

# Mediterranean diet as the diet of choice for patients with chronic kidney disease

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## ABSTRACT

Traditional dietary management of chronic kidney disease (CKD) focuses on the quantity within the diet of energy and protein, and the restriction of single micronutrients, with little mention of dietary quality. Dietary patterns that are more plant-based, lower in meat (including processed meat), sodium and refined sugar, and have a higher content of grains and fibres are now included in multiple clinical guidelines for chronic disease prevention. The Mediterranean diet (MD) has been associated with reduced cardiovascular disease incidence in both observational and interventional studies. A wealth of evidence links MD with other beneficial effects on chronic diseases such as diabetes, obesity or cognitive health. This review examines each constituent of the classical MD and evaluates their suitability for the management of patients with CKD. We also evaluate the potential hyperkalaemia risk of increasing fruit and vegetable intake. Overall, a decrease in net endogenous acid production and increase in fibre may lead to a better control of metabolic acidosis. This, together with other putative favourable effects of MD on endothelial function, inflammation, lipid profile and blood pressure, provide mechanistic pathways to explain the observed reduced renal function decline and improved survival in CKD patients adhering to an MD.

**Keywords:** kidney disease, Mediterranean diet, nutrition, vegetarian diet

## INTRODUCTION

The potential role of a healthy diet is far more complex than delivering a combination of nutrients. Public health recommendations for prevention of cardiovascular disease (CVD) have, for instance, moved from a single-nutrient focus to whole foods and dietary patterns [1], which are more easily translated into dietary recommendations. Patients with chronic kidney disease (CKD) are at high risk of CVD complications, contributing to the most common cause of death. Traditional dietary management of CKD focuses predominantly on the quantity within the diet of energy and protein, and the restriction of single micronutrients, with little mention of dietary quality. Emphasis on restriction of sodium, potassium and phosphorus in CKD may possibly compromise overall diet quality [2].

Fruit and vegetable-rich diets such as the Mediterranean diet (MD) are recommended for primary and secondary disease prevention. Emerging evidence in patients with CKD suggests these diets may be helpful to delay progression and prevent complications [3]. Reluctance to recommend an MD to the CKD patient may arise when some of the typical components of the MD pyramid conflict with the traditional dietary restrictions of CKD. The European Renal Nutrition (ERN) Working Group of the European Renal Association–European Dialysis Transplant Association (ERA-EDTA) aims, with this review, to summarize

arguments in favour of and against adopting the MD as a healthy dietary pattern and lifestyle for the CKD population.

## THE MD: A MODEL OF CARDIOPROTECTION

### Features

The traditional Mediterranean dietary pattern has the following characteristics [4]:

- High consumption of fruits, vegetables, bread and whole-grain cereals, potatoes, beans, nuts and seeds
- Extra virgin olive oil (cold pressed) as an important monounsaturated fat source
- Dairy products, fish and poultry are consumed in low-to-moderate amounts
- Eggs are consumed zero to four times a week
- Sweets are seldom consumed
- Red meat is eaten less often and in connection with special occasions
- Wine is consumed in low-to-moderate amounts, during meals

Despite some agreement on the characteristics of an MD, there is wide variation on the number and proportion of servings per week for the MD components as it appears in the literature. To account for this variability, estimates were averaged from literature review resulting in the diet pyramid (Figure 1), often recommended in public health prevention programmes.

We acknowledge that this ‘traditional’ MD pyramid is not necessarily aligned with current dietary trends in Mediterranean-border countries, which like most other societies are influenced by Western diets, with convenience, fast and ultra-processed foods [5, 6].

### Purported benefits

The salutary effects of the MD were first reported in the early 1950s by the pioneering Seven Countries Study [7], an observational analysis that reported a 2- to 3-fold lower coronary heart disease mortality in Mediterranean countries as opposed to northern European countries or the USA [8]. Since then, numerous studies, meta-analyses and even a randomized controlled trial have confirmed an inverse association between adherence to the MD and cardiovascular (CV) risk [9, 10]. Further, this dietary pattern has also gained recognition in its role for prevention of obesity or type II diabetes [11].

### Evidence from observational studies

Observational studies have explored the potential benefits of MD by analysing the adherence to such a diet. Adherence is defined through a diet score of up to nine most-representative items from the pyramid that are health-promoting and/or health-harming food groups. A semi-quantification/frequency of intake for these items results in a total score whose increase (from 0 to a maximum of 9 points) is used in observational studies to quantify the adherence of an individual to a MD pattern [12]. Note that in this way, the MD score is population specific.

