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

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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.

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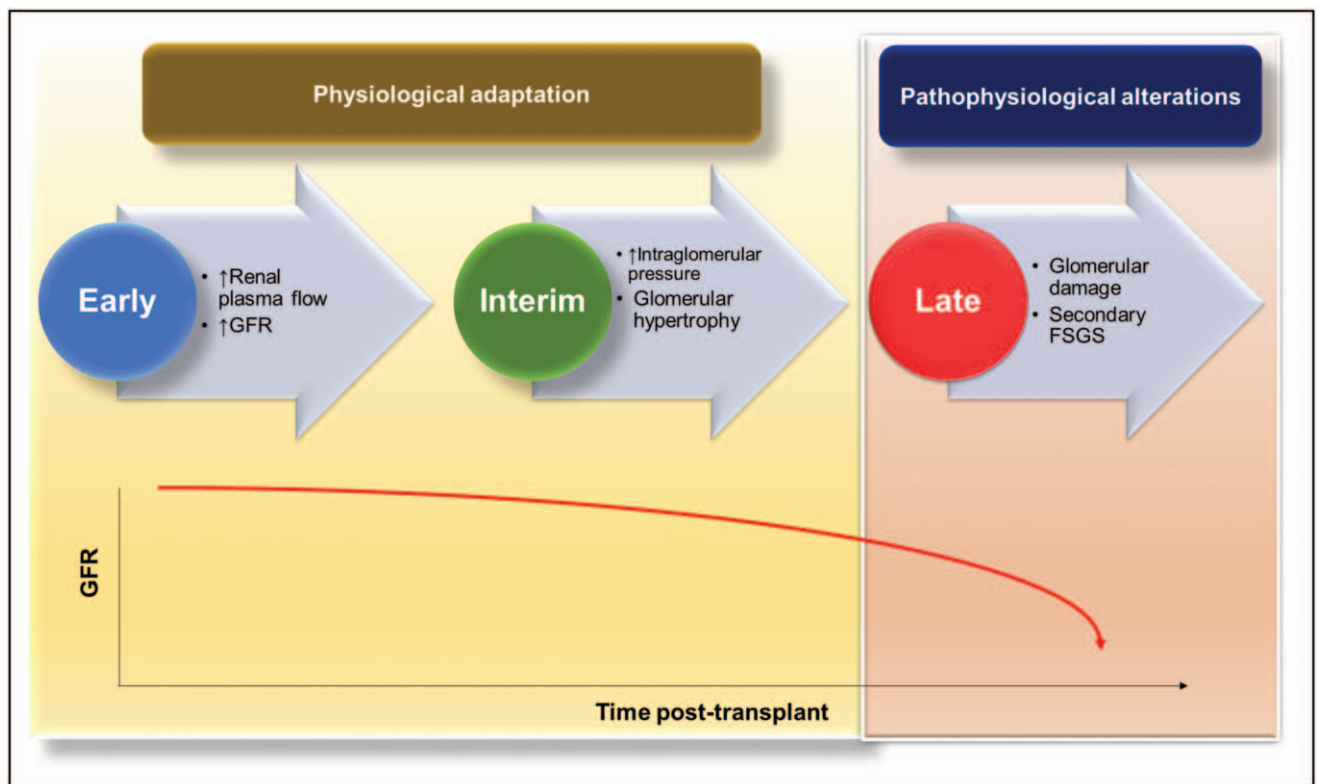
FIGURE 1. Physiological and pathophysiological alterations in kidney allograft hemodynamic. FSGS, focal segmental glomerulosclerosis; GFR, glomerular filtration rate.

