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REVIEW

Vegetarian diets and chronic kidney disease

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ABSTRACT

While dietary restriction of protein intake has long been proposed as a possible kidney-protective treatment, the effects of changes in the quality of ingested proteins on the prevalence and risk of progression of chronic kidney disease (CKD) have been scarcely studied; these two aspects are reviewed in the present article. The prevalence of hypertension, type 2 diabetes and metabolic syndrome, which are the main causes of CKD in Western countries, is lower in vegetarian populations. Moreover, there is a negative relationship between several components of plant-based diets and numerous factors related to CKD progression such as uraemic toxins, inflammation, oxidative stress, metabolic acidosis, phosphate load and insulin resistance. In fact, results from different studies seem to confirm a kidney-protective effect of plant-based diets in the primary prevention of CKD and the secondary prevention of CKD progression. Various studies have determined the nutritional safety of plant-based diets in CKD patients, despite the combination of a more or less severe dietary protein restriction. As observed in the healthy population, this dietary pattern is associated with a reduced risk of all-cause mortality in CKD patients. We propose that plant-based diets should be included as part of the clinical recommendations for both the prevention and management of CKD.

Keywords: kidney disease, nutrition, vegetarianism

INTRODUCTION

For more than a century, the quantitative reduction of dietary protein intake has been recognized as a therapeutic measure in chronic kidney disease (CKD). In contrast, the relationship between dietary protein sources and the risk of incident CKD and its progression has long been neglected. The purpose of the present article is to successively provide information on these two topics through recent data from the medical literature.

First, to date, there seems to be a lack of reports on the prevalence of renal disease in the vegetarian population, whereas numerous studies have shown a decrease in the risk of hypertension [1], type 2 diabetes [2] and metabolic syndrome (MetS) [3, 4], which are the main causes of CKD in Western countries, in vegetarian populations. Given these findings, it would seem reasonable to assume that the renal consequences of these diseases should also be less prevalent among vegetarians.

Second, numerous studies have shown that plant-based diets are associated with a decrease in many risk factors associated with CKD progression, such as hypertension [5], uraemic toxins [6], inflammation [7] and oxidative stress [8], preventing the development of some metabolic disorders [9]. Thus one could be led to speculate on the potential benefits of plant-based diets on renal outcomes in CKD patients. As a matter of fact, these benefits have already been confirmed in most studies [10, 11].

As Mariotti did in his book [12], in this review we used the term 'vegetarian' to include all forms of vegetarian diet, from lacto-ovo-vegetarian to strict vegan. In cases where a study referred to a particular diet, we mention the diet in question.

PREVALENCE OF THE MAIN CAUSES OF CKD (HYPERTENSION, TYPE 2 DIABETES AND METS) IN VEGETARIANS

Vegetarianism and blood pressure

Numerous cross-sectional studies have found that, in industrialized countries, after adjustments for age, sex and body weight, blood pressure (BP) was lower among vegetarians than non-vegetarians. In observational studies, vegetarians also experience a blunted increase in BP with age [13]. In black as well as white subjects of the Adventist Health Study-2, two different analyses showed that the vegetarian Adventists had lower systolic and diastolic BP than their omnivore counterparts [1, 14]. A recent meta-analysis, including seven controlled trials (311 participants) and 32 observational studies (21 604 participants), found that when omnivores are switched to a vegetarian diet, the mean systolic BP is reduced by 4.8 mmHg and the mean

diastolic BP by 2.2 mmHg in the controlled trials, and the mean systolic BP is reduced by 6.9 mmHg and the mean diastolic BP by 4.7 mmHg in observational studies [15].

Furthermore, vegetarian diets have beneficial effects on weight reduction, and low rates of overweight and obesity in vegetarians have been confirmed in different series. In a study including >90 000 Seventh-day Adventists, the body mass index (BMI) was 2.5 kg/m^2 lower in vegetarians compared with non-vegetarians [16]. In an analysis of three prospective cohort studies including >120 000 men and women, investigating the relationship between lifestyle factors and weight changes at 4-year intervals, consumption of plant-based foods was inversely associated with weight gain [17]. In a more recent meta-analysis, including 15 intervention trials, prescription of a vegetarian diet of >4-weeks duration, without energy intake limitations, was associated with a mean weight change of −3.4 kg ($P < 0.001$) [18].

