Moran S, Figueroa V *et al*. Successful pregnancy in a CKD patient on a low-protein, supplemented diet: an opportunity to reflect on CKD and pregnancy in Mexico, an emerging country. *J Nephrol* 2017;**30**:877–82.
129. Krznaric Z, Karas I, Ljubas Kelecic D *et al*. The Mediterranean and Nordic diet: a review of differences and similarities of two sustainable, health-promoting dietary patterns. *Front Nutr* 2021;**8**:683678.
130. Torreggiani M, Fois A, Njandjo L *et al*. Toward an individualized determination of dialysis adequacy: a narrative review with special emphasis on incremental hemodialysis. *Expert Rev Mol Diagn* 2021;**21**:1119–37.
131. Garofalo C, Borrelli S, De Stefano T *et al*. Incremental dialysis in ESRD: systematic review and meta-analysis. *J Nephrol* 2019;**32**:823–36.
132. Murea M, Moossavi S, Garneata L *et al*. Narrative review of incremental hemodialysis. *Kidney Int Rep* 2020;**5**:135–48.
133. Torreggiani M, Fois A, Chatrenet A *et al*. Incremental and personalized hemodialysis start: a new standard of care. *Kidney Int Rep* 2022;**7**:1049–61.
134. Bolasco P, Cupisti A, Locatelli F *et al*. Dietary management of incremental transition to dialysis therapy: once-weekly hemodialysis combined with low-protein diet. *J Ren Nutr* 2016;**26**:352–9.
135. Mitch WE, Sapir DG. Evaluation of reduced dialysis frequency using nutritional therapy. *Kidney Int* 1981;**20**:122–6.
136. Morelli E, Baldi R, Barsotti G *et al*. Combined therapy for selected chronic uremic patients: infrequent hemodialysis and nutritional management. *Nephron* 1987;**47**:161–6.
137. Caria S, Cupisti A, Sau G *et al*. The incremental treatment of ESRD: a low-protein diet combined with weekly hemodialysis may be beneficial for selected patients. *BMC Nephrol* 2014;**15**:172.
138. Locatelli F, Andrulli S, Pontoriero G *et al*. Supplemented low-protein diet and once-weekly hemodialysis. *Am J Kidney Dis* 1994;**24**:192–204.
139. Connor A, Lillywhite R, Cooke MW. The carbon footprints of home and in-center maintenance hemodialysis in the United Kingdom. *Hemodial Int* 2011;**15**:39–51.
140. Garneata L, Stancu A, Dragomir D *et al*. Ketoanalogue-supplemented vegetarian very low-protein diet and CKD progression. *J Am Soc Nephrol* 2016;**27**:2164–76.
141. Klahr S, Levey AS, Beck GJ *et al*. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. *N Engl J Med* 1994;**330**:877–84.
142. Levey AS, Greene T, Beck GJ *et al*. Dietary protein restriction and the progression of chronic renal disease: what have all of the results of the MDRD study shown? Modification of Diet in Renal Disease Study group. *J Am Soc Nephrol* 1999;**10**:2426–39.
143. Thilly N. Low-protein diet in chronic kidney disease: from questions of effectiveness to those of feasibility. *Nephrol Dial Transplant* 2013;**28**:2203–5.
144. D'Alessandro C, Piccoli GB, Calella P *et al*. "Dietaly": practical issues for the nutritional management of CKD patients in Italy. *BMC Nephrol* 2016;**17**:102.
145. Bellizzi V, Signoriello S, Minutolo R *et al*. No additional benefit of prescribing a very low-protein diet in patients with advanced chronic kidney disease under regular nephrology care: a pragmatic, randomized, controlled trial. *Am J Clin Nutr* 2022;**115**:1404–17.
146. Fu EL, Evans M, Carrero JJ *et al*. Timing of dialysis initiation to reduce mortality and cardiovascular events in advanced chronic kidney disease: nationwide cohort study. *BMJ* 2021;**375**:e066306.
147. Wasmann KA, Wijsman P, van Dieren S *et al*. Partially randomised patient preference trials as an alternative design to randomised controlled trials: systematic review and meta-analyses. *BMJ Open* 2019;**9**:e031151.
148. Torgerson DJ, Sibbald B. Understanding controlled trials. What is a patient preference trial? *BMJ* 1998;**316**:360.
149. Yadav A, Kumar A, Das M *et al*. Sodium benzoate, a food preservative, affects the functional and activation status of splenocytes at non cytotoxic dose. *Food Chem Toxicol* 2016;**88**:40–7.
150. Mpountoukas P, Vantarakis A, Sivridis E *et al*. Cytogenetic study in cultured human lymphocytes treated with three commonly used preservatives. *Food Chem Toxicol* 2008;**46**:2390–3.
151. Zengin N, Yuzbasioglu D, Unal F *et al*. The evaluation of the genotoxicity of two food preservatives: sodium benzoate and potassium benzoate. *Food Chem Toxicol* 2011;**49**:763–9.
152. Noorafshan A, Erfanizadeh M, Karbalay-Doust S. Stereological studies of the effects of sodium benzoate or ascorbic acid on rats' cerebellum. *Saudi Med J* 2014;**35**:1494–500.

153. Tang WH, Wang Z, Levison BS *et al*. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. *N Engl J Med* 2013;**368**:1575–84.
154. Roberts CL, Rushworth SL, Richman E *et al*. Hypothesis: increased consumption of emulsifiers as an explanation for the rising incidence of Crohn's disease. *J Crohns Colitis* 2013;**7**:338–41.