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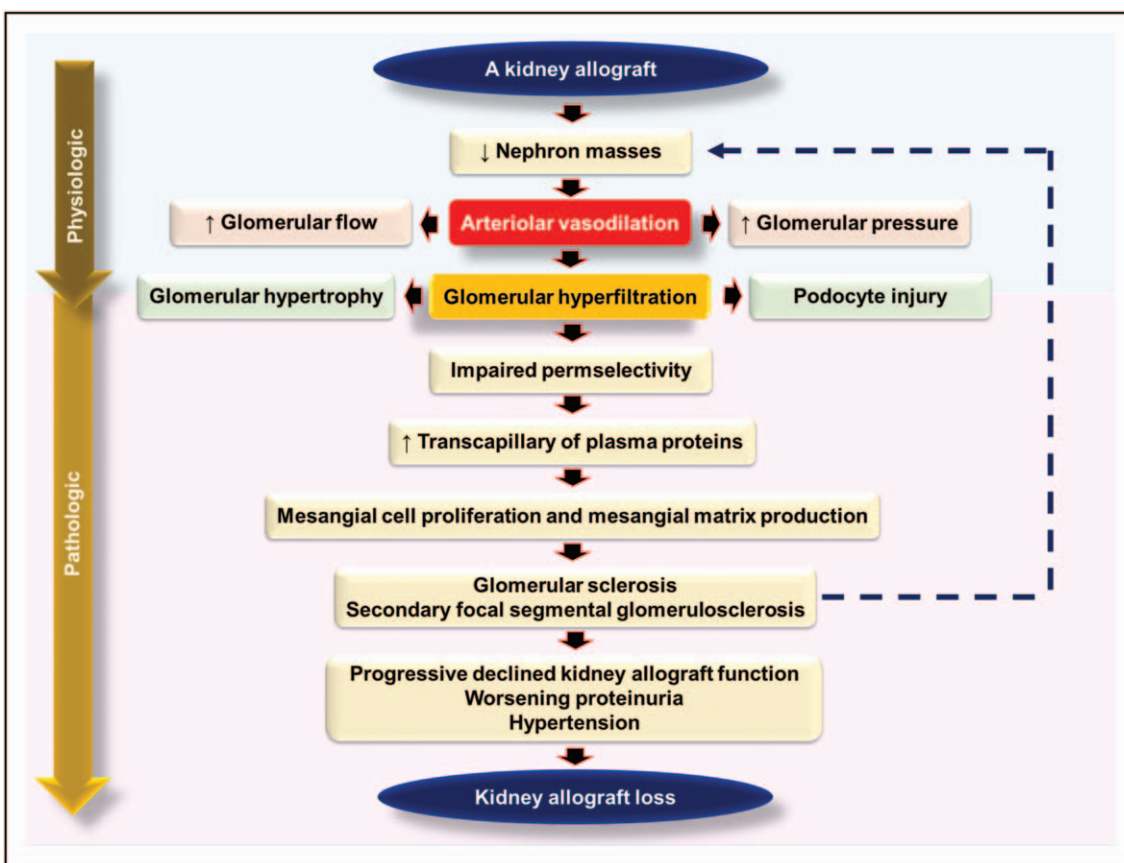
FIGURE 2. Pathophysiology of glomerular injury from a long-term kidney allograft hemodynamic alteration. FSGS, focal segmental glomerulosclerosis; GFR, glomerular filtration rate.

