

Hot Topics in Polycystic Kidney Disease (PKD) Nutrition

© 2024 Otsuka Pharmaceutical Development & Commercialization, Inc., Rockville, MD

February 2024 US.NephU.D.24.00001



This program is paid for by Otsuka Pharmaceutical Development & Commercialization, Inc.

Speakers are employees of Otsuka Pharmaceutical Development & Commercialization, Inc.

February 2024 US.NephU.D.24.00001

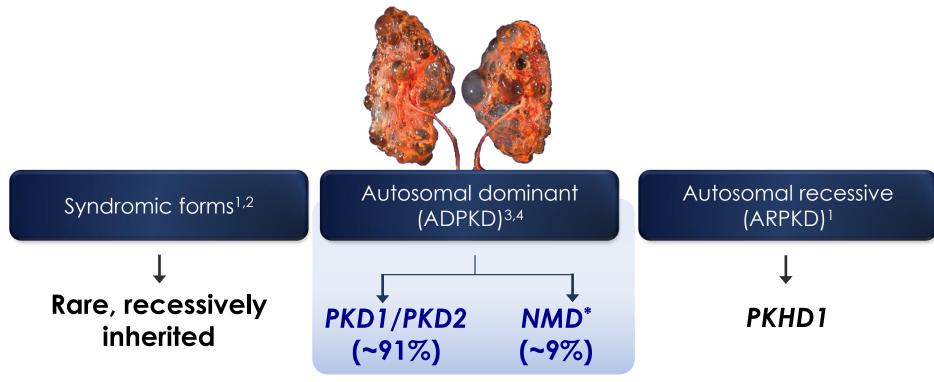
Objectives

- Overview of Polycystic Kidney Disease (PKD)
- Review the Current State of Nutrition Guidelines in PKD
- Discuss Hot Topics in PKD Nutrition
- Highlight Dietary Recommendations for PKD
- Explore Implementation Strategies
- Examine Resources



What Is PKD?

Polycystic kidney disease (PKD) is a group of monogenic disorders characterized by the propensity to develop numerous renal cysts¹



*The "no mutation detected" (NMD) group may contain those patients with mutations in other genes impacting cystic development, such as GANAB.⁵
ADPKD=autosomal dominant PKD; ARPKD=autosomal recessive PKD; GANAB=gene encoding glucosidase II subunit-a; NMD=no mutation detected; PKD=polycystic kidney disease; PKHD1=polycystic kidney and hepatic disease 1.



^{1.} Harris PC and Torres VE. (2009). Annu Rev Med. 60:321-337. 2. Jauregui AR et al. (2005). Exp Cell Res. 305(2):333-342. 3. Heyer CM et al. (2016). J Am Soc Nephrol. 27(9):2872-2884. 4. Irazabal MV et al. (2017). Nephrol Dial Transplant. 32(11):1857-1865. 5. Lanktree MB, Chapman AB. (2017). Nat Rev Nephrol. 13(12):750-768.

ADPKD Is the Most Common Life-threatening Inherited Renal Disease

ADPKD does not discriminate on gender, race, ethnicity, or geography^{1,2}

- ADPKD affects both sexes equally, and occurs in all ethnicities³
- ADPKD is the fourth leading cause of ESRD in the United States², and accounts for up to ~5% of all patients with ESRD²
- As many as 1:2000 people worldwide are currently diagnosed with ADPKD,⁴ and between 1:400 and 1:1000* people living today will be diagnosed with ADPKD in their lifetime¹
- The median age of death or kidney failure is patients with a PKD1 mutation is 53 years⁵
- The median age of death or kidney failure in patients with a PKD2 mutation is 69 years⁵

ADPKD=autosomal dominant polycystic kidney disease; ESRD=end-stage renal disease.



^{*}The higher prevalence value of 1:1000 is believed to be inaccurate because the data are based on a postmortem study and therefore report lifetime morbid risk rather than point prevalence.

Torres VE, Harris PC. (2009). Kidney Int. 76(2):149-168. 2. United States Renal Data System. 2016 USRDS Annual Data Report Volume

^{2.} ESRD in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2016 (accessed 14 February 2019).