These results may account for the lower BP in vegetarians, since numerous observational studies and clinical trials have shown that BP is directly associated with weight. Dietary data from different studies have shown that the calorie intake of vegetarians is typically lower than that of non-vegetarians, with a mean difference of ∼400 calories/day, as observed, for example, in the National Health and Nutrition Examination Survey (NHANES) 1999–2004 study [19]. This energy deficit can contribute to a reduction in BP as a result of weight loss; however, a lower BP effect through a vegetarian diet has also been observed in individuals with normal body weight [1]. The effects of the diet on BP cannot be explained by weight loss alone, and the different dietary components of vegetarian diets each individually contribute to lowering BP.

The dietary components capable of lowering BP include the following.

Salt intake. A reduced salt intake is one of the main dietary approaches to prevent and treat hypertension. But surprisingly, it was shown almost 30 years ago that while Seventh-day Adventist vegetarians had lower BP than non-vegetarian control subjects, their urinary sodium levels were similar [13].

Potassium intake. As shown in numerous observational and epidemiological studies, a high potassium intake, related to high consumption of fruits and vegetables, is associated with lower BP in both non-hypertensive and hypertensive individuals. In the Dietary Approaches to Stop Hypertension (DASH) Study, 8 weeks on a diet rich in fruits, vegetables and low-fat dairy products resulted in a mean reduction in systolic and diastolic BP of 5.6 and 3.0 mmHg, respectively [20, 21]. These findings should be related to the diuretic and natriuretic effects of potassium.

Whether a cause or consequence, hypertension is commonly associated with CKD, and because of a potential increased risk of hyperkalaemia in CKD patients, their diet is restricted in terms of fruit and vegetable intake. At first glance, the risk of hyperkalaemia seems all the more real since it is potentiated by the frequent use of drugs, such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers and non-steroidal anti-inflammatory agents, that can substantially impair urinary potassium excretion. However, in non-dialysed CKD patients, serum potassium concentration appears to be weakly associated with dietary potassium intake, and the alkaline load, linked to the increased intake of fruits and vegetables, favours the shift of potassium from extracellular to intracellular fluids [22]. Lastly, fibres associated with high-potassium plant foods correct the frequent constipation observed in these patients. As a result, the shorter the intestinal transit time, the less dietary potassium will be absorbed.

Therefore it seems reasonable and safe, in CKD Stage 4 and 5 patients with retained urine flow, to set the potassium intake at 4.7 g/day (120 mmol/day), which corresponds to the potassium content of the DASH diet.

Dietary fibre intake. Results of the International Study on Macro/micronutrients and Blood Pressure study have shown that a higher intake of fibre, especially insoluble ones, may contribute to lower BP [23]. Results from this study have confirmed previous meta-analyses of randomized controlled trials indicating that an increased intake of dietary fibre might contribute to the prevention of hypertension or to the reduction of BP in hypertensive patients [24]. Enhanced insulin sensitivity, improved vascular endothelial function and improved magnesium intestinal absorption have been proposed to explain the BP-lowering effect of dietary fibres [25].

It was noticed that when the intake of fibre is increased, in isolation from other dietary changes, no effects on BP were observed [26].

Fat intake. Vegetarians eat less total fat and also more polyunsaturated fatty acids, resulting in an elevation in the dietary polyunsaturated:saturated (P:S) ratio (1.0 versus 0.3), but most studies do not support the view that these changes have a direct BP-lowering effect [27]. However, in a cross-sectional study comparing age- and sex-matched vegetarians and non-vegetarians, a higher resting energy expenditure (REE) was found in vegetarians than in non-vegetarians, contributing to their lower BMI values, independent of exercise. This increase in REE was positively correlated with a specific component of the vegetarians' diet—vegetable fats [28].

Carbohydrate intake. The OmniHeart Study has shown that, under isocaloric conditions, partial substitution of carbohydrates with either protein, particularly from plant sources, or monounsaturated fat can reduce BP, improve lipid levels and reduce cardiovascular risks [25]. It remains uncertain whether these effects result from a reduction in carbohydrate or from a compensatory increase in other macronutrients [29].

