Title

Nutritional and dietary interventions to prolong renal allograft survival after kidney transplantation.

Journal

Current opinion in nephrology and hypertension, 31(1)

ISSN

1062-4821

Authors

Tantisattamo, Ekamol
Kalantar-Zadeh, Kamyar
Molnar, Miklos Z

Publication Date

2022

DOI

10.1097/mnh.0000000000000757

Nutritional and dietary interventions to prolong renal allograft survival after kidney transplantation

Ekamol Tantisattamo[a,b,c], *Kamyar Kalantar-Zadeh*[a,b,d], *and Miklos Z. Molnar*[e]

Purpose of review
Diet plays an important role in slowing progression of chronic kidney disease in native and transplanted kidneys. There is limited evidence on the association on dietary intake with renal allograft function. Mechanisms of major nutrients and dietary patterns with focusing on a plant-based diet related to kidney transplant health and longevity are reviewed.

Recent findings
High dietary protein intake may adversely affect renal allograft. Low protein plant-focused diets such as Dietary Approaches to Stop Hypertension, plant-dominant low-protein diet and Mediterranean diets appear associated with favorable outcomes in slowing renal allograft function decline. The mechanism may be related to a change in renal hemodynamic by decreasing glomerular hyperfiltration from low dietary protein intake and plant-based ingredients. Recent observational studies of association between dietary protein intake and kidney allograft outcomes are conflicting. Although strong evidence is still lacking, a low protein diet of 0.6–0.8 g/kg/day with at least 50% of the protein source from plant-based components in kidney transplant recipients with stable kidney allograft function should be considered as the dietary target.

Summary
Dietary intervention with low-protein plant-focused meals may improve outcomes in kidney transplant recipients, but the evidence remains limited and further studies are warranted.

Keywords
Dietary Approaches to Stop Hypertension diet, glomerular hyperfiltration, kidney allograft survival, Mediterranean diet, plant-dominant low-protein diet

INTRODUCTION

Although short-term renal allograft outcomes have been significantly improved over the past four decades, the long-term outcomes vary from different studies with little if any improvement [1–4]. Several factors, both immunological and nonimmunological, contribute to the long-term kidney allograft survival, which is critical to not only provide survival benefit for individual transplant recipients with the ideal goal of *'One organ for life'* to partly mitigate the organ shortage [5] but also enhance transplant access for advanced chronic kidney disease (CKD) and end-stage kidney disease (ESKD) patients at large (Supplemental Figure 1, http://links.lww.com/CONH/A31).

Recent evidence demonstrates the benefits of a modified diet to slow CKD progression in the nontransplant population; however, data in kidney transplant recipients remains limited. In this article, dietary interventions to prolong allograft survival especially by means of low dietary protein intake and plant-dominant diet will be the main focus of this review.

[a]Harold Simmons Center for Kidney Disease Research and Epidemiology, Division of Nephrology, Hypertension and Kidney Transplantation, Department of Medicine, University of California Irvine School of Medicine, Orange, [b]Nephrology Section, Department of Medicine, Tibor Rubin Veterans Affairs Medical Center, Veterans Affairs Long Beach Healthcare System, Long Beach, California, [c]Multi-Organ Transplant Center, Section of Nephrology, Department of Internal Medicine, William Beaumont Hospital, Oakland University William Beaumont School of Medicine, Royal Oak, Michigan, [d]Lundquist Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, California and [e]Division of Nephrology and Hypertension, Department of Medicine, University of Utah, Utah, USA

Correspondence to Miklos Z. Molnar, MD, PhD, FEBTM, FERA, FASN, Professor of Medicine, Division of Nephrology & Hypertension, Department of Medicine, University of Utah, 30 North 1900 East, Room 4C464, Salt Lake City, UT 84132, USA. Tel: +801 213 0622; fax: +801 581 5393; e-mail: miklos.molnar@hsc.utah.edu

Curr Opin Nephrol Hypertens 2022, 31:6–17
DOI:10.1097/MNH.0000000000000757

KEY POINTS

- Although immunological factors are one of the major causes of kidney allograft loss, nonimmunological factors also contribute to allograft longevity.
- The dietary intervention has been shown to slow the progression of chronic kidney disease in nontransplant and transplant populations, but the evidence in the transplant recipients is lacking.
- Even though individual nutrient demonstrates mechanism that can benefit to allograft survival such as lowered glomerular hyperfiltration and intraglomerular pressure from low protein and low diets, dietary patterns such as Low Protein Plant-Dominant Diet (PLADO), Dietary Approaches to Stop Hypertension (DASH), Mediterranean, or vegetarian-style diets are a practical way to be implemented in clinical care.
- Plant-focused meal plans with a low protein diet of 0.6–0.8 g/kg/day may be acceptable in kidney transplant recipients with stable allograft function with current evidence demonstrating a slow decline in allograft function, posttransplant diabetes mellitus, and metabolic syndrome, whereas the effects of protein intake are conflicting.
- Implementation science between additional research with strong evidence and clinical practice should assist to close to knowledge-practice gap to improve transplant outcomes by dietary interventions.

PATHOGENESIS OF KIDNEY ALLOGRAFT LOSS: OPPORTUNITIES TO PROLONG ALLOGRAFT SURVIVAL

Late allograft loss after the first posttransplant year is resulted primarily from death with a functioning graft (DWFG) and chronic allograft nephropathy [6]. The latter can be due to immunological or nonimmunological factors (Supplemental Table 1, http://links.lww.com/CONH/A32).

Several causes of allograft injury especially acute rejection have been the focus of targeted research to improve long-term outcomes and mitigate allograft loss; however, the majority of renal transplant recipients still encounter chronic allograft dysfunction specifically chronic rejection, which has practically no very effective therapy and which inevitably leads to late allograft loss [7]. There are only limited studies about outcomes of allograft hemodynamic alterations, which can cause allograft injury; interventions in the form of primarily dietary modification, can modify allograft hemodynamic affecting the long-term outcomes. Hemodynamic changes in the transplanted kidney will be reviewed, and the putative role of dietary interventions in enabling kidney allograft longevity will be discussed.

Pathophysiology of hemodynamically mediated glomerular injury in kidney allograft

Major alterations in renal hemodynamics in the allograft are inevitable. Similar to nontransplant patients with a native solitary kidney from any causes [8], kidney transplant recipients encounter major physiologic compensatory or adaptive mechanisms resulting from loss of nephron mass. A key (mal)adaptive change is arteriolar vasodilatation, which increases renal blood flow leading to increased glomerular capillary flow and intraglomerular pressure to maintain glomerular filtration rate (GFR) [9,10]. In addition to the functional and hemodynamic changes, there are structural changes as part of the adaptive mechanisms leading to glomerular hypertrophy.

The physiologic adaptation in response to reduced nephron mass is nonsustainable and will ultimately lead to pathological process (Fig. 1). Although this compensatory mechanism can maintain allograft function at an early posttransplant period, in the long-term, glomerular flow and pressure maintain glomerular hyperfiltration, and eventually impaired glomerular permselective properties will emerge [11]. The glomerular hyperfiltration increases the convective effect. This along with impaired glomerular permselectivity leads to heightened leakage of plasma proteins across the glomerular capillary wall. Increased transcapillary of plasma proteins leads to accumulation of proteins in the mesangium, which stimulates mesangial cell proliferation and mesangial matrix production, which leads to glomerular sclerosis [12,13]. Moreover, sustained glomerular hyperfiltration and intraglomerular pressure damages podocytes in the late posttransplant period and subsequently lead to pathophysiological changes of secondary focal segmental glomerulosclerosis (FSGS).

Loss of the affected glomeruli causes positive feedback to unaffected glomeruli leading to compensatory glomerular hyperfiltration. Eventually expanded glomerular injury will ensue. These developments cause the final common pathway of the chronic allograft dysfunction when transplant recipients present with progressive decline in allograft function, worsening proteinuria, typically associated hypertension, and ultimately allograft loss (Fig. 2).

Effect of diet and kidney allograft function: beneficial or harmful?