^{3.} Chebib FT, Torres VE. (2016). Am J Kidney Dis. 67(5):792-810.

^{4.} Willey C. DRAFT: The Descriptive Epidemiology of ADPKD in the U.S. 2017.

^{5.} Hateboer N et al. (1999) Lancet. 353(9147):103-107

ADPKD Variability in Disease Severity

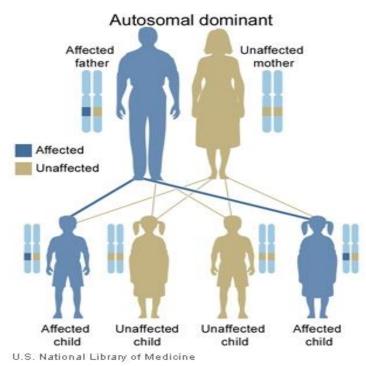


Figure adapted from U.S. National Library of Medicine

Inheritance pattern of autosomal dominant disease⁴

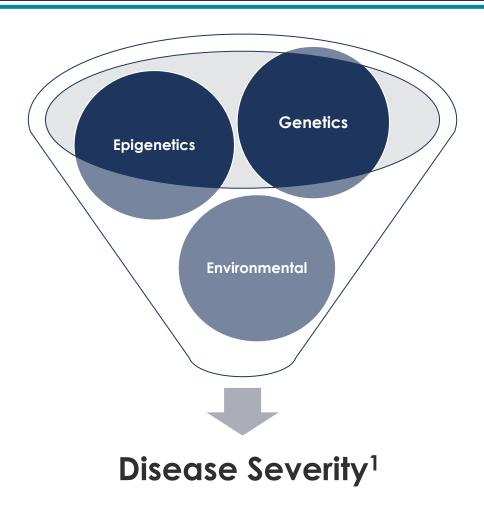
- ADPKD has a high degree of penetrance¹
- A child of an affected parent has a 50% chance of inheriting ADPKD¹
- Disease progression can be highly variable, even among family members sharing the same genetic mutation²

ADPKD=autosomal dominant polycystic kidney disease.

1. Harris PC, Rossetti S. (2010). Nat Rev Nephrol. 6(4):197-206. 2. Reed B et al. (2008). Am J Kidney Dis. 52(6):1042-1050.



Factors Affecting Disease Severity



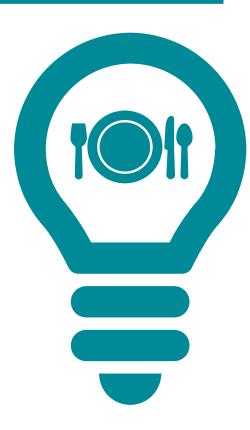
- Environmental Factors
 amenable to lifestyle
 modification can meaningfully
 impact disease progression²
- Obesity was found to be associated with a greater rate of kidney enlargement and functional decline in early-stage ADPKD²
- Components of metabolic syndrome are also associated with more severe ADPKD²



^{1.} Chebib FT, Torries VF. Am J Kidney Dis 2021; 78: 282-292. 2. Pickel et al (2022). Adv Nutr. 13:652-666

Nutrition and PKD

- Dietary intervention is a key part of the care of CKD patients and aims at preventing CKD progression, limiting the negative impact of CKD complications, or complications derived from the cause of CKD while preserving the nutritional status¹
- Nutrition guidelines for PKD generally follow the same guidelines for CKD², without specific dietary therapy to address mechanisms involved in cystogenesis, cyst growth, fibrosis, inflammation, and disease progression³
- However, recent evidence suggests that more tightly specified dietary regimens hold promise to slow disease progression, and the results of ongoing human clinical trials are eagerly awaited⁴