Protein intake. Data from several clinical trials suggest a small, but significant, inverse relationship between total dietary protein intake and BP, which was observed with protein intake from plant sources rather than with animal protein intake. This effect appears to be independent of changes in body weight and may be more apparent in populations with elevated BP and older populations.

The exact mechanisms linking plant proteins to BP have not yet been clarified and different explanations have been put forward. Dietary protein has been related to the synthesis of

cellular ion channels inducing natriuresis, thus leading to lower BP [30]. Dietary protein may result in a higher concentration of several amino acids that have BP-lowering effects [31]. Arginine, which serves as a substrate for nitric oxide (NO), is a potent vasodilator; its production improves endothelial function and contributes to BP lowering. Tryptophan may also reduce BP by augmenting NO production and by reducing adrenaline and noradrenaline. Higher protein intake may result in a higher concentration of histidine, which triggers a vasodilatory response [32].

To close this section concerning the relationship between vegetarianism and BP, we must mention that several non-dietary aspects of a vegetarian lifestyle (low to moderate alcohol intake, minimal cigarette smoking and regular physical activity) might also contribute to lower BP and more generally have a beneficial effect on the outcomes of patients [5].

Vegetarianism and type 2 diabetes

Comparison of ovo-lacto-vegetarians with omnivores showed that the former group were more insulin sensitive than their omnivore counterparts and that the degree of insulin sensitivity was correlated with years on a vegetarian diet [33].

Whole-grain products and vegetables generally have low glycaemic index values, and individuals following vegetarian diets are less than half as likely to develop diabetes compared with non-vegetarians; these figures were confirmed by the Adventists Health Study-2 that included >60 000 individuals who participated in the study conducted in 2002–06. After adjustment for age and different components of lifestyle, the prevalence of type 2 diabetes increased from 2.9% in vegans to 7.6% in non-vegetarians, while the prevalence was intermediate in participants consuming lacto-ovo-, pesco- and semi-vegetarian diets [2].

A systematic review and meta-analysis including 255 type 2 diabetic patients (17 lacto-ovo-vegetarians and 238 vegans) showed that consumption of a vegetarian diet, combined with exercise, was associated with a dramatic reduction in the use of glucose-lowering medications and in haemoglobin A1c, as well as a non-significant reduction in fasting blood glucose concentration [34].

Lastly, vegetable proteins have a lower impact on renal haemodynamics than animal proteins. Replacing animal proteins with vegetable proteins may decrease renal hyperfiltration, proteinuria and, theoretically, in the long-term, the risk of developing renal failure [35].

Vegetarianism and MetS

MetS is defined as the presence of at least three of the following criteria: abdominal obesity, low high-density lipoprotein, hypertriglyceridaemia, elevated fasting glucose and hypertension. The prevalence of MetS, which occurs in ∼20% of the population of the USA, is increasing in developing and developed countries [36]. Various dietary patterns have been proposed for preventing MetS, among which is a vegetarian diet. Several cross-sectional and case–control studies have confirmed an association between consumption of a vegetarian diet and an estimated 2-fold reduction in the prevalence or risk of developing MetS (except for low-density lipoprotein) [4, 36].

The proposed recommendation of a vegetarian diet was well illustrated in the prospective Atherosclerosis Risk in Communities (ARIC) Study, which included >10 000 middle-aged adults, free of diabetes and cardiovascular disease, with an estimated glomerular filtration rate (eGFR) >60 mL/min/1.73 m^2. Twenty-one per cent of the participants met the criteria for MetS at their initial visit, with prevalences of zero, one, two, three, four or five traits of MetS of 26, 30, 23, 15, 5 and 1%, respectively. After a 9-year follow-up, 7% of the participants developed CKD, and the risk of incident CKD increased significantly with the baseline number of traits of MetS. These data confirm that, in addition to hypertension and diabetes, MetS is also independently associated with an increased risk for incident CKD [37].

VEGETARIANISM AND EFFECTS ON THE FACTORS OF CKD PROGRESSION

In addition to their likely impact on the prevalence of the main causes of CKD, vegetarian diets should also be potentially beneficial to CKD patients because they inhibit the production of some of the deleterious factors proven responsible for adverse outcomes in CKD.