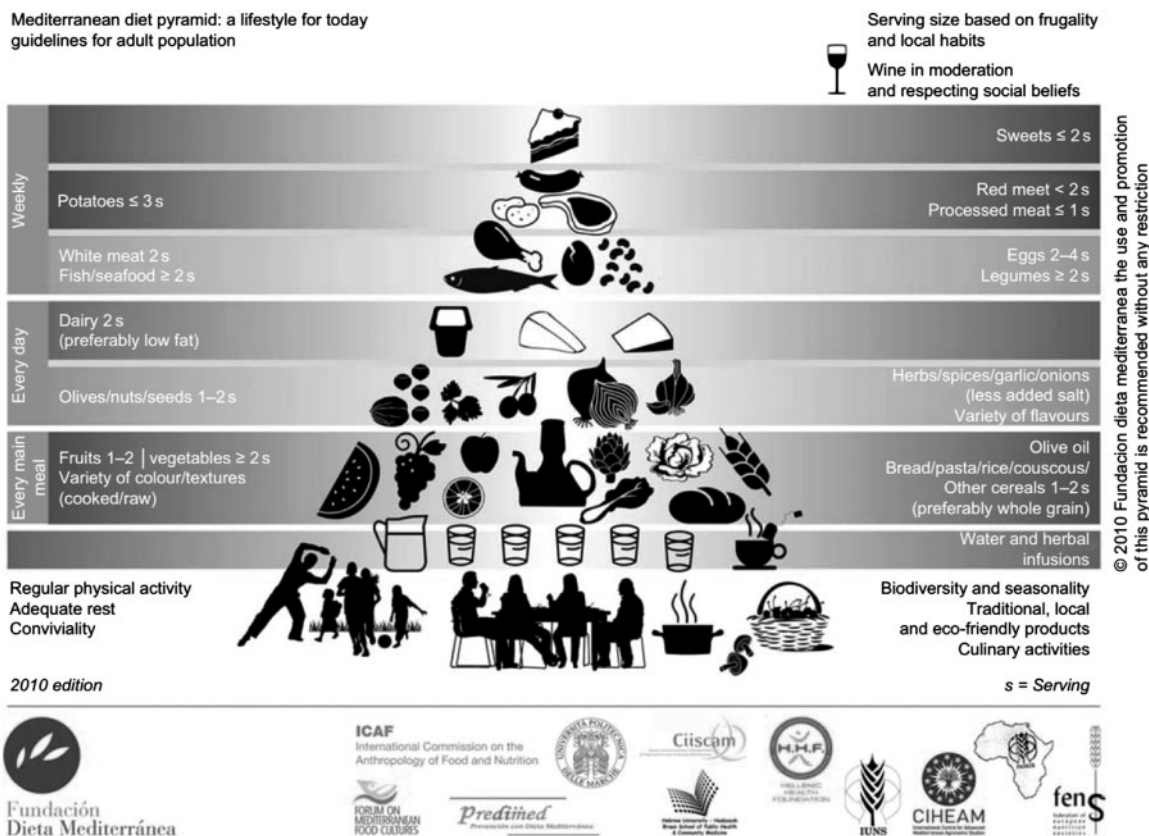


FIGURE 1: MD pyramid.

In other words, individuals consuming more olive oil in Scandinavia may be considered more adherent to a MD than those consuming less olive oil within the same Scandinavian population. However, the absolute amount of olive oil (g/day) consumed by this Scandinavian MD adherent population may be very low compared with what is consumed in an Italian or Spanish setting. Studies using this MD scoring have illustrated the positive health implications associated with this diet. A recent meta-analysis [9] summarized the consistency of available literature linking adherence to an MD with health. The meta-analysis included more than 2 million healthy subjects followed for up to 20 years and reported strong associations between MD and reduced incidence of cognitive diseases, overall mortality and CV mortality. They also observed consistent reductions in biochemical indicators (blood lipids, etc.) and an improvement in the individual's quality of life [13]. Adherence to the MD may accrue benefits up to 2 years of longer survival [13].

### Evidence from randomized controlled trials

Two major well-powered trials have explored the benefits of MD in primary and secondary prevention of CVD: The Lyon and Heart Study [14] was a randomized secondary prevention trial aimed at testing whether an MD may reduce the rate of recurrence after a first myocardial infarction (MI). Included were 423 consecutive survivors of an MI asked to either comply with a Mediterranean-type diet or follow regular dietary advice. Within 4 years of follow-up, the MD group had a lower rate of MI recurrence. The Prevencion con Dieta Mediterranea (PREDIMED) study was a multicentre randomized primary prevention trial that included nearly 7500 subjects at high CV risk. The trial showed that at a median follow-up of 4.8 years, the MD groups (supplemented with a daily intake of either

extra virgin olive oil or mixed nuts) experienced a 30% CVD risk reduction compared with a low-fat diet control group. The CVD beneficial effects were observed together with reductions in blood pressure, obesity prevalence, inflammation, oxidative stress, rate of progression of the carotid intima-media thickness and improved lipid profile, thus providing the best evidence to bring the MD to the forefront of primary prevention of CVD in the community [10].

### ARGUMENTS IN FAVOUR OF PRESCRIBING MEDITERRANEAN-LIKE DIETS TO PATIENTS WITH CKD: MUCH TO WIN

We should emphasize that no single component of the MD is responsible for the positive effects that can be attributed to this diet. Instead, it should be attributed to the balanced overall dietary pattern. Further, food plays a central role in the social and cultural life of the Mediterranean area and qualitative elements such as conviviality, culinary activities, physical activity, outdoor life and adequate rest strengthen the health effects of MD [9]. Table 1 summarizes these arguments and lists current evidence in both CKD and non-CKD populations.