Appropriate dietary management posttransplant needs to be modified by period posttransplant to improve allograft outcomes and avoid

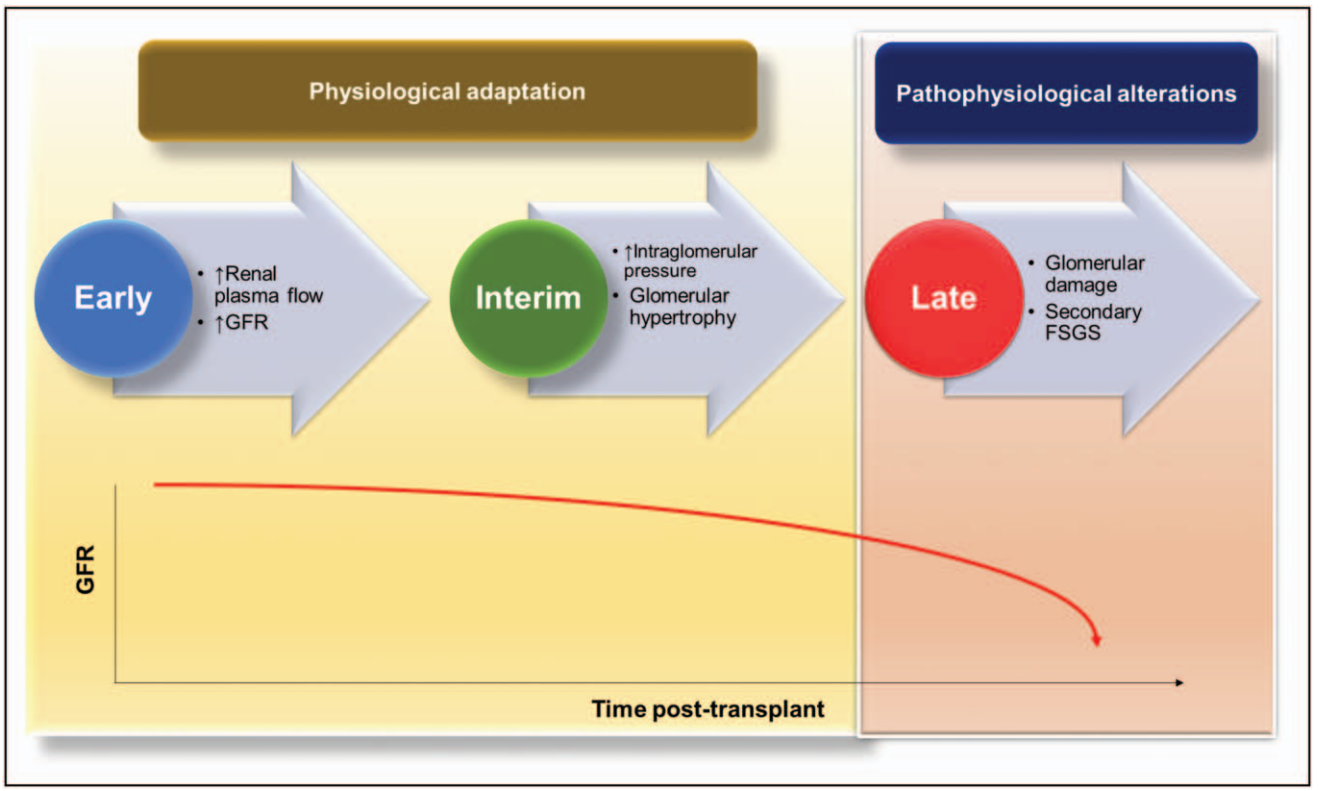

FIGURE 1. Physiological and pathophysiological alterations in kidney allograft hemodynamic. FSGS, focal segmental glomerulosclerosis; GFR, glomerular filtration rate.

complications such as obesity [14,15]. We focus our review on macronutrients and dietary patterns.

Dietary protein and plant-dominant source of protein

There has been growing evidence about the benefit of low dietary protein intake to slow progression of kidney disease; however, there are limited studies concerning the benefit of a low protein diet on allograft outcomes.

Given physiologic adaptation of allograft hemodynamic which can intern become pathologic alteration in the long-term, factors that can intervene in the process should slow or mitigate progressive allograft dysfunction.

Low dietary protein intake has long been known to possibly slow the decline in the function of native kidneys [16–19]. Ingested protein engenders urea and other nitrogenous end-products that need to be cleared by urinary excretion of urea. Low protein diet can suppress renin-angiotensin system [17,20,21] and blunt effects of glomerular capillary hemodynamics [10,22], kidney growth [21], ammoniagenesis [21], and metabolic rate [23].

On the contrary, high dietary protein intake is accounted for the higher workload of allograft. In addition, high dietary protein intake causes renal arteriolar vasodilatation. Together with the underlying physiologic renal arteriolar vasodilatation in an allograft, high dietary protein intake can increase glomerular hyperfiltration and glomerular damage [24].

In addition to the quantity, quality or source of dietary protein intake is also associated with different risks of declined kidney function. A prospective longitudinal cohort study of middle-aged participants with eGFR $\geq$60 ml/min/1.73 m^2 and no diabetes or cardiovascular disease (CVD) in the Atherosclerosis Risk in Communities (ARIC) cohort showed that participants who consumed red meat or processed food were at higher risk for developing CKD defined by drop in eGFR $\geq$25% from baseline resulting in eGFR $<$ 60 ml/min/1.73 m^2 while plant-based (nuts, legumes) or low-fat dairy product consumers had lower the risk [25].

Mechanism associated with an adverse effect of animal protein includes higher nonvolatile acid load, which is associated with declined kidney function [26–28], and greater risk of developing hypertension [29–31] and diabetes [32,33] from animal protein consumption.

In addition, an increase in GFR from short-term animal protein intake especially from meat had been shown in both animal [34] and human [35]

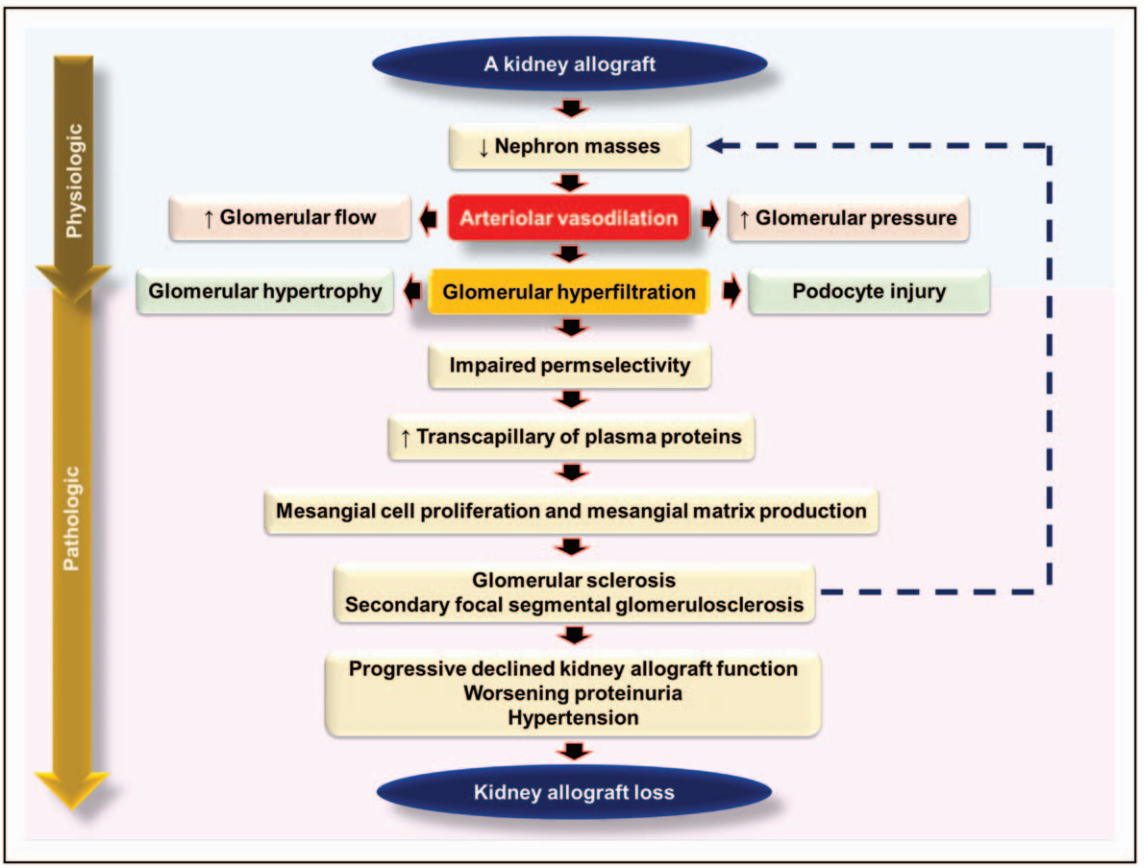

FIGURE 2. Pathophysiology of glomerular injury from a long-term kidney allograft hemodynamic alteration. FSGS, focal segmental glomerulosclerosis; GFR, glomerular filtration rate.

studies whereas soy protein consumption showed no or little effect on GFR [36,37]. Although animal protein increases GFR initially, glomerular hypertension and injury may occur in the long-term similar to those that occur from a high quantity of protein.