Uraemic toxins

Some protein-bound solutes are produced in the colon by the action of gut microbiota on food proteins and endogenous proteins that have escaped digestion in the small intestine. Indoxyl sulphate and *p*-cresyl sulphate, which result from bacterial metabolism of the amino acid substrates tryptophan and tyrosine, respectively, are some of the main protein-bound solutes. In CKD patients, prolonged colonic transit times, therapeutic interventions, changes in dietary habits and changes to the gut microbiota result in several changes in bacterial fermentation. These modifications lead to pathogen overgrowth, which affects the proteolytic bacterial species and results in an increased generation of toxic proteins [38]. These proteins, which are normally cleared by the kidneys, accumulate in the plasma of CKD patients, thus contributing to the syndrome of uraemia. They are involved in the progression of CKD and increased cardiovascular risk, contribute to inflammation and oxidative stress [39] and insulin resistance (IR) [40] and are independently associated with overall mortality.

It has been convincingly demonstrated that the production of these solutes could be influenced by dietary modifications. In individuals with normal renal function, a vegetarian diet rich in non-digestible fibre might reduce, by ∼60%, the urinary excretion of *p*-cresyl sulphate and indoxyl sulphate, which reflects their production [6]. Increasing dietary fibre for 6 weeks in haemodialysis (HD) patients significantly reduces the plasma free level of indoxyl sulphate and *p*-cresyl sulphate by 27% and 24%, respectively [41]. In a prospective randomized controlled study of 32 CKD patients not yet on dialysis, indoxyl sulphate levels were reduced after only 1 week on a supplemented very-low-protein diet of plant-based origin (0.3 g/kg body weight/day),

even when preceded by a conventional low-protein diet (0.6 g of mixed origins/kg body weight/day) [42].

Identical findings have been reported with trimethylamine (TMA) released through the action of gut microbiota from dietary compounds mainly found in animal proteins (lecithin, choline, *L*-carnitine). TMA is secondarily oxidized in the liver to trimethylamine-*N*-oxide (TMAO), which is normally cleared by the kidney. The accumulation of TMAO in patients with impaired renal function is associated with an advanced cardiometabolic risk profile and an increased risk for all-cause mortality [43]. Vegetarian diets that have a lower lecithin, choline and *L*-carnitine content result in less TMAO production.

Inflammation

Systemic low-grade inflammation, which is a common feature of CKD, favours the progression of renal dysfunction and is a major contributor to complications of CKD such as protein-energy wasting (PEW) and accelerated vascular ageing.

A key role in the pathogenesis of chronic inflammation in CKD patients has been attributed to the gut microbiome. Profound changes in the composition of the gut microbiome related to metabolic alterations of uraemia favour pathogen overgrowth. This intestinal dysbiosis, associated with an increased intestinal permeability, which is linked to a decreased expression of tight junction proteins, contributes greatly to systemic inflammation and oxidative stress in CKD patients through the translocation of living bacteria and bacterial components into the systemic circulation [44, 45].

Nutrients also play a central role in the regulation of inflammation, and there is a significant relationship between the type of diet, which shapes the gut microbiota, and chronic low-grade inflammation. Diets high in non-digestible fibres, fruits and vegetables, vitamins and antioxidants have a lower dietary inflammatory score and have been associated with reduced levels of interleukin-6 (IL-6) and C-reactive protein (CRP) [46]. The anti-inflammatory effects of these diets in CKD patients are linked to the correction of the gut microbiota dysbiosis. Consumption of plant-based diets is associated with an enhanced richness and diversity of the gut microbiota, resulting in a better state of health and metabolic profile. The consequent decrease in pathobionts and the greater abundance of anti-inflammatory bacteria are also favoured by the increased bowel transit. Moreover, some of the bacteria, which participate in the fermentation of carbohydrates that have escaped digestion in the small intestine, promote the generation of short-chain fatty acids that, besides their anti-inflammatory action, contribute to maintain colorectal tissue integrity [47].