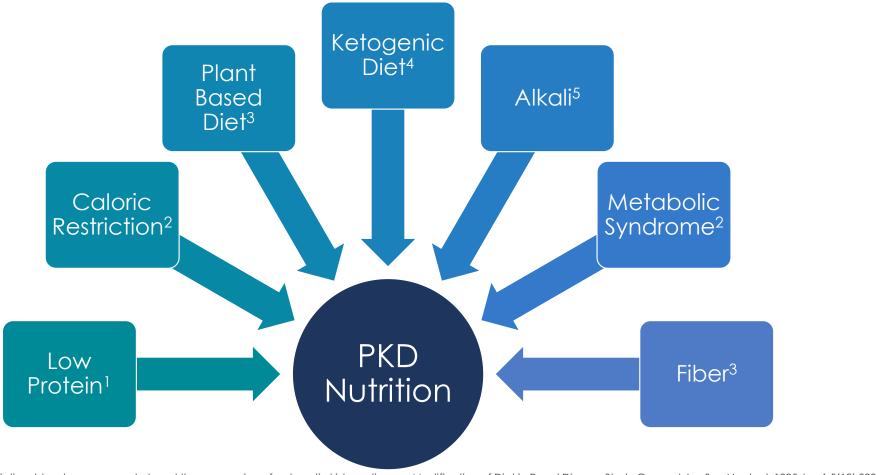
^{1.} Carriazo S, Perez-Gomez MV, Cordido A, García-González MA, Sanz AB, Ortiz A, Sanchez-Niño MD. Dietary Care for ADPKD Patients: Current Status and Future Directions. Nutrients. 2019 Jul 12;11(7):1576.

^{2.} Meijer E, Gansevoort RT. Emerging non-pharmacological interventions in ADPKD: an update on dietary advices for clinical practice. Curr Opin Nephrol Hypertens. 2021;30(5):482-492.

^{3.} Bruen DM, Kingaard JJ, Munits M, Paimanta CS, Torres JA, Saville J, Weimbs T. Ren.Nu, a Dietary Program for Individuals with Autosomal-Dominant Polycystic Kidney Disease Implementing a Sustainable, Plant-Focused, Kidney-Safe, Ketogenic Approach with Avoidance of Renal Stressors. Kidney and Dialysis. 2022; 2(2):183-203.

^{4.} Pickel L, Iliuta LA, Scholey J, Pei Y, Sung HK, Dietary Interventions in Autosomal Dominant Polycystic Kidney Disease, Advances in Nutrition, Volume 13, Issue 2, March 2022, Pages 652–666.

Hot Topics

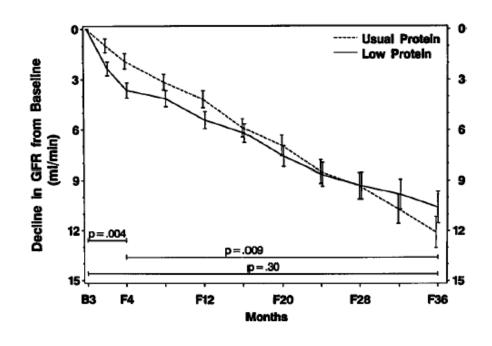


1. Klahr S et al. Dietary protein restriction, blood pressure control, and the progression of polycystic kidney disease. Modification of Diet in Renal Disease Study Group. J Am Soc Nephrol. 1995 Jun 1;5(12):2037–47. 2. Pickel L eta;, Dietary Interventions in Autosomal Dominant Polycystic Kidney Disease, Advances in Nutrition, Volume 13, Issue 2, March 2022, Pages 652–666. 3. Joshi S, McMacken M, Kalantar-Zadeh K. Plant-Based Diets for Kidney Disease: A Guide for Clinicians. Am J Kidney Dis. 2021;77(2):287-296. 4. Bruen DM, Kingaard JJ, Munits M, Paimanta CS, Torres JA, Saville J, Weimbs T. Ren.Nu, a Dietary Program for Individuals with Autosomal-Dominant Polycystic Kidney Disease Implementing a Sustainable, Plant-Focused, Kidney-Safe, Ketogenic Approach with Avoidance of Renal Stressors. Kidney and Dialysis. 2022; 2(2):183-203. 5. Kalantar-Zadeh K, Fouque D. Nutritional management of chronic kidney disease. N Engl J Med. 2017;377(18):1765–76.