#### The MD provides a healthy protein and fat intake profile

Protein intake in the MD aligns with a controlled protein diet for CKD (~0.8 g/kg/day). An interesting aspect is the source of protein, which in the MD comes predominantly from vegetables, fish and white meat. Red meat and processed meats are less often consumed, which may convey a lower amount of dietary sodium, phosphate and potassium. Such habits have been associated with lower CV and cancer risk in the

**Table 1. Arguments in favour of prescribing MDs to patients with CKD**

Features of the MD	Purported benefits from non-CKD studies	Purported benefits from CKD studies
Provision of a healthy protein and fat intake aligned with CKD recommendations		
Predominance of vegetal and fish protein versus meat protein	Lower cardiovascular and cancer risk [15, 16] Lower risk of incident CKD and of ESRD [17, 18]	Reduced phosphate load (lower bioavailability) Lower mortality risk [19]
Predominance of MUFA and PUFA over SFA	Decreased systemic inflammation and (LDL) cholesterol	Decreased blood pressure, CVD risk and inflammation [21]
Favour consumption of olive oil	Lower CVD risk [20] Anti-inflammatory, antioxidant and vasculoprotective properties [20, 22]	Ameliorates constipation in HD patients [23]
High dietary fibre intake		
High fibre intake	Lower blood pressure, decreased inflammation and blood lipids. Lower CVD, cancer and mortality risk [24, 25] Lower risk of CKD [26]	Reduction of CV risk factors and uraemic toxins  Reduced inflammation and mortality risk [27]
Moderate carbohydrate consumption preferably whole grain		
Low glycaemic index and glycaemic load	Beneficial effects on glucose control, hyperinsulinaemia, insulin resistance, blood lipids and satiety [28, 29]	Reduction of oxidative stress and inflammation [30]
Wine in moderation		
Moderate wine intake	Lower all-cause and cardiovascular mortality. Improved lipoprotein metabolism, reduced inflammation and oxidative stress	Reduction of oxidative stress and of inflammation [31] Lower risk of CKD progression [32]
Choice of local and eco-friendly products over processed foods		Decrease in sodium, potassium and phosphate load [33, 34]

community [15, 16], but also with lower risk of incident CKD and of end-stage renal disease (ESRD) in individuals with normal kidney function [17, 18]. In patients with manifest CKD, the benefits of plant-based versus animal-based protein have been little studied. Old studies addressing the impact of acute protein loading (short-term interventions of 4–12 weeks) show no or mixed effects of protein sources on estimated glomerular filtration rate (eGFR) change [35–37]. A problem in the interpretation of those studies is that the outcome in these studies is creatinine-based eGFR estimation, which can be affected by protein intake. Two more recent short-term randomized controlled trials (RCTs) in patients with CKD Stages 3–5 showed that adherence to a plant-based diet as compared with a meat-based diet was effective in maintaining serum phosphate targets and reducing FGF23 [38, 39].

A typical MD provides 50% of the lipid-derived energy from monounsaturated fatty acids (MUFA), 25% from polyunsaturated fatty acids (PUFA) and 25% from saturated fatty acids (SFA). Oleic acid is the main MUFA representative and is present in extra virgin olive oil, which is also rich in polyphenols and vitamin E, and collectively has additive anti-inflammatory, antioxidant and vasculoprotective properties [20, 22]. Increased olive oil consumption has been consistently associated with a lower risk of all-cause mortality, CV mortality, CV events and stroke in the general population and in individuals with manifest CVD. Such reductions are not always observed in other studies in which MUFA sources contemplated both animal and plant origin [9]. The MD is also rich in n-3 PUFAs (both from marine origin and from plants), which have hypotriglyceridemic, anti-inflammatory and anti-thrombotic properties [4]. Lastly, because of an often low consumption of dairy, red meat and meat products in Mediterranean countries, SFA intake is low, not exceeding 7–8%. This is an important point since SFA is one of the pro-inflammatory nutrients which favour the development of atherosclerosis, being associated with increased blood [low-density lipoprotein (LDL)]cholesterol and increased systolic blood pressure [40].

### **The MD provides a low glycaemic index and low glycaemic load**

Carbohydrates, which represent >50% of total energy intake in most modern-style diets, feature less in MD. Nearly all carbohydrates are from high-quality, nutrient-dense carbohydrates coming from fruits, vegetables, whole grains and nuts, not refined sugars, and having a low glycaemic index which attenuates postprandial glucose and insulin responses. Epidemiological studies have shown that the intake of whole-grain cereals and their products such as whole-wheat bread are associated with a 20–30% reduction in the risk of type II diabetes and with a strong reduction of CV events [41]. Lastly, reduction in carbohydrate intake *per se*, has beneficial effects on serum lipid profile [42]. The MD is characterized by a low glycaemic index, that is, predominance of slowly absorbed carbohydrates in the diet. A low glycaemic index has been shown in some studies to produce beneficial effects on glucose control, hyperinsulinaemia, insulin resistance, blood lipids and satiety [28, 29]. A low glycaemic index may also be relevant for dialysis patients. In the only study

available so far, dietary glycaemic load significantly associated with markers of oxidative stress and inflammation among 58 patients undergoing dialysis, independent of body composition and adipocytokines [30].