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.
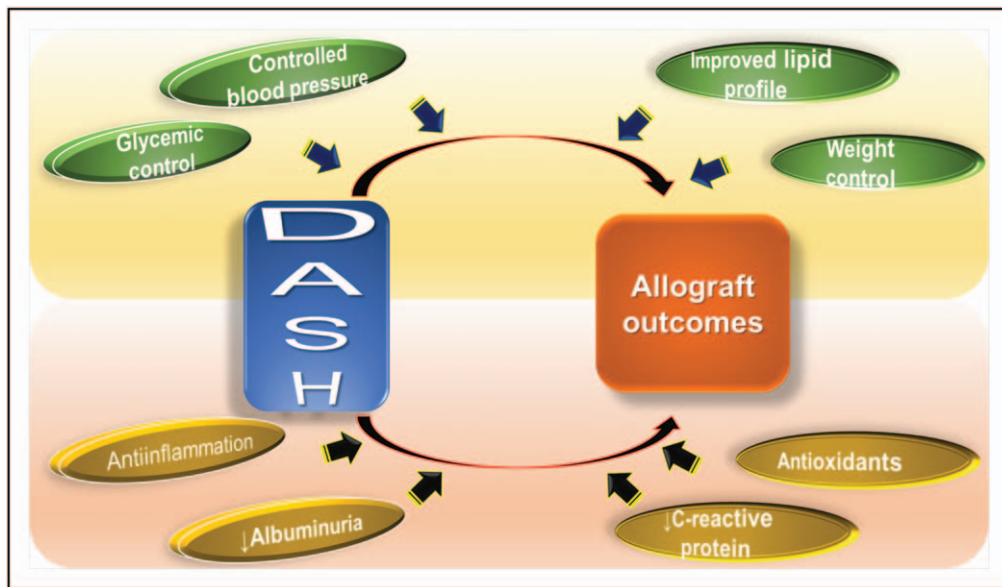
Dietary approach to stop hypertension diet

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

| Main components | Non immune-related | | Immune-related | |
	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.
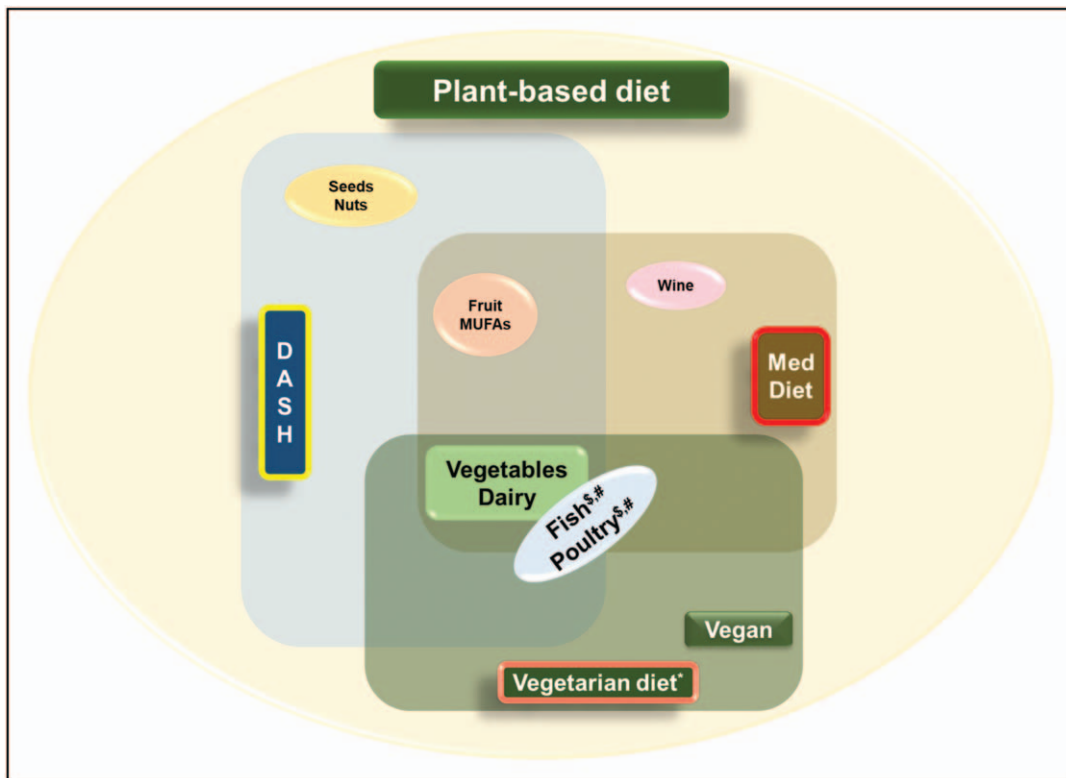
Mediterranean diet

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 Med-Diet 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 Med-Diet 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.

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.

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- ■ of special interest
- ■■ of outstanding interest

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