Low Protein

- Animal studies investigating the effect of protein source on PKD progression report better outcomes with soy (plant) compared to casein (animal)¹
- In the Modification of Diet in Renal Disease (MDRD) study of 200 patients with ADPKD, a low-protein diet (0.58 g/kg/d) showed no protective effect for a GFR range of 25-55 mL/min/1.73 m^{22,3}
- A secondary analysis of the MDRD study showed a 28% slower mean GFR decline in the low protein diet group from 4 moths to end of follow-up (36 months)³
- An observational study following 589 patients with ADPKD for 4 years found that higher salt (9.1 g/day), but not higher protein intake (84 g/day), was significantly associated with kidney function decline⁴



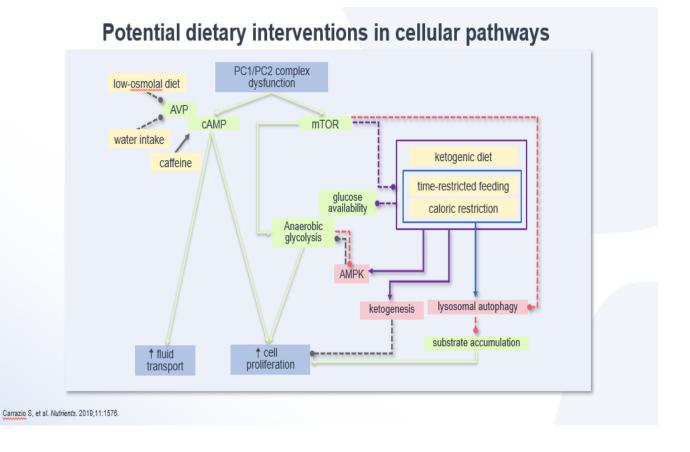
Although evidence on protein restriction is mixed for patients with PKD, many experts recommend avoiding excess protein to prevent an increased rate of kidney function decline

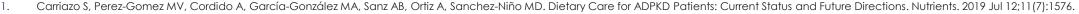
1. Pickel L eta;, Dietary Interventions in Autosomal Dominant Polycystic Kidney Disease, Advances in Nutrition, Volume 13, Issue 2, March 2022, Pages 652–666. 2. Klahr S et al. Dietary protein restriction, blood pressure control, and the progression of polycystic kidney disease. Modification of Diet in Renal Disease Study Group. J Am Soc Nephrol. 1995 Jun 1;5(12):2037–47. 3. Levey A. et al. Dietary protein Restriction and the Progression of Chronic Renal Disease: What Have All of the Results of the MDRD Study Shown? J Am Soc Nephrol 1999 10: 2426-2439. 4. Kramers BJ, Koorevaar IW, Drenth JPH, et al. Salt, but not protein intake, is associated with accelerated disease progression in autosomal dominant polycystic kidney disease. Kidney Int. 2020;98(4):989-998.



Caloric Restriction

- The mammalian target of rapamycin (mTOR) signaling pathway is irregularly activated in renal cysts in patients with ADPKD¹
- Suppression of the mTOR pathway via caloric restriction has been shown in animal models to effectively slow the course of disease progression in ADPKD¹







Caloric Restriction

- In general, caloric restriction has many benefits for metabolic health and increasing lifespan¹
- A recent pilot study that suggested that weight loss due to daily caloric restriction or intermittent fasting in obese and overweight individuals with ADPKD correlated with slowed kidney growth²

Dietary interventions: benefits, risks, and status in PKD EVIDENCE IN ADPKD METABOLIC BENEFITS Non-orthologous Orthologous TRIAL SIDE EFFECTS DIET Caloric restriction Daily restriction blood pressure irritability (NCT03342742: Yes (22, 63) † insulin sensitivity of energy intake fatigue 34% CR) Improve lipids loss of lean mass Ongoing Intermittent fasting Alternating days of (NCT03342742; ad libitum eating and 34% CR) fasting period 0% CR, 3 fasting or severe CR blood pressure days/week insulin sensitivity during TRE, may resolve with time) glycemic control Time-restricted improve lipids of feeding window Ongoing eating (TRE) Yes (87) Yes (63) (NCT04534985) ad libitum feeding challenges Ketogenic diet High fat, moderate transient flu-like protein, very low | blood pressure symptoms Ongoing, 2 Yes (87) (Persian cats n=4, carbohydrate † glycemic control potential (29; NCT04472624) (<20 g/day) Pickel L, et al. Adv Nutrition. 2022;13:652-666.