Besides their already mentioned beneficial effect on BP, dietary fibre has a regulatory role in the inflammatory response, as confirmed by NHANES 1999–2000 that included 3920 participants >20 years of age and showed that dietary fibre intake was inversely associated with the concentration of serum CRP, with the association persisting after adjusting for multiple variables [48]. A recent epidemiological study showed that in a cohort of nearly 1 000 000 non-CKD individuals, higher dietary fibre intake was associated with a reduced risk of all-cause mortality [49]. It can be concluded from these different studies performed on healthy people that dietary habits, such as vegetarian diets, thus represent one of the potential therapeutic interventions to counteract systemic low-grade inflammation of digestive origin. On the other hand, different cross-sectional studies have shown that higher saturated fat intake of animal origin is directly associated with an increased intestinal permeability, with negative consequences on microalbuminuria and inflammation [50].

In the CKD population, dietary fibre intake is usually low, particularly in patients on maintenance HD, mainly because of dietary recommendations. In a pool of 102 HD patients, dietary fibre intake was lower than in control subjects (12.4 ± 5.8 g/day versus 17.9 ± 10.6 g/day; $P < 0.02$), far below the 30 g/day usually recommended for the general population. Data from NHANES III that included 14 543 participants confirmed that the CKD group of the cohort had a higher prevalence of high serum CRP levels (>3 mg/L) compared with the non-CKD group (44.5% versus 24.5%; $P < 0.001$). In CKD and non-CKD groups, intake of fibre was negatively associated with serum CRP levels. Moreover, during the 8.4 years of follow-up, fibre intake was negatively associated with the risk of death, but only in the CKD group [51].

Oxidative stress

Oxidative stress results from an imbalance between the excessive production of reactive oxygen species during metabolic processes and the more or less reduced antioxidant defence system of cells and tissues.

Compared with healthy age-matched omnivores, long-term vegetarians have a better antioxidant status and coronary heart disease profile [52]. The age-dependent increase in the products of oxidative damage to cellular DNA, lipids and proteins and the age-dependent decrease in antioxidant vitamins are not observed in long-term vegetarians [53]. These results were confirmed by a study comparing 45 long-term (>15 years) vegetarians with 30 age- and sex-matched omnivores that showed the level of oxidative stress was lower in long-term vegetarians than in omnivores. The lack of a significant difference in endogenous antioxidant activities between the two groups suggests that the observed difference in oxidative stress level was related to the different dietary patterns. Unlike Western-type diets that lead to increased oxidative stress, plant-based diets have a low saturated fatty acid content and provide twice the antioxidant vitamins, such as vitamins A and C, than do Western-type diets. Moreover, fruits and vegetables contain various phytochemicals, such as polyphenols and flavonoids, which are powerful antioxidants and effectively prevent free radical generation [8].

The high prevalence of oxidative stress observed in CKD patients is linked to an imbalance between the increased production of reactive oxygen species favoured by age, hypertension, diabetes and inflammation and the low antioxidant status related to a reduced activity of the glutathione system and a low intake of antioxidants from the usual diet. Oxidative stress is present from the early stages of CKD and increases as CKD progresses [54, 55]. Damage resulting from oxidative stress may influence the progression of renal injury and plays a prominent

role in the cardiovascular complications of uraemia, constituting one of the major causes of morbidity and mortality [56].

To date, study findings on the effects of antioxidant therapy on cardiovascular disease and mortality in CKD patients have remained inconclusive. Antioxidant therapy was found to delay CKD progression to end-stage renal disease (ESRD), but these results were derived from a very small number of cases with short-term follow-up, so larger clinical trials are needed to confirm the possible effectiveness of antioxidant therapy [57].

Metabolic disorders

IR. IR is present at all stages of CKD. As in the general population, IR is an independent predictor of cardiovascular events, related with impaired vascular endothelial function [58], and is also strongly associated with increased muscle protein breakdown, contributing to protein energy wasting (PEW) and malnutrition commonly observed in CKD patients [59]. Lastly, there is a possible link between IR and progression of renal failure [60]. Alterations in post-insulin receptor signalling pathways responsible for IR are mediated by the retention of nitrogenous waste products, oxidative stress, high angiotensin II levels, metabolic acidosis, vitamin D deficiency and systemic inflammation.