A low-protein diet that is 'plant dominant', also abbreviated as ' Plant-dominant low-protein diet (PLADO)', is a patient-centered low protein diet of 0.6–0.8 g/kg/day composed of >50% plant-based sources [38▪]. PLADO based meal plans should be administered by dietitians trained in providing nutrition care to patients with nondialysis-dependent CKD and transplant recipients. PLADO's composition and meal plans can be designed and adjusted based on individualized needs and according to the principles of precision nutrition. The goal of PLADO is to slow kidney disease progression in both native and transplanted kidney, to avoid or delay dialysis therapy initiation or re-initiation, and to ensure cardiovascular health and longevity. The ideal type of PLADO is a heart-healthy, safe, flexible, and feasible diet that could be the centerpiece of the kidney preserving therapy and to avoid or defer dialysis [39▪]. Randomized and other prospective studies are urgently needed to examine the effect of PLADO on shot- and long-term renal outcomes in transplant recipients.

Carbohydrate

Evidence of the direct effect of low or high carbohydrate intake on allograft function is lacking. In the nontransplant population, a low carbohydrate diet (LCD) is associated with a lower rate of kidney function decline. A systematic review and meta-analysis of randomized control trial (RCT) including 1,687 overweight and obese participants with normal kidney function (861 LCD)and 826 control diet) from 9 studies showed that the LCD group had 0.13 ml/min per 1.73 m^2 greater increase in mean eGFR than those of the control diet [40]. Another systematic review and meta-analysis of RCT including 12 studies including 942 type 2 diabetic participants (500 LCD and 442 control diet) revealed no difference in markers of kidney markers including eGFR, creatinine clearance, urinary albumin, serum creatinine, and serum uric acid between two groups [41].

A recent observational cohort study mainly based on the UK Biobank utilizing Mendelian

randomization analysis demonstrated no association between carbohydrate intake and risk of ESKD in participants with eGFR $\geq$60 ml/min/1.73 m^2 [42].

Although the effect of carbohydrates on kidney function in the nontransplant population is inconclusive, a calorie from carbohydrate intake which may contribute to overweight or obesity in the setting of diabetogenic effect from immunosuppressive medications may lead to worsening allograft function. High carbohydrate intake is converted to glucose which leads to increased risk for posttransplant diabetes mellitus (PTDM), hyperlipidemia, and metabolic syndrome [43]. Although average tacrolimus trough levels were significantly associated with the first hyperglycemic incidence [44], steroid withdrawal compared to chronic steroid use had little impact on PTDM [45] and weight loss.

Until there are further studies with strong evidence, carbohydrate intake may need to be individualized but can avoid metabolic complications from high carbohydrate intake.

Fat

Similar to a carbohydrate diet, there is a lack of evidence of the direct effect of dietary fat intake on allograft function. However, one animal study demonstrated high-fat diet (HFD)-induced obesity that stimulated alloresponse and poor graft outcome. HFD-induced obesity mice had altered composition and phenotype of splenic antigen-presenting cells led to their enhanced capacity to stimulate T cells. Modestly accelerated cardiac allograft rejection occurred in HFD mice compared to aged-matched low-fat diet mice [46].

Another animal study examined changes in kidney morphology and function in adult rats with HFD intake compared to those with a normal diet. After 8 weeks, the formerly developed glucose intolerance and insulin resistance. Although a decrease in GFR was less in HFD, this group had a significantly higher retraction in glomeruli and an increased kidney lipid deposition as well as increased pro-inflammatory cytokines interleukin (IL)-6 and IL-1b, but no alteration in anti-inflammatory cytokine IL-10 [47].

A recent study of C57BL/6 mice fed HFD for 16 weeks caused obesity, diabetes, and kidney dysfunction determined by albuminuria and elevated BUN and creatinine. Kidney injury was resulted in part from tissue lipid accumulation, increased oxidative stress, and mitochondrial dysfunction, which promotes excess programmed cell death [48]. The aforementioned study using two-sample Mendelian randomization showed that increased relative fat intake causally increased the risk of CKD [42].

Not only the quantity of fat intake, but also the quality of dietary fat may contribute to allograft survival. A study in kidney transplanted rats divided into five groups receiving pre and postoperative diets high in saturated fat, linoleic acid, monoenoic acid, containing fish oil, and standard commercial chow showed that rats receiving a high linoleic acid-containing diet had significantly better graft function compared to other groups [49].

n-3 long-chain polyunsaturated fatty acids (n-3 LC-PUFA) such as fish oil, flaxseed oil, and ground flaxseed are showed to mediated immune response. An RTC compared fish oil 9 g/day vs placebo starting at the time of engraftment for a 1-year study period showed a higher GFR in the fish oil group (45 vs 31 ml/min) [50]. Another RTC showed no benefit of decreased rejection from 2.4 g/day of eicosapentaenoic acid (EPA) + docosahexaenoic acid for 1 year [51]. A double-blinded RTC including patients with stable graft function and receiving 9 g of EPA, 18 g of EPA, 9 g of corn oil, or 18 g of corn oil or 26 weeks showed no difference in an episode of rejection, GFR, renal blood flow, and creatinine clearance. However, only the corn oil group experienced acute cyclosporine nephrotoxicity [52].

Given no clear benefit of n-3 LC-PUFA for allograft outcomes, it is not recommended for routine use in transplant recipients [53▪▪].

According to the 2020 update to the Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guideline for Nutrition in CKD, energy intake for transplant recipients who are metabolically stable should be 25–35 kcal/kg body weight per day based on age, sex, level of physical activity, body composition, weight status goals, CKD stage, and concurrent illness or presence of inflammation to maintain normal nutritional status [53▪▪].

SPECIAL DIETS

Although every single nutrient can contribute to allograft function from different mechanisms, dietary patterns including different proportions of each nutrient are practically implemented to patients. Since potential adverse effects of high dietary protein intake, a plant-based diet that mainly contains vegetables and fruit becomes one of the food choices with evidence demonstrating slow kidney function decline.

Plant-based diet

In addition to the PLADO diet described above, three main plant-based diets are vegetarian (including vegan), Dietary Approach to Stop Hypertension (DASH), and Mediterranean diets (MedDiet) [54▪].