### **The MD allows a moderate consumption of wine**

Regular but moderate intake of wine during meals (1–2 glasses/day) is recommended in the MD pyramid. Epidemiologic studies from geographically distant populations show that individuals with daily moderate wine consumption are associated with a lower risk of all-cause and, particularly, CV mortality when compared with individuals who abstain or who drink excess alcohol [43, 44]. The beneficial effects of red wine are thought to be due to the polyphenol compounds, such as resveratrol, that are found in high concentrations in various plants, including red grapes and their derivatives, exhibiting potent anti-inflammatory and antioxidant activity by enhancing the expression of antioxidant enzymes [45]. Phenolic compounds in wine contribute more particularly to the overall antioxidant effects of the MD when the body is under conditions of low-grade inflammation and oxidative stress that occur after a meal as result of postprandial hyperglycaemia and hyperlipidaemia [46]. White wine, although lacking polyphenols, contains simple phenols, such as tyrosol and hydroxytyrosol, which have similar antioxidant and anti-inflammatory properties. Moderate wine consumption may also benefit patients with CKD. A prospective, randomized trial studied this among 10 healthy volunteers and 10 patients with CKD Stages 3–4. The combined consumption, for 2 weeks, of 2–3 glasses/day of white wine and extra virgin olive oil resulted in a significant reduction of plasma markers of chronic inflammation while no significant variation was observed with extra virgin olive oil alone [31]. In North European settings, alcohol consumption has been associated with a lower risk of CKD progression [32]. The inability of that study to differentiate wine from spirits makes our comment, though, speculative.

### **The MD favours reduced inflammation and reduced oxidative stress—the case for increased olive oil consumption**

Collectively, several characteristics of the MD (dietary fat profile, moderate wine intake and fruit/vegetable intake) prompt anti-inflammatory and antioxidant effects. The intake of these nutrients and foods has been associated with the beneficial effects that the MD has in reducing oxidative stress and inflammation [47]. In the PREDIMED trial, 1 year of MD was successful in reducing inflammatory markers ICAM-1, IL-6 and TNF- $\alpha$  receptors compared with baseline values and with the placebo group. The authors also showed a strong negative relationship between the consumption of some components of MD (olive oil and vegetables) and CRP and IL-6 plasma concentrations [48]. Olive oil contains not only oleic acid, but also abundant polyphenols that have been shown to reduce E-selectin levels and improve flow-mediated vasodilation [49]. Polyphenols also exert beneficial effects on blood pressure, lipids and insulin resistance. As shown by PREDIMED, the total polyphenol intake, calculated from the sum of the polyphenol content from different reported food items, was associated with lower mortality risk [50]. Antioxidants also include high

amounts of vitamin C, vitamin E, glutathione, selenium, folate and phenolic compounds from red wine (resveratrol), coffee, tea, nuts, herbs and spices [12]. In the Attica Study, total antioxidant capacity (TAC) was positively correlated with the MD score. Participants in the highest TAC tertile had an average 19% lower oxidized LDL-cholesterol concentration than participants in the lowest tertile. TAC was positively correlated with the consumption of olive oil, fruits and vegetables, was inversely associated with the consumption of red meat, and was not associated with either cereals or whole grains intake [51]. It has been suggested that the health-related quality of life reported by individuals consuming an MD is strongly related to the TAC content of the diet [52]. The potential benefits of this healthy eating on the persistent inflammation and oxidative stress of CKD deserve further study. A small RCT in haemodialysis patients demonstrated that the daily use of olive oil was as effective as mineral oil in the treatment of constipation [23]

### The MD favours natural versus processed foods

The traditional MD is associated with traditional, local and eco-friendly products, with low use of processed foods. The impact of MD is therefore not only explained by its specific nutrients and foods, but also by the way these foods are produced, cooked and eaten [53]. Food-processing techniques can profoundly modify nutrient content and food properties from the crop to the table. For instance, the content of antioxidant and phytochemicals in fruits and vegetables depends on agronomic practices (fertilizer +/–, organic or conventional), ripeness when harvested, post-harvest handling, storage, types of processing, distances transported, consumption and eating patterns. Food processing may affect the effects of food on health and disease. For instance, in community-based studies it has been observed that high red meat consumption was associated with progressively shorter survival, largely because of the consumption of processed red meat. Consumption of non-processed red meat alone was not associated with shorter survival [54]. Further, processed foods contain a higher content of sodium and phosphorus to preserve and enhance textures and flavours, which may impact on CKD progression and its complications [33]. Replacing processed foods by natural choices has shown clear benefits in ESRD patients [34].

### The MD promotes increased dietary fibre intake

The MD provides 30–50 g/day of fibre with a 1:1 ratio of soluble to insoluble fibres. Dietary fibre has important health-promoting properties. Besides its well-known benefits to the gastrointestinal tract, individuals with high intakes of dietary fibre appear to be at significantly lower risk for developing coronary heart disease, stroke, hypertension, diabetes, obesity and certain gastrointestinal diseases. Increasing fibre intake lowers blood pressure and serum cholesterol levels, improves glycaemia and insulin sensitivity, and reduces inflammation [24, 25]. The MD, with its abundant supply of quality carbohydrates (>50% whole grains) and dietary fibre, lowers glycaemic load and increases plasma levels of anti-inflammatory adiponectin. A NHANES III Study showed that fibre intake was low in most individuals (14.5 g of fibre/day compared with daily recommendations of 25 g/day). It also showed that high fibre intake

showed strong inverse associations with inflammation and mortality in the subpopulations with CKD. Specifically, each 10 g/day increase in total dietary fibre intake was associated with a 17% lower mortality risk [26]. Results were later confirmed in a Swedish population [55]. Finally, as phytate reduces the bioavailability of potassium and phosphate, the rather high-fibre content of the MD has certainly a very small impact on mineral availability.