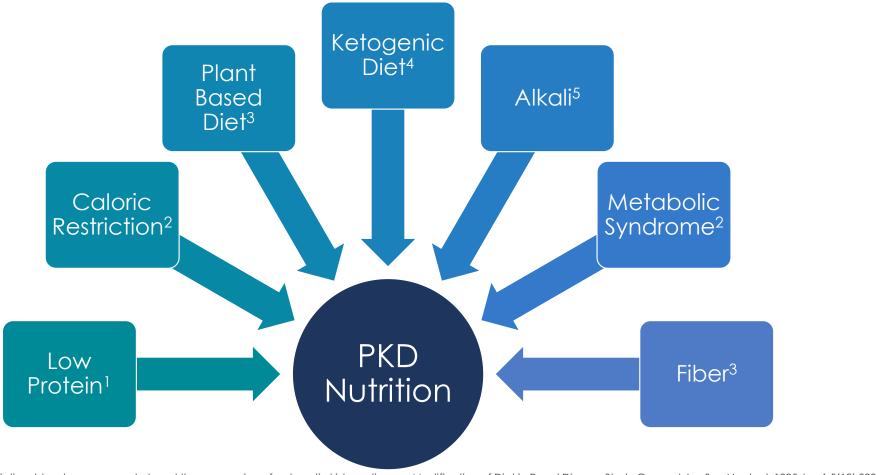
Dietary regimens including caloric restriction have shown promise in slowing ADPKD progression. Clinical trials currently underway promise to improve our understanding of the impact of diet on ADPKD.

- 1. Picca A. et al (2017). Clin Interv Aging. 12:1887-1902.
- 2. Hopp K, Catenacci VA, Dwivedi N, et al. iScience. 2021;25(1):103697. Published 2021 Dec 27.
- 3. Pickel L. et al (2022). Adv Nutr. 13:652-666