Table 1. Clinical studies of dietary patterns and outcomes in kidney transplant recipients

References	Exposures of types of a plant-based diet	Study population	Study period	Outcomes
Osté *et al.* 2017 [55]	DASH (Overall DASH-score from 177-item FFQ)	632 stable KTR The median time between baseline and KT 5.7 (IQR 1.9–12.1) years	Median 5.4 (IQR 4.1–6) years	The highest tertile of the DASH score was associated with a lower risk of both allograft function decline (HR 0.57, 95%CI 0.33–0.96, p 0.03) and all-cause mortality (HR = 0.52, 95%CI 0.32–0.83, p 0.006) compared to the lowest tertile.
Nafar *et al.* 2009 [56]	MedDiet (Routine dietary intakes assessed with FFQ)	160 adult KTR of a first or second LDKT without metabolic syndrome	1 year	The highest tertile of scores for the Mediterranean diet was associated with a significantly lower odds of metabolic syndrome than those in the lowest tertile.
Osté *et al.* 2017 [57]	MedDiet (9-point MDS from a 177-item validated FFQ)	468 KTR with allograft function >1 year	Median 4 (IQR 0.4–5.4) years	High MDS was significantly associated with both a lower risk of PTDM (HR 0.23, 95%CI 0.09, 0.64, p 0.004) and all-cause mortality (HR 0.51, 95%CI 0.29, 0.89, p 0.02) compared to low MDS.
Gomes-Neto *et al.* 2020 [58▪▪]	MedDiet (9-point MDS from a 177-item validated FFQ)	632 KTR with allograft function >1 year	Median 5.4 (IQR 4.9–6) years	MDS was inversely associated with all graft failure (HR 0.68, 95%CI 0.5, 0.91), allograft kidney function decline (HR 0.68, 95%CI 0.55, 0.85), allograft loss (HR 0.74, 95%CI 0.63, 0.88) per a two-point increase in MDS. The associations were stronger in participants with higher 24-h urinary protein excretion and those transplanted more recently.
Said *et al.* 2021 [59▪▪]	White and red meat intakes determined by 24-h urinary 1- and 3-methylhistidine, respectively	678 KTR after 1-year posttransplant and stable allograft function	Median 5.4 (IQR 4.9–6.1) years	Inverse association between urinary 1-methylhistidine and graft loss confounders (HR per doubling 0.84, 95%CI 0.73, 0.96, $P = 0.01$). Inverse association of urinary 3-methylhistidine with graft failure (HR per doubling 0.59, 95%CI 0.41, 0.85, p 0.004) and mortality (HR per doubling 0.55, 95%CI 0.42, 0.72, $P < 0.001$)
Yeung *et al.* 2021 [60▪▪]	Dietary acid load assessed by FFQ and 24-h urinary urea and potassium excretion	642 KTR with allograft function >1 year	Median 5.3 (IQR 4.1–6) years	Association of net endogenous acid production with graft failure and doubling plasma creatinine (food frequency questionnaires: HR 1.33, 95%CI 1.12, 1.57, p 0.001 and urinary excretion (per SD higher): HR 1.44, 95%CI 1.24, 1.69, $P < 0.001$)

CI, confidence interval; DASH, Dietary Approach to Stop Hypertension; FFQ, food frequency questionnaire; HR, hazard ratio; IQR, interquartile range; KTR, kidney transplant recipient; LDKT, living donor kidney transplant; MDS, Mediterranean Style Diet Score; MedDiet, Mediterranean diet; PTDM, posttransplant diabetes.

The majority of evidence is performed in the non-transplant population with limited studies in transplant recipients (Table 1) [55–57,58▪▪,59▪▪,60▪▪].

Vegetarian diet

A vegetarian diet is a food pattern that contains no or very limited meat including red meat, poultry, seafood, and the flesh of any other animal or by-products of animal slaughter [61]. Religious, cultural, environmental, economic, or personal preferences may determine this food pattern. A variety of vegetarian diets is shown in supplemental Table 2, http://links.lww.com/CONH/A33 [62]. A large multicenter prospective cohort study using the ARIC cohort showed that adherence to healthy plant-based and provegetarian diets in the general population was associated with a lower risk of CKD. However, the association was significant in only normal-weight patients. A plant-based diet was also associated with slower eGFR decline [63].

Potential explanations for favorable renal outcomes in plant-based dietary adherence are decreased acid load, which is the risk for CKD [28,64]. Inflammation, oxidative stress, and endothelial dysfunction are decreased [65]. Indirectly, fibers improve glycemic control [66] and decrease the risk of diabetes and hypertension [67,68].

Although a vegetarian diet is showed to be beneficial to kidney function, dietary protein restriction may not provide all essential nutrients [62] without supplantation (Supplemental Table 3, http://links.lww.com/CONH/A34).

Other concerns for plant-based diet include inadequate protein intake and hyperkalemia from low dietary protein and high potassium intakes, respectively, although the recommended dietary allowance (RDA) of dietary protein intake is 0.8 g/kg ideal body weight/day. There have been no studies showing protein-energy wasting from low protein diets at this RDA range [69]. Also, there is no clear evidence that hyperkalemia may happen more frequently from a plant-based diet whereas this notion is practiced widely [70].

In transplant recipients, effects or association of vegetarian diet with allograft function is lacking and studies with strong evidence are required.

Dietary approach to stop hypertension diet

DASH diet is a dietary pattern containing high vegetables, fruit, whole grains, low-fat dairy products, legumes, and nuts as well as low sodium, sugar-sweetened beverages, and red processed meat [71,72]. It is known to be associated with decreased risk of rapid decline in kidney function [73], CKD [74,75], and mortality including in populations with underlying cardiovascular comorbidities such as hypertension [76], heart failure [77].

DASH diet is also associated with a slow decline in allograft function and lower mortality in transplant recipients. A prospective cohort study including 632 stable transplant recipients showed that those adhering to a higher DASH diet defined by higher an overall-DASH score from a validated 177-item food frequency questionnaire (FFQ) had a lower rate of allograft function decline and mortality after a median follow-up period of 5.4 years. The mortality benefit of DASH was demonstrated in patients with eGFR $\geq$45 ml/min/1.73m^2 and smokers, whereas better allograft outcomes were revealed in smokers [55].

Possible mechanism of protective effects of the DASH diet on allograft function includes improved blood pressure control [78], lipid profiles [79–81] with lowering triglyceride and increasing high-density lipoprotein (HDL) levels [55], anti-inflammatory effects [82,83] demonstrating by a reverse association of allograft outcomes with c-reactive protein [84,85], and antioxidant properties of DASH diet components [86] (Fig. 3).

Given high plant-based, low sodium and meat as well as possible beneficial effects of components of the DASH diet, it is one of the dietary patterns that likely prolong allograft function and appear to have major similarities with PLADO, although protein range is not as restricted as in PLADO. Some components of the DASH diet such as red meats, which may affect kidney function, are cooperated to avoid less palatable effects on diet nonadherence and to publicly implement the DASH diet. Therefore, RCT to investigate the benefit and safety of the DASH diet in transplant recipients should be conducted before widely implementing DASH in this population.

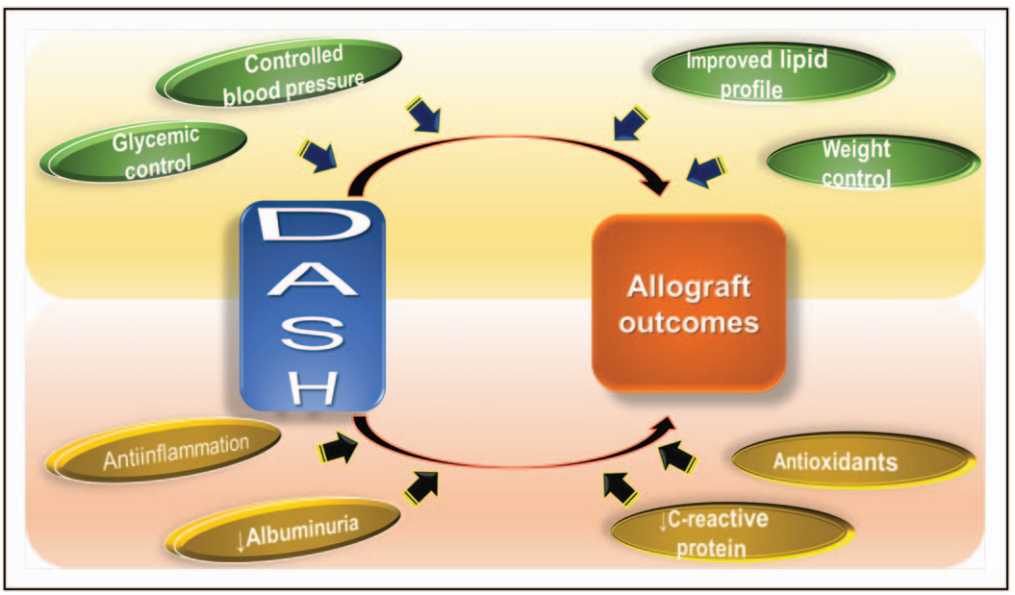

FIGURE 3. Mechanism of Dietary Approach to Stop Hypertension (DASH) diet to mitigate a decline in kidney allograft function.