The beneficial effect of dietary fibre may also be linked to the shift of gut microbial activity from a proteolytic towards a saccharolytic fermentation pathway. This results in a reduced generation of indoles and phenols waste products from the colonic proteolytic fermentation, which are potential factors in vascular inflammation and may contribute to CV and bone disease, insulin resistance and accelerate the progression of renal disease [56]. In support of this a significant difference in generation rates of two major nephrovascular toxins, indoxyl sulfate and p-cresyl sulphate, between omnivores and vegetarians has been demonstrated, in healthy adults, presumably owing to their different protein and fibre profiles (i.e. higher protein/fibre ratio in omnivores) [27]. Furthermore, the ratio of dietary protein–fibre intake was strongly associated with the serum concentration of these toxins in a small study of CKD patients [57]. A high-fibre intake relative to protein has been linked to reduced CV risk in individuals with mild CKD [58]. It has been proposed that an MD style diet, in combination with probiotic/prebiotic formulations, could be a valid therapeutic approach for individuals with CKD [59].

## ARGUMENTS AGAINST PRESCRIBING MEDITERRANEAN-LIKE DIETS TO PATIENTS WITH CKD: FEAR REGARDING FRUITS AND VEGETABLES

A legitimate concern when prescribing this diet to patients with CKD is the frequent intake of fruit and vegetables that characterizes the MD. In CKD, these foods are particularly known to be high in potassium, and are typically cautioned due to their potential to contribute to hyperkalaemia, affect electrolyte balance and impact on serum acidity. On the other hand the cardioprotective effects of the associated vitamins, fibre and antioxidants discussed above are well-established and are important in both CV and kidney disease prevention. This needs to be balanced with the potential electrolyte toxicity and therefore monitored regularly. In this section we, however, counterbalance those arguments and revisit recent literature suggesting further benefits of fruits and vegetables in CKD. Table 2 summarizes these fears and lists our counterarguments based on studies emerging from both CKD and non-CKD populations.

### The MD favours high potassium versus low sodium intake—dangerous?

Fruits and vegetables contain potassium and are naturally low in sodium. The intake ratio of these two electrolytes has been implicated in blood pressure control and the risk of CV events in the general population [60]. According to the WHO, the dietary sodium-to-potassium ratio should be close to 1. However, in Dietary Approaches to Stop Hypertension

**Table 2. Arguments against prescribing MDs to patients with CKD**

Features of the MD	Counterarguments from non-CKD studies	Counterarguments from CKD studies
High consumption of fruits and vegetables Increased consumption of potassium; fear of hyperkalaemia	A high potassium intake leads to better blood pressure control [60] Lower risk of incident CKD and of ESRD [61]	Lower risk of mortality [62], but perhaps higher risk of CKD progression [63] Overall, no clear association with hyperkalaemia risk [64], but careful potassium monitoring is advocated
Dietary acid load misbalance, favouring low acid load	A low dietary acid load may have modest positive effects in reducing the risk of diabetes, fractures, hypertension and mortality [65, 66] A low dietary acid load associates with a lower incidence of CKD [67]	A low dietary acid load associates with a slower decline in renal function [68, 69] A low dietary acid load is effective for the control of serum bicarbonate [64]

(DASH) diet, which was effective in decreasing blood pressure levels, had targets of 2300 mg and 4700 mg/day for sodium and potassium, respectively, i.e. a sodium-to-potassium ratio close to 0.5 [70]. In the MD, the sodium-to-potassium ratio is typically in the range of 0.4–0.6 and observational studies have indeed associated this with reduced blood pressure and CV risk [71, 72]. Population-based studies indicate that higher potassium intake, probably as a proxy of the overall beneficial effects of fruits and vegetables, associates with lower odds of CKD [61]. In individuals with normal renal function, higher urinary potassium has been associated with a lower incidence of CV complications and reduced risk of ESRD [73, 74]. These beneficial results are thought to be mediated by the reduction of blood pressure, the upregulation of renal kinins leading to the reduction of renal vascular resistance, or by the dietary antioxidants that have anti-inflammatory activity [75]. On the basis of this evidence, we conclude that fruit and vegetable intake may be of benefit in primary prevention of CKD, but adequately designed RCTs are needed to prove this.

In referred CKD patients, however, results are conflicting and warrant caution. In the MDRD Study, urinary potassium excretion was associated with lower risk for all-cause mortality but not for ESRD [62]. In CRIC, urinary potassium excretion was instead associated with increased risk of CKD progression [63]. These issues require further study and confirmation. Although there are multiple factors influencing urinary potassium excretion beyond potassium intake in patients with CKD/dialysis [76], we recommend that choice of fruits and vegetables with low potassium content and close potassium monitoring may be advocated in patients with CKD (see section on implementation of the MD in CKD patients). Pharmacological strategies (such as the novel potassium binders) may favour a more liberal consumption of these foods.