12

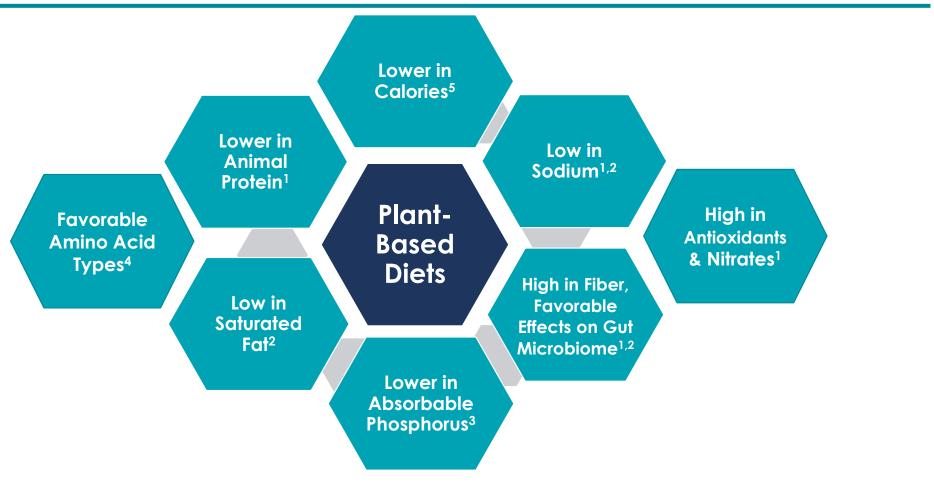
Hot Topics



1. Klahr S et al. Dietary protein restriction, blood pressure control, and the progression of polycystic kidney disease. Modification of Diet in Renal Disease Study Group. J Am Soc Nephrol. 1995 Jun 1;5(12):2037–47. 2. Pickel L eta;, Dietary Interventions in Autosomal Dominant Polycystic Kidney Disease, Advances in Nutrition, Volume 13, Issue 2, March 2022, Pages 652–666. 3. Joshi S, McMacken M, Kalantar-Zadeh K. Plant-Based Diets for Kidney Disease: A Guide for Clinicians. Am J Kidney Dis. 2021;77(2):287-296. 4. Bruen DM, Kingaard JJ, Munits M, Paimanta CS, Torres JA, Saville J, Weimbs T. Ren.Nu, a Dietary Program for Individuals with Autosomal-Dominant Polycystic Kidney Disease Implementing a Sustainable, Plant-Focused, Kidney-Safe, Ketogenic Approach with Avoidance of Renal Stressors. Kidney and Dialysis. 2022; 2(2):183-203. 5. Kalantar-Zadeh K, Fouque D. Nutritional management of chronic kidney disease. N Engl J Med. 2017;377(18):1765–76.



Some Potential Benefits of Plant-Based Diets



- 1. Joshi S, et al. Plant-based diets and hypertension. Am J Lifestyle Med. 2019, 14(4): 397-405.
- Cases A, et al. Vegetable-based diets for chronic kidney disease? It is time to reconsider. Nutrients 2019; 11: 1263.
- 3. Joshi S, Shah S, Kalantar-Zadeh K. Adequacy of plant-based proteins in chronic kidney disease. *J Renal Nutr.* 2019; 29 (2):112-117.
- 4. Tuttle KR, et al. Dietary amino acids and blood pressure: A cohort study of patients with cardiovascular disease. Am J Kidney Dis. 2012; 59(6):803-809.
- Turner-McGrievy et al. A plant-based diet for overweight and obesity prevention and treatment. JGC 2017; 14: 369-374



17

Examples and Descriptions of Various Plant-Based Diets

DASH Diet

• A specific dietary strategy designed to emulate the health-promoting effects of plant-based diet but allow for some animal-based foods, such as lean meat and low-fat dairy. Modern iterations have emphasized the unprocessed forms of fruits, vegetables, legumes, and grains (as opposed to fruit juices, refined grains, etc).

Mediterranean

•The Mediterranean diet typically emphasizes whole plant foods from that area with moderate consumption of lean meats, dairy, and seafood. Added sugars, processed foods, and red meat are generally excluded but healthy fats such as olive oil are included.

Flexitarian

• Also commonly referred to as a "semi-vegetarian." Represents a diet that emphasizes plant-based foods but may periodically include meat and other animal-based foods.

Vegetarian

• A diet that excludes meat (beef, pork, chicken) but may include fish, dairy, or eggs and often specified as a pescatarian, lactovegetarian, or ovovegetarian, respectively. Combinations of these are possible.

Whole-Food Plant Based

• A diet that emphasizes the consumption of whole plant-based foods as opposed to refined or processed plant foods (such as potato chips or white bread) while still typically avoiding animal-based foods. It is also the diet most widely promulgated by health professionals recommending a plant-based diet.

Vegan

• A diet and in some cases a lifestyle that avoids the use of products derived from animals.

PLADO

•Plant-dominant low-protein diet for patients with kidney disease: 0.6-0.8 g/kg per day of dietary protein with >50% from plant-based sources, dietary sodium < 4 g/d (<3 g/d if uncontrolled hypertension or edema), and dietary energy of 30-35 Cal per kilogram of ideal body weight per day.

1. Joshi S, McMacken M, Kalantar-Zadeh K. Plant-Based Diets for Kidney Disease: A Guide for Clinicians. Am J Kidney Dis. 2021;77(2):287-296.