Few studies have been performed on the effect of vegetarian diets on IR in non-diabetic CKD patients, which confirmed an improved insulin sensitivity by vegetarian diets. After 3 months on a diet affording 0.3 g/kg/day of plant-based protein associated with a mixture of essential amino acids and ketoanalogues, fasting serum glucose levels, blood glucose levels and endogenous glucose production were reduced in six patients with CKD Stages 4–5 [61].

Metabolic acidosis. Metabolic acidosis, which is observed in the majority of CKD patients when the GFR decreases to $<30\%$ of normal, results in several adverse consequences of which muscle wasting, bone loss, impaired insulin sensitivity, chronic inflammation and progression of renal failure are the most important, which may be corrected by oral alkali supplementation [62].

The daily acid load is partly dependent on the type of food ingested. For a quantitatively identical protein intake, the acid load linked to animal proteins is higher than that linked to plant proteins. Western-type diets are usually characterized by a high consumption of animal proteins, which increases the net endogenous acid production and tends to worsen metabolic acidosis in CKD patients. In adults with normal renal function who are on a Western-type diet, the acid–base equilibrium is maintained, but mild metabolic acidosis with deleterious effects may develop in older men and women as a consequence of the normal decline in renal function with increasing age.

While a usual Western-type diet induces an acid excess of 50–100 mEq/day and a urinary pH close to 5.5, an increased consumption of fruits and vegetables results in a renal acid excretion of <10 mEq/day and urinary pH values of 6.6–6.8; in vegans, the acid load is close to neutrality [63]. Fruits and vegetables are base-inducing foods, and increasing their daily intake, as achieved with vegetarian diets, might lower the dietary acid load and induce results similar to those achieved with alkali therapy. It has been shown that, in patients with CKD Stage 2, adding 2–4 cups of fruits and vegetables to their daily diet was comparable to the administration of 0.5 mEq/kg/day of sodium bicarbonate [64].

On the other hand, a high dietary acid load is associated with an increased incidence of CKD. During a mean follow-up of 21 years, incident CKD developed in 15.6% of the participants in the prospective ARIC study. After adjusting for established risk factors, a higher dietary acid load, estimated by using the potential renal acid load method, was associated with a higher risk of incident CKD [65], which may be due to activation of the renin–angiotensin system or an increase in endothelin-1 levels [66].

Dietary acid load is also correlated with progression of renal failure. In a recent study on 1486 adults with CKD enrolled in NHANES III, with a median of 14.2 years of follow-up, 20.9% of the participants developed ESRD. The risk of ESRD was associated with the dietary acid load tertile, particularly in patients with albuminuria; in contrast, a diet rich in fruits and vegetables was inversely associated with albuminuria, indirectly suggesting a dampening effect on the progression to ESRD [67].

The results of these various studies suggest that fruits and vegetables could represent an effective intervention to correct metabolic acidosis and the consequences of CKD.

Hyperphosphataemia. Changes in calcium phosphate metabolism, which are partly linked to a positive phosphorus balance, start early in the course of CKD, favoured by the typical Western-type diet usually rich in dairy products and protein of animal sources and often worsened by food additives [68]. The resulting hyperphosphataemia and the linked compensatory secondary hyperparathyroidism and increase in fibroblast growth factor 23 (FGF-23) are associated with progression of renal disease, vascular calcification and mortality.

Dietary control of phosphate intake should not be limited to the phosphate content in foods, but the source of phosphorus should also be considered. While phosphates derived from animal sources are easily hydrolyzed and absorbed, phosphate bioavailability from plants is relatively low in humans, because phosphorus from plant-derived proteins is bound in larger molecules, such as phytates, which cannot be broken down in the digestive tract due to the absence of human phytase activity. The intestinal absorption of dietary phosphorus, which is close to 70% in meat eaters, does not exceed 30–40% in vegetarians [69]. Moe *et al.* [70] reported that in CKD patients not yet on dialysis treatment, despite equivalent energy, protein and phosphorus intake, a vegetarian diet, compared with a meat diet, was associated with a significant reduction in serum phosphorus and FGF-23 levels and a decrease in 24-h urinary phosphorus excretion. Similar results have been reported in CKD patients on a very-low-protein diet supplemented with ketoanalogues, which is in fact a vegetarian diet [71]. Lastly, even if not strictly vegetarian, consumption of a greater percentage of plant-based proteins is associated with lower FGF-23 levels [72].