### The MD impacts on dietary acid load—good or bad?

Fruits and vegetables are sources of potassium salts of organic acids that generate bicarbonate. The MD is, therefore, net-base-yielding and has the potential to decrease the dietary acid load (DAL) and prevent the low-grade, subclinical metabolic acidosis that typically accompanies Western diets. The possible benefits of a low DAL in community-dwelling individuals with normal renal function come from observational

studies that tend to suggest potential (modest) benefits in reducing the incidence of diabetes, fractures, hypertension, CVD or mortality [65, 66, 77, 78]. It has also been suggested that low DAL associates with a reduced risk of incident CKD [67], suggesting a potential avenue for preventing CKD through diet. No RCTs have, to our knowledge, been performed. DAL has recently gained attention in nephrology as manifest CKD patients retain dietary ions and electrolytes, which influence bodies' pH and metabolic acidosis leading to worse outcomes. Several observational studies report an association between higher DAL and faster decline in kidney function [68, 69]. Based on this, it has been hypothesized that decreasing DAL might be an effective kidney-protective therapy [79]. A small trial of patients with early CKD confirmed that a diet rich in fresh fruits and vegetables can lower DAL and control metabolic acidosis in a comparable manner to sodium bicarbonate [64]. No hyperkalaemia events were reported in this high-fruit consumption intervention, attributed by the authors to the fact that potassium was ingested together with non-chloride anions in fruits/vegetables that facilitated urine potassium excretion [64]. However, whether long-term DAL control can ameliorate progression in CKD patients remains to be tested. The recent observation [80] that dietary estimated net acid excretion (NAE) and measured NAE (sum of urine ammonium and titratable acidity in 24-h urine) have opposing associations with the risk of kidney function decline brings a new degree of complexity in this area. The authors proposed the novel hypothesis that the risk of CKD progression related to low NAE or acid load may be due to diet-independent changes in acid production.

### THE MD AND CKD—WHAT DO WE CURRENTLY KNOW?

The favourable effects of the MD on endothelial function, inflammation, lipid profile and blood pressure suggest that this type of diet could be linked to better preserved renal function. A number of studies, mostly of observational nature, have explored possible health benefits in individuals with CKD (Table 2). For example, observational studies from Scandinavia reported that in community-dwelling older men, higher MD adherence was negatively and significantly associated with the

Table 3. Description of studies reporting on the association or the effect of MDs and CKD outcomes

Author	Country	Participants	Age, years	Men (%)	Exposure or intervention	Sample size	Follow-up	Outcomes	Main findings
Observational studies									
Asghari <i>et al.</i> [86]	Iran	Community-dwelling adults	43.5	51	MD score (MDS)	1212	6.1 years	<ul style="list-style-type: none"> <li>Incident CKD (eGFR &lt; 60 mL/min)</li> </ul>	<ul style="list-style-type: none"> <li>Individuals within the lowest quartile associated with lower odds of incident CKD (OR 0.53; 95% CI: 0.31–0.91)</li> </ul>
Chrysohoou <i>et al.</i> [87]	Greece	Community-dwelling adults	45	50	MDS	3042	NA	Cross-sectional serum urea, creatinine and creatinine-clearance (CCr)	Increased adherence to MDS was independently associated with reduced urea and creatinine as well as increased CCr rates
Huang <i>et al.</i> [81]	Sweden	Community-dwelling elderly men	70	100	MDS	1110 (506 with eGFR < 60)	10 years	<ul style="list-style-type: none"> <li>Cross-sectional CKD (eGFR &lt; 60 mL/min)</li> <li>Survival</li> </ul>	<ul style="list-style-type: none"> <li>Increasing adherence to MDS was associated with lower odds of CKD at baseline [OR 0.77 (0.57–1.05) for medium and 0.58 (0.38–0.87) for high adherents versus low]</li> <li>In those with CKD, increasing adherence to MDS associated with survival</li> </ul>
Khatri <i>et al.</i> [82]	USA	Community-dwelling adults free from stroke	64	41	Alternative Mediterranean diet score (MeDi, 9-points)	803 with eGFR > 60	6.9 years	<ul style="list-style-type: none"> <li>Incidence of eGFR &lt; 60 mL/min</li> <li>Annual eGFR decline</li> </ul>	<ul style="list-style-type: none"> <li>A higher score was associated with a lower CKD incidence (OR 0.83; 0.7–0.96, per 1-point increase in the MeDi score)</li> <li>A higher score associated with slower CKD progression (OR 0.88; 0.79–0.98)</li> </ul>
Mazaraki <i>et al.</i> [88]	Greece	Community-dwelling adolescents	14	58	MD Quality Index for adolescents (KIDMED)	365	NA	Albumin to creatinine ratio (ACR)	Adolescents with low KIDMED had higher ACR values [22.4 versus 13.4 (medium score) or 12.1 mg/g (high score), $P < 0.05$ ]
Smyth <i>et al.</i> [73]	USA	Community-dwelling adults	62	59	MDS, among others	544 635	14.3 years	Composite of RRT or death due kidney disease	Compared with the lowest quintile of MDS, the highest quintile had a lower CKD risk (HR 0.84; 95% CI 0.74–0.95)
Interventional studies									
Díaz-López <i>et al.</i> [83]	Spain	Community-dwelling participants age > 50 years and high CVD risk	67	45	Secondary analysis in a subset of PREDIMED trial Three interventions: 1. MD + olive oil; 2. MD + mixed nuts; 3. Control low-fat diet	785 (665 finished 1-year intervention)	1 year	eGFR and ACR change	After a 1-year intervention, the eGFR or ACR change was similar in the three study arms
Díaz-López <i>et al.</i> [84]	Spain	PREDIMED participants with type 2 diabetes	67	48	Secondary analysis in a subset of PREDIMED trial (same as above)	3614	6 years	<ul style="list-style-type: none"> <li>De novo nephropathy (eGFR &lt; 60 mL/min and urinary ACR &gt; 30 mg/g)</li> </ul>	No association between treatment arms and 6-year nephropathy incidence
Mekki <i>et al.</i> [85]	Algeria	CKD patients Stage 2	57	54	Randomized intervention to traditional dietary advice (control) or dietary advice aligned with MD	40	90 days	Change in serum lipid and renal function	Significant reduction in triglycerides, total and LDL cholesterol and CRP in MD group vs control. No change in renal function parameters