A Plant-Focused Ketogenic Diet for Patients with Polycystic Kidney Disease

Design and Features

- Beta-test of 24 participants with Autosomal Dominant Polycystic Kidney Disease
- No control arm
- 12-week program
- Plant-based diet with some dairy, eggs, and fish
- Low-carb, high fat diet to promote ketone production
- Protein intake < 0.8 g/kg/day
- 2 servings of a medical food containing beta-hydroxybutyrate, citrate, electrolytes, and alkali

Key Outcomes

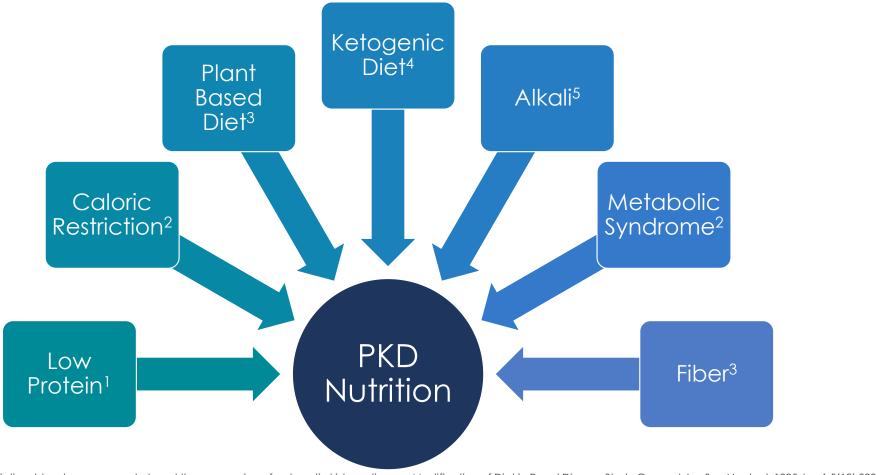
- 20 participants completed the beta test
- Favorable results in regard to satisfaction with the dietary program
- Average weight loss 8.9 lbs
- Fasting blood sugar decreased by 19 mg/dL
- BP improved (data not reported)
- Average creatinine decreased by 0.1 mg/dL and average eGFR increased by 4.4 mL/min/1.73m²

Initial studies of plant-focused ketogenic diets for PKD have been encouraging, but more research is needed

Bruen DM, Kingaard JJ, Munits M, Paimanta CS, Torres JA, Saville J, Weimbs T. Ren.Nu, a Dietary Program for Individuals with Autosomal-Dominant Polycystic Kidney Disease Implementing a Sustainable, Plant-Focused, Kidney-Safe, Ketogenic Approach with Avoidance of Renal Stressors. Kidney and Dialysis. 2022; 2(2):183-203.



Hot Topics



1. Klahr S et al. Dietary protein restriction, blood pressure control, and the progression of polycystic kidney disease. Modification of Diet in Renal Disease Study Group. J Am Soc Nephrol. 1995 Jun 1;5(12):2037–47. 2. Pickel L eta;, Dietary Interventions in Autosomal Dominant Polycystic Kidney Disease, Advances in Nutrition, Volume 13, Issue 2, March 2022, Pages 652–666. 3. Joshi S, McMacken M, Kalantar-Zadeh K. Plant-Based Diets for Kidney Disease: A Guide for Clinicians. Am J Kidney Dis. 2021;77(2):287-296. 4. Bruen DM, Kingaard JJ, Munits M, Paimanta CS, Torres JA, Saville J, Weimbs T. Ren.Nu, a Dietary Program for Individuals with Autosomal-Dominant Polycystic Kidney Disease Implementing a Sustainable, Plant-Focused, Kidney-Safe, Ketogenic Approach with Avoidance of Renal Stressors. Kidney and Dialysis. 2022; 2(2):183-203. 5. Kalantar-Zadeh K, Fouque D. Nutritional management of chronic kidney disease. N Engl J Med. 2017;377(18):1765–76.



Alkali

- Metabolic acidosis is associated with more rapid kidney disease progression and an increase in the overall risk of death¹
- In patients with PKD, low serum bicarbonate within the normal range is associated with worse kidney function and further eGFR decline²
- Plant-based foods have natural dietary alkali in the form of citrate and malate, which can be converted to bicarbonate. Natural alkali in these foods may facilitate the intracellular movement of potassium, especially in metabolic acidosis³
- Adjunctive alkali therapy can also be considered to mitigate acidosis in patients with chronic kidney disease¹