Food additives represent another source of phosphorus that must also be taken into consideration in the estimation of dietary phosphorus. Phosphorus intake is also reduced in

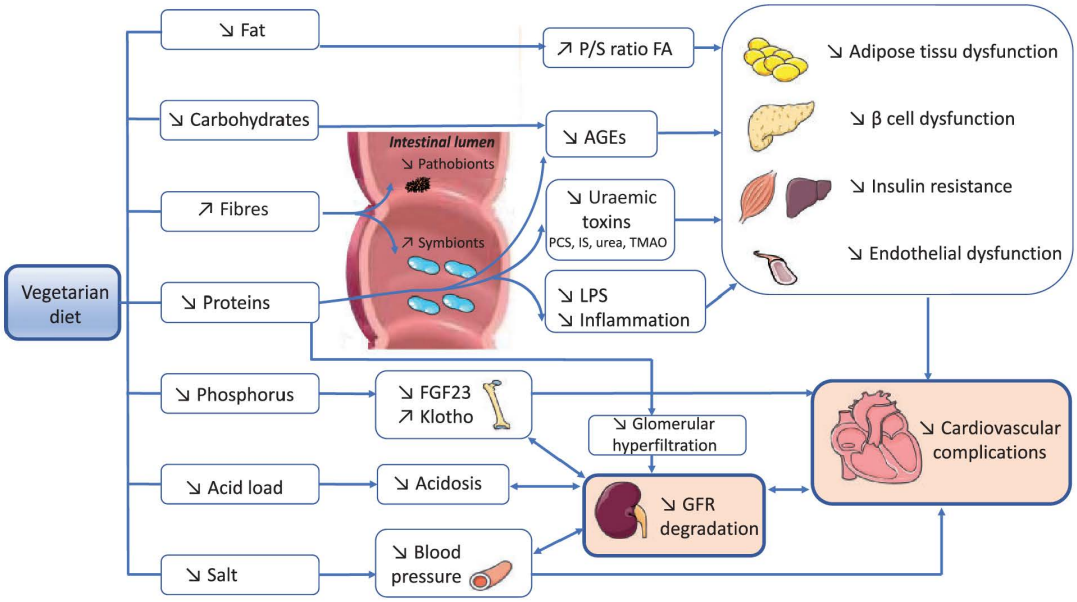

FIGURE 1: Hypothesized effects of a vegetarian diet and its components on CKD. AGEs, advanced glycation end-products; FGF23, fibroblast growth factor 23; IS, indoxyl sulphate; LPS, lipopolysaccharide; PCS, *p*-cresyl sulphate; P/S ratio FA, polyunsaturated/saturated ratio of fatty acids; TMAO, triméthylamine-N-oxyde.

vegetarians because their diet is almost free of phosphorus-containing food additives that are currently added to a large number of processed foods, particularly meat and poultry. The 'enhancement' of fresh meat and poultry products with phosphorus-containing food additives increases the phosphorus content of these samples by 7–100% [73]. Lastly, phosphorus in food additives has a higher availability than phosphorus contained in unprocessed foods, since it is almost completely absorbed in the intestinal tract.

Effect of vegetarian diets on nutritional status, renal function and risk of all-cause mortality in patients with CKD

An often raised problem concerns nutritional tolerance of vegetarian diets in CKD patients, especially since plant-based diets are normally associated with lower energy and protein intake than omnivorous diets. In fact, several studies have confirmed that, similar to vegetarians with normal renal function, CKD patients on a vegetarian diet maintained a good nutritional status at any stage of CKD [74], including patients on maintenance HD treatment [75]. A favourable consensus seems to emerge from various studies on the nutritional tolerance of plant-based diets in CKD patients, provided these diets supply adequate energy in the normal to high range (30–35 kcal/kg/day). Even without being on a strict vegetarian diet, the inclusion of a greater amount of protein from plant-based sources (60–70%) in a conventional low-protein diet (0.6 g/kg/day) brings many benefits to CKD patients—such a diet results in higher energy intake because its greater palatability allows to add more calories to foods derived from plants, provides a more positive nitrogen balance, higher serum bicarbonate levels and more stable renal function and improves compliance, appetite and well-being [76].