Table 2. Mechanism of kidney allograft protection from a characteristic of the Mediterranean diet

	Non immune-related		Immune-related	
Main components	**Nutrients**	**Effects on kidney function**	**Nutrients**	**Effects on kidney function**
Fruit	High fibers	Decrease acid load [28,95]	High antioxidants	Decreased oxidative stress and inflammation [73,96,97] Lower risk of insulin resistance and pancreatic β-cell dysfunction [100] Lower risk of PTDM [57]
Vegetable	High fibers	Decrease acid load [28,95] Decreased plasma insulin levels favoring glucose metabolism [101]		
Seeds, legumes, nuts			High magnesium	Decreased risk of PTDM [57,101–103]
Olive oil	High ratio of monounsaturated saturated fatty acids	Improves insulin sensitivity [106] MUFA stimulates GLP-1 secretion [105], which increases insulin secretion and inhibits glucagon [104]		
Fish			ω-3 fatty acid	Decreased oxidative stress and inflammation [73,96,97]
Olive oil, vegetables, cereals, and nuts	Anticoagulant effects [99]	Lower prothrombotic biomarkers e.g. fibrinogen [110] Lower CV risk		
Plant-based protein	Improved lipid profile	Decreased risk of CKD, ESKD [25,111,112]		
Overall components	Improved CV risk factors	Decreased CVD [89,90,93,94] Diabetes [57] Hypertension [107] Obesity [108,109]	Inflammation and endothelial dysfunction [98,99] A lower concentration of biomarkers for inflammation and endothelial dysfunction; C reactive protein, interleukin-6, E-selectin, and soluble intercellular cell adhesion molecule-1 [96]	Decreased CVD

ω, omega; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; ESKD, end-stage kidney disease; GLP-1, glucagon-like peptide-1; MUFA, monounsaturated fatty acid.

Mediterranean diet

MedDiet is originally in the 1960s from eating habits among the population of the lands surrounding the Mediterranean Sea [87]. It includes a high proportion of olive oil, legumes, unrefined cereals, fruit, and vegetables, moderate to high portion of fish, moderate dairy products (mostly cheese and yogurt), moderate wine, and low in nonfish meat products. One literature review concluded nutrient content of the MedDiet containing approximately 37% total fat, 18% monounsaturated, 9% saturated, 33 g of fiber, and calorie 9300 kJ per day. It ranges from 3 to 9 serves of vegetables, 0.5 to 2 serves of fruit, 1 - 13 serves of cereals, and up to 8 serves of olive oil daily [88].

In nontransplant population, consuming MedDiet is associated with better kidney function [89,90], delayed kidney function decline, CKD prevention [91], and deceased albuminuria [92–94].

Evidence regarding the beneficial effects of MedDiet in transplant recipients is limited. MedDiet is associated with decreased risk of metabolic syndrome [56] and PTDM [57]. A recent prospective cohort study investigated the association between MedDiet intake and allograft outcomes in transplant recipients with stable allograft function ≥1 year and revealed lowered risk of allograft failure, graft loss (including DWFG), and allograft functional decline in patients with higher MedDiet adherence determined by a nine-point Mediterranean Diet Score. The association was greater in patients with higher urinary albumin excretion rates and those more recently transplanted [58▪▪].

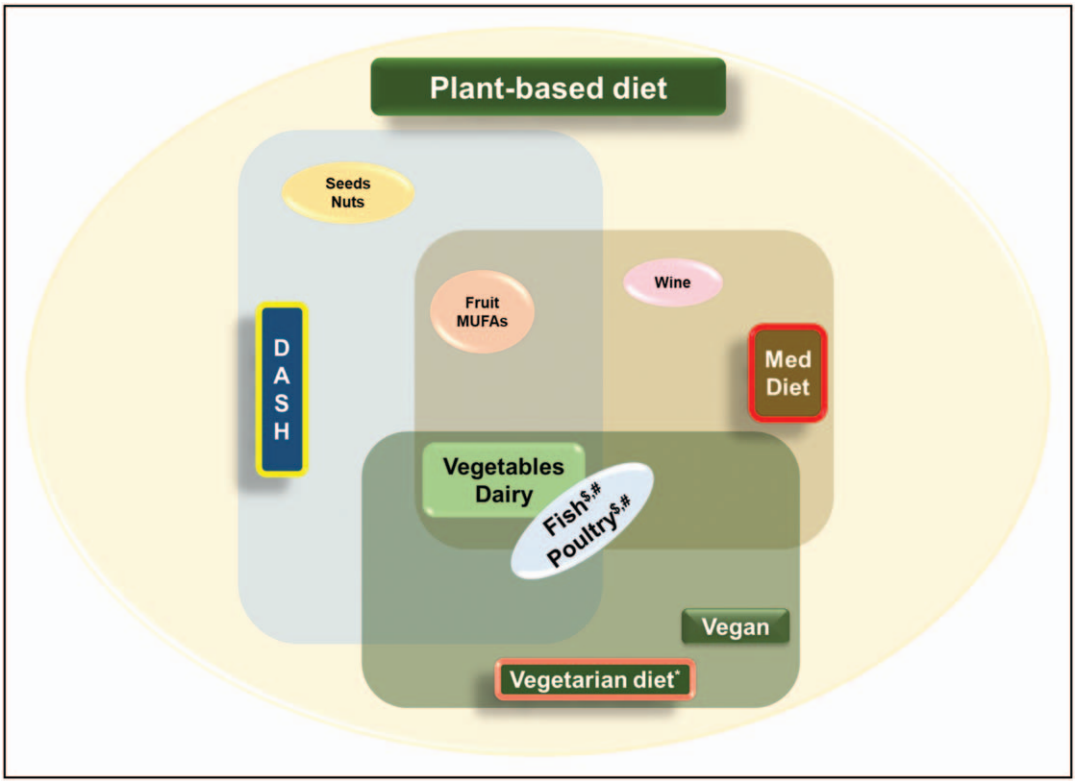

FIGURE 4. Compare the characteristics of three main plant-based diets with vegetables as the main overlapped food. DASH, Dietary Approaches to Stop Hypertension; MedDiet, Mediterranean diet. * = 4 variants including vegetarian (Lacto-ovo vegetarian), semi-vegetarian (Flexitarian), pescatarian, and vegan. $ = Semi-vegetarian (Flexitarian). # = Pescatarian.

Mechanism of the protective effect of MedDiet on allograft function may result from direct and indirect effects on the allograft. The direct effects include decreased acid load [28,95], antioxidative effects [73,96,97], endothelial dysfunction [96,98,99], and protein intake [58▪▪]. Indirect effects of MedDiet on allograft function involve lowered cardiovascular risk factors which are commonly associated with impaired allograft function such as PTDM via improved insulin resistance [57,100,101] from high magnesium [57,101–103], monounsaturated fatty acid [104–106], hypertension [107], obesity [108,109], thrombotic risk [110], and improved lipid profiles [25,111,112]. Some of these contributing factors may be mediated via nonimmune- and/or immune-related pathways (Table 2).

Similar to the DASH diet, stronger evidence of MedDiet is warranted before recommending MedDiet in the transplant population.

The three main types of a plant-based diet have some overlapped mainly in the plant-based components (Fig. 4). Although there is evidence of the favorable effect of a plant-based diet on kidney function, some characteristics of patients may determine this association such as greater benefit in higher proteinuria for healthy plant-based [58▪▪] and lesser in advanced allograft function for DASH diets [55]. In addition, a recent prospective cohort study demonstrated a protective effect of meat intake. Higher red meat intake determined by greater 24-h urinary 3-methylhistidine was associated lower allograft loss and patient mortality as well as lower allograft loss was found to be associated with higher white meat intake determined by higher 24-h urinary 1-methylhistidine [59▪▪]. However, net endogenous acid production assessed by FFQ and 24-h urinary urea and potassium were recently found to be associated with allograft loss or doubling of plasma creatinine [60▪▪]. Given a conflicting evidence of dietary patterns especially protein intake, stronger evidence is warranted before these diets should be widely implemented in clinical practice.