NA, not applicable; RRT, renal replacement therapy; OR, odds ratio.

**Table 4. Considerations for implementing the MD in CKD**

Food groups	CKD diet recommendations	MD	Considerations for CKD
Meat and alternatives <sup>a</sup>			
Meat	>50% high-biological value	White 2/week Red <2/week	Protein intake in the MD aligns with a controlled protein diet (~0.8 g/kg/day). Requires monitoring and may require more in dialysis settings
Fish	No specific recommendation	2/week	Limit processed meat (high in additives of sodium, phosphate and potassium)
Legumes	No specific recommendation	2/week	Phosphorus content of low biological availability
Nuts	No specific recommendation	1–2/day	Unsalted; 30 g (small handful) is the equivalent of one meat serving
Dairy products <sup>b</sup>	1/day	2/day	MD recommends low-fat options. If phosphorus is a problem, try non-dairy substitutes (i.e. nut-based milk)
Fruit and vegetables <sup>a</sup>			Low potassium alternatives and cooking methods (boiling), if required
Fruit	2–3 servings/day (low potassium)	1–2/main meal	
Vegetables	Up to 3 servings/day (low potassium)	2/main meal	
Fats and oils			
Olive oil	No specific recommendation	1/main meal	Aim for 2–3 × 15 mL (one tablespoon) servings per day; replace other cooking oils with olive oil
Products with added sugars	No specific recommendation	2/week	Limit where possible. Be aware potassium and phosphate additives are abundant in the food supply and are highly bioavailable

<sup>a</sup>1 serving = 100–150 g.

<sup>b</sup>1 serving = 250 mL milk, 40 g cheese, 200 g yoghurt.

risk of having CKD. During the 9.9 years follow-up, 33% of patients with CKD died. Survival rates were significantly worse for low-adherent participants than for those in the other two groups [81]. Similar results were reported in the longitudinal Northern Manhattan Study in USA, where increasing adherence to an MD was associated with decreased odds of incident CKD [82]. Also from the USA, the NIH-AARP Diet and Health Study, including over 500 000 community-dwelling adults, aged 51–70 years, reported that a better adherence to a MD was consistently associated with a reduced risk of ESRD [hazards ratio (HR) 0.84; 95% confidence interval (CI) 0.74–0.95 per MD score increase] [73].

Conversely to these studies, *post-hoc* analyses from the PREDIMED trial do not observe any effect of MD intensification on renal outcomes. In an analysis of 665 PREDIMED participants, those assigned to MD had a similar eGFR decline after 2 years than the control low-fat diet [83]. In a larger subset of 3614 PREDIMED participants with type 2 diabetes and free of microvascular complications at enrolment, those assigned to an MD diet associated with a reduced incidence of diabetic retinopathy, but no association was found with diabetic nephropathy [84]. These discrepant findings may be partly explained by the characteristics of PREDIMED population—healthy individuals in their 50s with dyslipidaemia, where the follow-up, and the rate of renal outcomes, albuminuria progression or eGFR decline within 2 years may be low. Also, they were participants from Spain, following presumably a Mediterranean-like diet. PREDIMED actually tested the intensification of an MD in an already MD population of middle-age range and relatively healthy. It is possible that the MD may be more beneficial in societies with dietary patterns more distant from this concept, as suggested by the above-mentioned observational studies from Northern Europe and USA.

Nonetheless, MD may have beneficial effects in intermediate outcomes that associate with renal and CVD risk. A small RCT implemented an MD in 40 participants with CKD Stage 2 in a 90-day intervention [85]; although the intervention time was not

sufficient to denote eGFR changes (which remained, as expected, stable), the authors report a significant reduction in triglycerides, total and LDL-cholesterol, and CRP in the MD group, improvements altogether in metabolic profile that may link to some of the mechanistic explanations mentioned above.