155. Etemadi A, Sinha R, Ward MH *et al*. Mortality from different causes associated with meat, heme iron, nitrates, and nitrites in the NIH-AARP Diet and Health Study: population based cohort study. *BMJ* 2017;**357**:j1957.
156. Hosseini F, Majdi M, Naghshi S *et al*. Nitrate-nitrite exposure through drinking water and diet and risk of colorectal cancer: a systematic review and meta-analysis of observational studies. *Clin Nutr* 2021;**40**:3073–81.
157. Crowe W, Elliott CT, Green BD. A review of the in vivo evidence investigating the role of nitrite exposure from processed meat consumption in the development of colorectal cancer. *Nutrients* 2019;**11**:2673.
158. Song P, Wu L, Guan W. Dietary nitrates, nitrites, and nitrosamines intake and the risk of gastric cancer: a meta-analysis. *Nutrients* 2015;**7**:9872–95.
159. Quist AJL, Inoue-Choi M, Weyer PJ *et al*. Ingested nitrate and nitrite, disinfection by-products, and pancreatic cancer risk in postmenopausal women. *Int J Cancer* 2018;**142**:251–61.
160. Leandro JG, Espindola-Netto JM, Vianna MC *et al*. Exogenous citrate impairs glucose tolerance and promotes visceral adipose tissue inflammation in mice. *Br J Nutr* 2016;**115**:967–73.
161. Ashbrook MJ, McDonough KL, Pituch JJ *et al*. Citrate modulates lipopolysaccharide-induced monocyte inflammatory responses. *Clin Exp Immunol* 2015;**180**:520–30.
162. Ritz E, Hahn K, Ketteler M *et al*. Phosphate additives in food—a health risk. *Dtsch Arztebl Int* 2012;**109**:49–55.
163. McCarty MF, DiNicolantonio JJ. Bioavailable dietary phosphate, a mediator of cardiovascular disease, may be decreased with plant-based diets, phosphate binders, niacin, and avoidance of phosphate additives. *Nutrition* 2014;**30**:739–47.
164. Chassaing B, Koren O, Goodrich JK *et al*. Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome. *Nature* 2015;**519**:92–6.
165. Naimi S, Viennois E, Gewirtz AT *et al*. Direct impact of commonly used dietary emulsifiers on human gut microbiota. *Microbiome* 2021;**9**:66.
166. Bhattacharyya S, O-Sullivan I, Katyal S *et al*. Exposure to the common food additive carrageenan leads to glucose intolerance, insulin resistance and inhibition of insulin signalling in HepG2 cells and C57BL/6J mice. *Diabetologia* 2012;**55**:194–203.
167. Bhattacharyya S, Feferman L, Unterman T *et al*. Exposure to common food additive carrageenan alone leads to fasting hyperglycemia and in combination with high fat diet exacerbates glucose intolerance and hyperlipidemia without effect on weight. *J Diabetes Res* 2015;**2015**:1.
168. Swidsinski A, Ung V, Sydora BC *et al*. Bacterial overgrowth and inflammation of small intestine after carboxymethylcellulose ingestion in genetically susceptible mice. *Inflamm Bowel Dis* 2009;**15**:359–64.
169. Ataseven N, Yuzbasioglu D, Keskin AC *et al*. Genotoxicity of monosodium glutamate. *Food Chem Toxicol* 2016;**91**:8–18.
170. Chakraborty SP. Patho-physiological and toxicological aspects of monosodium glutamate. *Toxicol Mech Methods* 2019;**29**:389–96.
171. He K, Du S, Xun P *et al*. Consumption of monosodium glutamate in relation to incidence of overweight in Chinese adults: China Health and Nutrition Survey (CHNS). *Am J Clin Nutr* 2011;**93**:1328–36.
172. Palmnas MS, Cowan TE, Bomhof MR *et al*. Low-dose aspartame consumption differentially affects gut microbiota-host metabolic interactions in the diet-induced obese rat. *PLoS One* 2014;**9**:e109841.
173. Bandyopadhyay A, Ghoshal S, Mukherjee A. Genotoxicity testing of low-calorie sweeteners: aspartame, acesulfame-K, and saccharin. *Drug Chem Toxicol* 2008;**31**:447–57.
174. Suez J, Korem T, Zeevi D *et al*. Artificial sweeteners induce glucose intolerance by altering the gut microbiota. *Nature* 2014;**514**:181–6.
175. Abou-Donia MB, El-Masry EM, Abdel-Rahman AA *et al*. Splenda alters gut microflora and increases intestinal p-glycoprotein and cytochrome p-450 in male rats. *J Toxicol Environ Health A* 2008;**71**:1415–29.
176. Bian X, Chi L, Gao B *et al*. Gut microbiome response to sucralose and its potential role in inducing liver inflammation in mice. *Front Physiol* 2017;**8**:487.
177. Soffritti M, Padovani M, Tibaldi E *et al*. Sucralose administered in feed, beginning prenatally through lifespan, induces hematopoietic neoplasias in male swiss mice. *Int J Occup Environ Health* 2016;**22**:7–17.
178. Kalantar-Zadeh K, Joshi S, Schlueter R *et al*. Plant-dominant low-protein diet for conservative management of chronic kidney disease. *Nutrients* 2020;**12**:1931.
179. Dagnelie PC, Mariotti F. 1 - Vegetarian diets: definitions and pitfalls in interpreting literature on health effects of vegetarianism. In: Mariotti F (ed.), *Vegetarian and Plant-Based Diets in Health and Disease Prevention*. Cambridge, Massachussets, USA: Academic Press, 2017;3–10.