CONCLUSION

The longevity of kidney allograft involves immunological and nonimmunological factors. Quantity and quality of nutrients especially low protein plant-based diet, also known as PLADO, have been associated with allograft function although there are

some inconsistent data. Dietary patterns especially plant-based diets have also been shown to be associated with favorable allograft outcomes, whereas recent studies related to protein intake and allograft outcomes are conflicting. Studies with strong evidence are required to implement this diet into clinical practice. Additionally, other dietary patterns that have been emerged and known to social media require further studies in the kidney transplant population.

Acknowledgements

The authors would like to thank our kidney and kidney transplant patients as well as living kidney donors to motivate us to research and expand our knowledge in the field of kidney transplantation.

Financial support and sponsorship

Supported by research grants from the National Institute of Diabetes, Digestive and Kidney Disease of the National Institutes of Health K24-DK091419 and philanthropic grants from Mr. Louis Chang and Dr Joseph Lee.

Conflicts of interest

K.K.Z. has received honoraria and/or grants from Abbott, Abbvie, Alexion, Amgen, DaVita, Fresenius, Genzyme, Keryx, Otsuka, Shire, Rockwell, and Vifor, the manufacturers of drugs or devices and/or providers of services for CKD patients. K.K.Z. serves as a physician in a US Department of Veterans Affairs medical center with part compensation and is a part-time employee of a US Department of Veterans Affairs medical center. Opinions expressed in this paper are those of the authors and do not represent the official opinion of the US Department of Veterans Affairs.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Meier-Kriesche HU, Schold JD, Kaplan B. Long-term renal allograft survival: have we made significant progress or is it time to rethink our analytic and therapeutic strategies? Am J Transplant 2004; 4:1289–1295.
2. Gondos A, Dohler B, Brenner H, Opelz G. Kidney graft survival in Europe and the United States: strikingly different long-term outcomes. Transplantation 2013; 95:267–274.
3. Coemans M, Susal C, Dohler B, *et al.* Analyses of the short- and long-term graft survival after kidney transplantation in Europe between 1986 and 2015. Kidney Int 2018; 94:964–973.
4. Sexton DJ, O'Kelly P, Williams Y, *et al.* Progressive improvement in short-, medium- and long-term graft survival in kidney transplantation patients in Ireland - a retrospective study. Transplant Int 2019; 32:974–984.
5. Tantisattamo E, Leventhal JR, Mathew JM, Gallon L. Chimerism and tolerance: past, present and future strategies to prolong renal allograft survival. Curr Opin Nephrol Hypertens 2021; 30:63–74.
6. Pascual M, Theruvath T, Kawai T, *et al.* Strategies to improve long-term outcomes after renal transplantation. N Engl J Med 2002; 346:580–590.
7. Dennis MJ, Foster MC, Ryan JJ, *et al.* The increasing importance of chronic rejection as a cause of renal allograft failure. Transplant Int 1989; 2:214–217.
8. Tantisattamo E, Dafoe DC, Reddy UG, *et al.* Current management of patients with acquired solitary kidney. Kidney Int Rep 2019; 4:1205–1218.
9. Deen WM, Maddox DA, Robertson CR, Brenner BM. Dynamics of glomerular ultrafiltration in the rat. VII. Response to reduced renal mass. Am J Physiol 1974; 227:556–562.
10. Hostetter TH, Olson JL, Rennke HG, *et al.* Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation. Am J Physiol 1981; 241:F85–93.
11. 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; 307:652–659.
12. Couser WG, Stilmant MM. Mesangial lesions and focal glomerular sclerosis in the aging rat. Lab Investig 1975; 33:491–501.
13. Velosa JA, Glasser RJ, Nevins TE, Michael AF. Experimental model of focal sclerosis. II. Correlation with immunopathologic changes, macromolecular kinetics, and polyanion loss. Lab Investig 1977; 36:527–534.
14. Tantisattamo E. Posttransplant weight gain and obesity: an opportunity for renal dietary management. Adv Obes Weight Manag Control 2017; 7:276–279.
15. Hong SH, Kim EM, Rha MY. Nutritional intervention process for a patient with kidney transplantation: a case report. Clin Nutr Res 2019; 8:74–78.
16. Rosman JB, ter Wee PM, Meijer S, *et al.* Prospective randomised trial of early dietary protein restriction in chronic renal failure. Lancet 1984; 2:1291–1296.
17. Rosenberg ME, Swanson JE, Thomas BL, Hostetter TH. Glomerular and hormonal responses to dietary protein intake in human renal disease. Am J Physiol 1987; 253(6 Pt 2):F1083–F1090.
18. Ihle BU, Becker GJ, Whitworth JA, *et al.* The effect of protein restriction on the progression of renal insufficiency. N Engl J Med 1989; 321:1773–1777.
19. Zeller K, Whittaker E, Sullivan L, *et al.* Effect of restricting dietary protein on the progression of renal failure in patients with insulin-dependent diabetes mellitus. N Engl J Med 1991; 324:78–84.
20. Paller MS, Hostetter TH. Dietary protein increases plasma renin and reduces pressor reactivity to angiotensin II. Am J Physiol 1986; 251(1 Pt 2):F34–F39.
21. Rosenberg ME, Chmielewski D, Hostetter TH. Effect of dietary protein on rat renin and angiotensinogen gene expression. J Clin Investig 1990; 85:1144–1149.
22. Nath KA, Kren SM, Hostetter TH. Dietary protein restriction in established renal injury in the rat. Selective role of glomerular capillary pressure in progressive glomerular dysfunction. J Clin Investig 1986; 78:1199–1205.
23. Nath KA, Croatt AJ, Hostetter TH. Oxygen consumption and oxidant stress in surviving nephrons. Am J Physiol 1990; 258(5 Pt 2):F1354–F1362.
24. Kalantar-Zadeh K, Fouque D. Nutritional management of chronic kidney disease. N Engl J Med 2017; 377:1765–1776.
25. Haring B, Selvin E, Liang M, *et al.* Dietary protein sources and risk for incident chronic kidney disease: results from the atherosclerosis risk in Communities (ARIC) Study. J Ren Nutr 2017; 27:233–242.
26. Engberink MF, Bakker SJ, Brink EJ, *et al.* Dietary acid load and risk of hypertension: the Rotterdam Study. Am J Clin Nutr 2012; 95:1438–1444.
27. Fagherazzi G, Vilier A, Bonnet F, *et al.* Dietary acid load and risk of type 2 diabetes: the E3N-EPIC cohort study. Diabetologia 2014; 57:313–320.
28. Rebholz CM, Coresh J, Grams ME, *et al.* Dietary acid load and incident chronic kidney disease: results from the ARIC Study. Am J Nephrol 2015; 42:427–435.
29. Wang L, Manson JE, Buring JE, Sesso HD. Meat intake and the risk of hypertension in middle-aged and older women. J Hypertens 2008; 26:215–222.
30. Borgi L, Curhan GC, Willett WC, *et al.* Long-term intake of animal flesh and risk of developing hypertension in three prospective cohort studies. J Hypertens 2015; 33:2231–2238.
31. Weng LC, Steffen LM, Szklo M, *et al.* A diet pattern with more dairy and nuts, but less meat is related to lower risk of developing hypertension in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) study. Nutrients 2013; 5:1719–1733.
32. Pan A, Sun Q, Bernstein AM, *et al.* Changes in red meat consumption and subsequent risk of type 2 diabetes mellitus: three cohorts of US men and women. JAMA Intern Med 2013; 173:1328–1335.
33. Aune D, Norat T, Romundstad P, Vatten LJ. Dairy products and the risk of type 2 diabetes: a systematic review and dose-response meta-analysis of cohort studies. Am J Clin Nutr 2013; 98:1066–1083.
34. Jolliffe N, Smith HW. The excretion of urine in the dog 1931; 99:101–107.
35. Wetzels JF, Wiltink PG, van Duijnhoven EM, *et al.* Short-term protein restriction in healthy volunteers: effects on renal hemodynamics and renal response to a meat meal. Clin Nephrol 1989; 31:311–315.
36. Kontessis P, Jones S, Dodds R, *et al.* Renal, metabolic and hormonal responses to ingestion of animal and vegetable proteins. Kidney Int 1990; 38:136–144.
37. Nakamura H, Ito S, Ebe N, Shibata A. Renal effects of different types of protein in healthy volunteer subjects and diabetic patients. Diabetes Care 1993; 16:1071–1075.
38. 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.