Plant-based diets have a kidney-protective effect, and several observational studies have confirmed that healthy dietary patterns usually rich in fruits, vegetables, legumes and whole grains and low in red meat, saturated fat, refined sugars and processed foods are more protective than usual diets in the primary prevention of CKD.

These points are well summarized in the ARIC Study, which is a large longitudinal observational study including almost 12 000 adults with normal renal function at baseline. The primary endpoint was incident CKD Stage 3 (defined as an eGFR <60 mL/min/1.73 m^2, accompanied by a decrease in eGFR $>25\%$ from baseline) occurring during a median follow-up of 23 years. To assess the association between dietary protein sources and the incidence of CKD Stage 3, patients were divided into quintiles of dietary food and protein intake. A total of 2 632 cases of incident CKD Stage 3 were observed during follow-up. There was no significant association between total protein consumption and incident CKD Stage 3; however, there was a significantly higher risk of incident CKD in individuals consuming more proteins from red and processed meat [hazard ratio (HR) 1.23; $P<0.01$]. On the other hand, proteins from vegetable and dairy sources were found to be protective and participants consuming the highest quintile of vegetable protein had a reduced risk of incident CKD compared with individuals with the lowest intake (HR 0.76; $P<0.002$). Lastly, substituting one serving per day of red and processed meat for one serving of low-fat dairy products, nuts or legumes was associated with a lower risk of incident CKD. The authors concluded that there was an association between the development of CKD and the

type of dietary protein sources rather than the total protein intake [10].

With regard to the effect of plant-based diets on the risk of incident ESRD, results available to date are not unanimous. While some studies have reported such diets to be protective against the risk of incident ESRD [11], this effect has not been found in two recent studies [77, 78].

Regarding the mortality rate, it is widely recognized that in the general population, adherence to plant-based diets is associated with significantly increased longevity. This point is well illustrated in a multi-adjusted analysis including 73 308 Seventh-day Adventists recruited between 2002 and 2007 and comprising 48.2% of non-vegetarians and 51.8% of those on different vegetarian dietary patterns. During a mean follow-up period of almost 6.0 years, there were 2570 deaths, with an overall mortality rate of 6.05 per 1000 person-years. Vegetarians had 0.88 times the risk of all-cause mortality and 0.48 times the risk of renal mortality compared with non-vegetarians [79].

Similar findings were reported in several other studies that focused on the effect of plant-based diets on the risk of all-cause mortality in CKD patients. In the recent NHANES III study comprising a cohort of 14 866 participants stratified by eGFRs <60 or >60 mL/min/1.73 m^2, the mean total protein intake and plant protein:total protein ratio estimated from 24-h dietary recalls were 24.6 ± 13.2 g/day and $33.0 \pm 14\%$, respectively. During an average follow-up of 8.4 years, there were 2163 deaths (14.6%). In the subgroup of patients with eGFR <60 mL/min/1.73 m^2, each 33% increase in the plant protein:total protein ratio was associated with a lower mortality risk (HR 0.77). These data suggest that in CKD patients, at a given total protein intake, a diet with a higher proportion of vegetal protein is associated with lower mortality [80]. These results are in agreement with a recent meta-analysis of seven cohort studies including 15 285 adults with CKD. Healthy dietary patterns (i.e. higher content of fruits and vegetables, fish, legumes, cereals, whole grains and fibre and lower content of red meat, salt and refined sugars) were associated with a reduced risk of all-cause mortality [77].

CONCLUSION

To confirm these interesting but scattered data, additional studies are needed, first to assess the prevalence of CKD in vegetarian populations, second to evaluate, through large-scale randomized controlled trials, the benefits of plant-based diets for their potential inclusion in clinical recommendations for the prevention and management of CKD.

CONFLICT OF INTEREST STATEMENT

None declared. This paper has not been published previously or submitted to another journal.

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