#### WHAT WOULD AN MD PRESCRIPTION LOOK LIKE FOR A PATIENT WITH CKD?

Based on the above, practical modifications are required for making a ‘Mediterranean-style’ diet realistic in patients with manifest CKD in order to meet the needs of individuals prescribed a specific restriction to potassium or phosphorus and modification of protein intake and other potential permutations as detailed in Table 4. This further emphasizes the need for close contact and support by a registered dietician specialized in renal nutrition. Monitoring of laboratory values and patient-reported symptoms is a key strategy to safely implement such dietary changes. In addition to nutrient considerations, the potential burden on shifting dietary habits toward incorporating a more MD approach warrants attention. CKD patients have a preference for interventions that are tailored and supported with frequent interactions, monitoring and feedback, including group support [89]. Reflecting on the intervention delivery attributes from the PREDIMED study, a combination of individual- and group-interaction-supported participants, and those with the greatest increase in adherence had the worst diets at baseline [90]. However, the supplemental food products provided, not the dietary advice alone, resulted in the most striking changes in intakes in PREDIMED [10, 91]. Substantial provision of extra virgin olive oil and nuts to participants resulted in a sustained increase in intake. The take-home message from such studies appears to be that simple exchange and addition of food products such as oil and nuts may support a cardioprotective dietary profile, as an adjunct to dietary advice. Although not formally tested in CKD patients, simplified assessment tools



can promote self-monitoring based on dietary pattern recommendations. ‘Your Med Diet Score’ (<http://oldwayspt.org/sites/default/files/files/RateYourMedDietScore.pdf>) is one of such one-time assessment tools for patients to self-evaluate their adherence to the MD. General feedback, motivational messages and tips to increase intake to reach the amounts recommended are provided.

## CONCLUSION

A broad range of evidence suggests that an MD can substantially improve or even prevent the development of several chronic diseases, especially CVD, leading to a significant reduction of all-cause and CV mortality. A smaller number of studies suggest similar benefits of an MD for renal health. Concerns for hyperkalaemia risk when increasing fruit and vegetable intake are legitimate and overall this dietary pattern requires certain adaptations to fit current dietary recommendations for CKD. Overall, most of this evidence comes from large observational studies and/or small interventions in CKD patients, and in order to move forward adequately designed intervention studies would be needed. Unfortunately, such efforts are still lacking in all fields of renal nutrition so far. Here we analysed the purported benefit of an MD through its salutary effects of individual constituents. While this was done for a neat argumentation of the mechanistic pathways affected, the MD should, however, be considered as a whole dietary pattern and, in addition, part of a healthy lifestyle that also includes physical activity, outdoor life and conviviality. An MD for renal patients may go beyond its potential health impacts.

## ACKNOWLEDGEMENTS

The European Renal Nutrition Working Group is an initiative of and supported by the European Renal Association–European Dialysis Transplant Association.

## CONFLICT OF INTEREST STATEMENT

P.C. is advisory board member at Fresenius Kabi. V.B. acknowledges speaker honoraria from Shire and Fresenius Kabi. P.M. acknowledges speaker honoraria from Abbott Nutrition. S.S. acknowledges speaker honoraria from Sanofi Aventis and Abbie. P.M.t.W. acknowledges speaker honoraria from Fresenius Kabi. D.T. acknowledges speaker honoraria from Abbott Nutrition and advisory commitments from Nestlé Switzerland. D.F. received honoraria from Fresenius Medical Care, Fresenius Kabi, Sanofi, Vifor. J.J.C. acknowledges speaker honoraria from Abbott Nutrition and Baxter, and institutional grants from Vifor Pharma and AstraZeneca. M.A., C.W., L.J., K.C., X.H. and A.K. have no conflicts of interest.

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Received: 11.1.2017; Editorial decision: 5.4.2017

Nephrol Dial Transplant (2018) 33: 735–741

doi: 10.1093/ndt/gfx194

Advance Access publication 8 July 2017

## Gremlin and renal diseases: ready to jump the fence to clinical utility?

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### ABSTRACT

The current therapeutic strategy for the treatment of chronic kidney diseases only ameliorates disease progression. During renal injury, developmental genes are re-expressed and could be potential therapeutic targets. Among those genes reactivated in the adult damaged kidney, Gremlin is of particular relevance since recent data suggest that it could be a mediator of diabetic nephropathy and other progressive renal diseases. Earlier studies have shown that Gremlin is upregulated in trans-differentiated renal proximal tubular cells and in several chronic kidney diseases associated with fibrosis. However, not much was known about the mechanisms by which Gremlin acts in renal pathophysiology. The role of Gremlin as a bone morphogenetic protein antagonist has clearly been demonstrated in

organogenesis and in fibrotic-related disorders. Gremlin binds to vascular endothelial growth factor receptor 2 (VEGFR2) in endothelial and tubular epithelial cells. Activation of the Gremlin–VEGFR2 axis was found in several human nephropathies. We have recently described that Gremlin activates the VEGFR2 signaling pathway in the kidney, eliciting a downstream mechanism linked to renal inflammatory response. Gremlin deletion improves experimental renal damage, diminishing fibrosis. Overall, the available data identify the Gremlin–VEGFR2 axis as a novel therapeutic target for kidney inflammation and fibrosis and provide a rationale for unveiling new concepts to investigate in several clinical conditions.

**Keywords:** diabetic nephropathy, fibrosis, Gremlin, inflammation, TGF- $\beta$ 1, VEGF