■ This article provides a comprehensive mechanism and evidence of a plant-based diet and low dietary protein intake as the so-called Plant-Dominant Low-Protein Diet (PLADO).

39. ■ Kalantar-Zadeh K, Jafar TH, Nitsch D, *et al.* Chronic kidney disease. Lancet 2021; 398:786–802.

This article provides a comprehensive review of several aspects of chronic kidney disease including management by low dietary protein intake and a plant-based diet.

40. Oyabu C, Hashimoto Y, Fukuda T, *et al.* Impact of low-carbohydrate diet on renal function: a meta-analysis of over 1000 individuals from nine randomised controlled trials. Br J Nutr 2016; 116:632–638.
41. Suyoto PST. Effect of low-carbohydrate diet on markers of renal function in patients with type 2 diabetes: a meta-analysis. Diabetes Metab Res Rev 2018; 34:e3032.
42. Park S, Lee S, Kim Y, *et al.* Causal effects of relative fat, protein, and carbohydrate intake on chronic kidney disease: a Mendelian randomization study. Am J Clin Nutr 2021; 113:1023–1031.
43. Nolte Fong JV, Moore LW. Nutrition trends in kidney transplant recipients: the importance of dietary monitoring and need for evidence-based recommendations. Front Med 2018; 5:302.
44. Boloori A, Saghafian S, Chakkera HA, Cook CB. Characterization of remitting and relapsing hyperglycemia in post-renal-transplant recipients. PLoS One 2015; 10:e0142363.
45. Pirsch JD, Henning AK, First MR, *et al.* New-onset diabetes after transplantation: results from a double-blind early corticosteroid withdrawal trial. Am J Transplant 2015; 15:1982–1990.
46. Molinero LL, Yin D, Lei YM, *et al.* High-fat diet-induced obesity enhances allograft rejection. Transplantation 2016; 100:1015–1021.
47. Muller CR, Leite APO, Yokota R, *et al.* Postweaning exposure to high-fat diet induces kidney lipid accumulation and function impairment in adult rats. Front Nutr 2019; 6:60.
48. Sun Y, Ge X, Li X, *et al.* High-fat diet promotes renal injury by inducing oxidative stress and mitochondrial dysfunction. Cell Death Dis 2020; 11:914.
49. Kort WJ, de Keijzer MH, Hekking-Weijma I, Vermeij M. Dietary fatty acids and kidney transplantation in the rat. Ann Nutr Metab 1991; 35:148–157.
50. Berthoux FC, Guerin C, Burgard G, *et al.* One-year randomized controlled trial with omega-3 fatty acid-fish oil in clinical renal transplantation. Transplant Proc 1992; 24:2578–2582.
51. Maachi K, Berthoux P, Burgard G, *et al.* Results of a 1-year randomized controlled trial with omega-3 fatty acid fish oil in renal transplantation under triple immunosuppressive therapy. Transplant Proc 1995; 27:846–849.
52. Bennett WM, Carpenter CB, Shapiro ME, *et al.* Delayed omega-3 fatty acid supplements in renal transplantation. A double-blind, placebo-controlled study. Transplantation 1995; 59:352–356.
53. ■■ 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(3 Suppl 1):S1–S107.

This article provides an extensive systematic review related to renal nutrition field including dietary intervention in chronic kidney disease, end-stage kidney disease, and kidney transplant recipients.

54. ■ Goldfarb Cyrino L, Galpern J, Moore L, *et al.* A narrative review of dietary approaches for kidney transplant patients. Kidney Int Rep 2021; 6:1764–1774.

This article focuses on variety and commonly consumed dietary food patterns in kidney transplant recipients.

55. Oste MCJ, Gomes-Neto AW, Corpeleijn E, *et al.* Dietary Approach to Stop Hypertension (DASH) diet and risk of renal function decline and all-cause mortality in renal transplant recipients. Am J Transplant 2018; 18:2523–2533.
56. Nafar M, Noori N, Jalali-Farahani S, *et al.* Mediterranean diets are associated with a lower incidence of metabolic syndrome one year following renal transplantation. Kidney Int 2009; 76:1199–1206.
57. Oste MC, Corpeleijn E, Navis GJ, *et al.* Mediterranean style diet is associated with low risk of new-onset diabetes after renal transplantation. BMJ Open Diabetes Res Care 2017; 5:e000283.
58. ■■ Gomes-Neto AW, Oste MCJ, Sotomayor CG, *et al.* Mediterranean style diet and kidney function loss in kidney transplant recipients. Clin J Am Soc Nephrol 2020; 15:238–246.

This article is the first clinical study demonstrating the potential benefits of the Mediterranean diet on kidney allograft function and can motivate the extension of studies related dietary intervention in kidney transplant recipients.

59. ■■ Said MY, Rodriguez-Nino A, Post A, *et al.* Meat intake and risk of mortality and graft failure in kidney transplant recipients. Am J Clin Nutr 2021; 114:1505–1517.

This is the first prospective observational study demonstrated a possible protective effect of red and white meat consumptions on mortality and kidney allograft loss, respectively. The findings of this study that is conflicting with renal protection of low protein diet can lead to studies to further confirm the results.

60. ■■ Yeung SMH, Gomes-Neto AW, Oste MCJ, *et al.* Net endogenous acid excretion and kidney allograft outcomes. Clin J Am Soc Nephrol 2021; 16:1398–1406.

This prospective study showed a potential adverse association between net endogenous acid production and kidney allograft outcomes. The result of this study is in the opposite direction with the above study and should also motivate further studies.

61. The Vegetarian Society of the United Kingdom. What is a Vegetarian? https://vegsoc.org/info-hub/definition/ Accessed on October 29th, 2021.
62. Gee PO. A Nutritional Lie or Lifestyle? Clin J Am Soc Nephrol 2019; 14:643–644.
63. Kim H, Caulfield LE, Garcia-Larsen V, *et al.* Plant-based diets and incident CKD and kidney function. Clin J Am Soc Nephrol 2019; 14:682–691.
64. Goraya N, Simoni J, Jo C, Wesson DE. Dietary acid reduction with fruits and vegetables or bicarbonate attenuates kidney injury in patients with a moderately reduced glomerular filtration rate due to hypertensive nephropathy. Kidney Int 2012; 81:86–93.
65. Farhadnejad H, Asghari G, Mirmiran P, *et al.* Micronutrient intakes and incidence of chronic kidney disease in adults: tehran lipid and glucose study. Nutrients 2016; 8:217.
66. Fioretto P, Bruseghin M, Berto I, *et al.* Renal protection in diabetes: role of glycemic control. J Am Soc Nephrol 2006; 17(4 Suppl 2):S86–S89.
67. Meyer KA, Kushi LH, Jacobs DR Jr, *et al.* Carbohydrates, dietary fiber, and incident type 2 diabetes in older women. Am J Clin Nutr 2000; 71:921–930.
68. Streppel MT, Arends LR, van 't Veer P, *et al.* Dietary fiber and blood pressure: a meta-analysis of randomized placebo-controlled trials. Arch Intern Med 2005; 165:150–156.
69. Rhee CM, Ahmadi SF, Kovesdy CP, Kalantar-Zadeh K. Low-protein diet for conservative management of chronic kidney disease: a systematic review and meta-analysis of controlled trials. J Cachexia Sarcopenia Muscle 2018; 9:235–245.
70. St-Jules DE, Goldfarb DS, Sevick MA. Nutrient nonequivalence: does restricting high-potassium plant foods help to prevent hyperkalemia in hemodialysis patients? J Ren Nutr 2016; 26:282–287.
71. Fung TT, Chiuve SE, McCullough ML, *et al.* Adherence to a DASH-style diet and risk of coronary heart disease and stroke in women. Arch Intern Med 2008; 168:713–720.
72. Struijk EA, May AM, Wezenbeek NL, *et al.* Adherence to dietary guidelines and cardiovascular disease risk in the EPIC-NL cohort. Int J Cardiol 2014; 176:354–359.
73. Lin J, Fung TT, Hu FB, Curhan GC. Association of dietary patterns with albuminuria and kidney function decline in older white women: a subgroup analysis from the Nurses' Health Study. Am J Kidney Dis 2011; 57:245–254.
74. Crews DC, Kuczmarski MF, Miller ER 3rd, *et al.* Dietary habits, poverty, and chronic kidney disease in an urban population. J Ren Nutr 2015; 25:103–110.
75. Asghari G, Yuzbashian E, Mirmiran P, Azizi F. The association between Dietary Approaches to Stop Hypertension and incidence of chronic kidney disease in adults: the Tehran Lipid and Glucose Study. Nephrol Dial Transplant 2017; 32(suppl_2):ii224–ii230.
76. Parikh A, Lipsitz SR, Natarajan S. Association between a DASH-like diet and mortality in adults with hypertension: findings from a population-based follow-up study. Am J Hypertens 2009; 22:409–416.
77. Levitan EB, Lewis CE, Tinker LF, *et al.* Mediterranean and DASH diet scores and mortality in women with heart failure: The Women's Health Initiative. Circ Heart Fail 2013; 6:1116–1123.
78. Sacks FM, Svetkey LP, Vollmer WM, *et al.* Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. N Engl J Med 2001; 344:3–10.
79. Obarzanek E, Sacks FM, Vollmer WM, *et al.* Effects on blood lipids of a blood pressure-lowering diet: the Dietary Approaches to Stop Hypertension (DASH) Trial. Am J Clin Nutr 2001; 74:80–89.
80. Roussell MA, Hill AM, Gaugler TL, *et al.* Beef in an Optimal Lean Diet study: effects on lipids, lipoproteins, and apolipoproteins. Am J Clin Nutr 2012; 95:9–16.
81. Asemi Z, Samimi M, Tabassi Z, *et al.* Effects of DASH diet on lipid profiles and biomarkers of oxidative stress in overweight and obese women with polycystic ovary syndrome: a randomized clinical trial. Nutrition 2014; 30:1287–1293.
82. Saneei P, Salehi-Abargouei A, Esmaillzadeh A, Azadbakht L. Influence of Dietary Approaches to Stop Hypertension (DASH) diet on blood pressure: a systematic review and meta-analysis on randomized controlled trials. Nutr Metab Cardiovasc Dis 2014; 24:1253–1261.
83. Neale EP, Batterham MJ, Tapsell LC. Consumption of a healthy dietary pattern results in significant reductions in C-reactive protein levels in adults: a meta-analysis. Nutr Res 2016; 36:391–401.
84. van Ree RM, Oterdoom LH, de Vries AP, *et al.* Elevated levels of C-reactive protein independently predict accelerated deterioration of graft function in renal transplant recipients. Nephrol Dial Transplant 2007; 22:246–253.
85. Ozdemir NF, Elsurer R, Ibis A, *et al.* Serum C-reactive protein surge in renal transplant recipients: link with allograft survival. Transplant Proc 2007; 39:934–937.
86. Most MM. Estimated phytochemical content of the dietary approaches to stop hypertension (DASH) diet is higher than in the Control Study Diet. J Am Diet Assoc 2004; 104:1725–1727.
87. Trichopoulou A, Martinez-Gonzalez MA, Tong TY, *et al.* Definitions and potential health benefits of the Mediterranean diet: views from experts around the world. BMC Med 2014; 12:112.
88. Davis C, Bryan J, Hodgson J, Murphy K. Definition of the Mediterranean Diet; a literature review. Nutrients 2015; 7:9139–9153.

89. Chrysohoou C, Panagiotakos DB, Pitsavos C, *et al.* Adherence to the Mediterranean diet is associated with renal function among healthy adults: the ATTICA study. J Ren Nutr 2010; 20:176–184.
90. Huang X, Jimenez-Moleon JJ, Lindholm B, *et al.* Mediterranean diet, kidney function, and mortality in men with CKD. Clin J Am Soc Nephrol 2013; 8:1548–1555.
91. Hu EA, Steffen LM, Grams ME, *et al.* Dietary patterns and risk of incident chronic kidney disease: the Atherosclerosis Risk in Communities study. Am J Clin Nutr 2019; 110:713–721.
92. Mazaraki A, Tsioufis C, Dimitriadis K, *et al.* Adherence to the Mediterranean diet and albuminuria levels in Greek adolescents: data from the Leontio Lyceum ALbuminuria (3L study). Eur J Clin Nutr 2011; 65:219–225.
93. Khatri M, Moon YP, Scarmeas N, *et al.* The association between a Mediterranean-style diet and kidney function in the Northern Manhattan Study cohort. Clin J Am Soc Nephrol 2014; 9:1868–1875.
94. Asghari G, Farhadnejad H, Mirmiran P, *et al.* Adherence to the Mediterranean diet is associated with reduced risk of incident chronic kidney diseases among Tehranian adults. Hypertens Res 2017; 40:96–102.
95. Siener R. Dietary treatment of metabolic acidosis in chronic kidney disease. Nutrients 2018; 10:512.
96. Fung TT, McCullough ML, Newby PK, *et al.* Diet-quality scores and plasma concentrations of markers of inflammation and endothelial dysfunction. Am J Clin Nutr 2005; 82:163–173.
97. Smidowicz A, Regula J. Effect of nutritional status and dietary patterns on human serum C-reactive protein and interleukin-6 concentrations. Adv Nutr 2015; 6:738–747.
98. Esposito K, Marfella R, Ciotola M, *et al.* Effect of a mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. JAMA 2004; 292:1440–1446.
99. Delgado-Lista J, Perez-Martinez P, Garcia-Rios A, *et al.* Mediterranean diet and cardiovascular risk: beyond traditional risk factors. Crit Rev Food Sci Nutr 2016; 56:788–801.
100. Evans JL, Goldfine ID, Maddux BA, Grodsky GM. Are oxidative stress-activated signaling pathways mediators of insulin resistance and beta-cell dysfunction? Diabetes 2003; 52:1–8.
101. Schroder H. Protective mechanisms of the Mediterranean diet in obesity and type 2 diabetes. J Nutr Biochem 2007; 18:149–160.
102. Kao WH, Folsom AR, Nieto FJ, *et al.* Serum and dietary magnesium and the risk for type 2 diabetes mellitus: the Atherosclerosis Risk in Communities Study. Arch Intern Med 1999; 159:2151–2159.
103. Lopez-Ridaura R, Willett WC, Rimm EB, *et al.* Magnesium intake and risk of type 2 diabetes in men and women. Diabetes Care 2004; 27: 134–140.
104. Komatsu R, Matsuyama T, Namba M, *et al.* Glucagonostatic and insulinotropic action of glucagonlike peptide I-(7-36)-amide. Diabetes 1989; 38:902–905.
105. Rocca AS, LaGreca J, Kalitsky J, Brubaker PL. Monounsaturated fatty acid diets improve glycemic tolerance through increased secretion of glucagon-like peptide-1. Endocrinology 2001; 142:1148–1155.
106. Martinez-Gonzalez MA, de la Fuente-Arrillaga C, Nunez-Cordoba JM, *et al.* Adherence to Mediterranean diet and risk of developing diabetes: prospective cohort study. BMJ 2008; 336:1348–1351.
107. Cowell OR, Mistry N, Deighton K, *et al.* Effects of a Mediterranean diet on blood pressure: a systematic review and meta-analysis of randomized controlled trials and observational studies. J Hypertens 2021; 39:729–739.
108. D'Innocenzo S, Biagi C, Lanari M. Obesity and the Mediterranean Diet: a review of evidence of the role and sustainability of the Mediterranean Diet. Nutrients 2019; 11:1306.
109. Estruch R, Ros E. The role of the Mediterranean diet on weight loss and obesity-related diseases. Rev Endocr Metab Disord 2020; 21:315–327.
110. Carter SJ, Roberts MB, Salter J, Eaton CB. Relationship between Mediterranean Diet Score and atherothrombotic risk: findings from the Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994. Atherosclerosis 2010; 210:630–636.
111. Jenkins DJ, Kendall CW, Vidgen E, *et al.* High-protein diets in hyperlipidemia: effect of wheat gluten on serum lipids, uric acid, and renal function. Am J Clin Nutr 2001; 74:57–63.
112. Lew QJ, Jafar TH, Koh HW, *et al.* Red meat intake and risk of ESRD. J Am Soc Nephrol 2017; 28:304–312.