Alkali improves acidosis, and slows progression of chronic kidney disease⁴

1. Kalantar-Zadeh K, Fouque D. Nutritional management of chronic kidney disease. N Engl J Med. 2017;377(18):1765–76. 2. Charles J Blijdorp, David Severs, Usha M Musterd-Bhaggoe, Ronald T Gansevoort, Robert Zietse, Ewout J Hoorn, DIPAK Consortium, Serum bicarbonate is associated with kidney outcomes in autosomal dominant polycystic kidney disease, Nephrology Dialysis Transplantation, Volume 36, Issue 12, December 2021, Pages 2248–2255. 3. Joshi S, McMacken M, Kalantar-Zadeh K. Plant-Based Diets for Kidney Disease: A Guide for Clinicians. Am J Kidney Dis. 2021;77(2):287-296. 4. Kalantar-Zadeh K, Jafar TH, Nitsch D, Neuen BL, Perkovic V. Chronic kidney disease. Lancet. 2021;398(10302):786-802.



18

Obesity and Metabolic Syndrome

- In the HALT PKD trial, overweight body mass and particularly obesity were strong independent predictors of TKV growth and GFR decline in early-stage ADPKD¹
- There is increasing evidence that in ADPKD, a defective metabolism exists involving a dysregulated lipid and mitochondrial metabolism, and a defective glucose mechanism, similar to the Warburg effect in cancer²
- Abnormalities in metabolic regulation observed in the cystic kidney share common features in individuals with metabolic disease and associated with obesity, including alterations in nutrient signaling pathways and the activation of chronic inflammation³

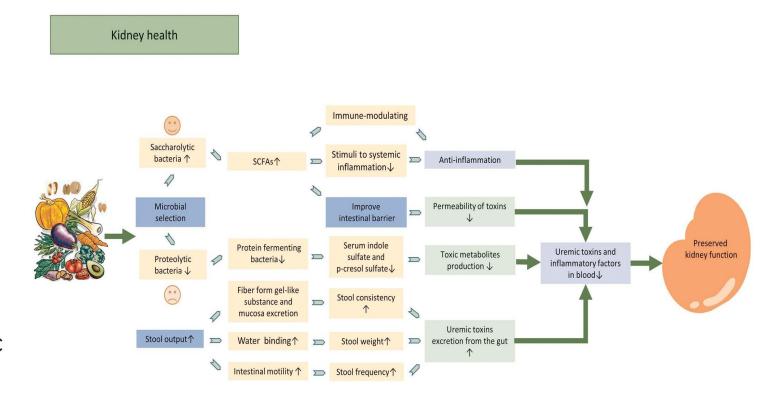
There is intriguing possibility to decrease cyst growth by influencing glucose metabolism by dietary interventions¹

1. Carriazo S, Perez-Gomez MV, Cordido A, García-González MA, Sanz AB, Ortiz A, Sanchez-Niño MD. Dietary Care for ADPKD Patients: Current Status and Future Directions. Nutrients. 2019 Jul 12;11(7):1576. 2. Meijer E, Gansevoort RT. Emerging non-pharmacological interventions in ADPKD: an update on dietary advices for clinical practice. Curr Opin Nephrol Hypertens. 2021;30(5):482-492. 3. Pickel L eta;, Dietary Interventions in Autosomal Dominant Polycystic Kidney Disease, Advances in Nutrition, Volume 13, Issue 2, March 2022, Pages 652–666.



Fiber

- High fiber intake has been associated with lower mortality and incidence of chronic diseases both in general and CKD populations, by decreasing inflammation²
- Fibers are emerging as nutritional components fundamental in promoting gut microbiota balance, regulating uremic toxins, and decreasing local and systemic inflammation suggesting a potential nephroprotective role²



1. Guobin Su, Xindong Qin, Changyuan Yang, Alice Sabatino, Jaimon T Kelly, Carla Maria Avesani, Juan Jesus Carrero, on behalf of the ERA European Renal Nutrition Working Group, an official body of the ERA, Fiber intake and health in people with chronic kidney disease, Clinical Kidney Journal, Volume 15, Issue 2, February 2022, Pages 213–225. 2. Carriazo S, Perez-Gomez MV, Cordido A, García-González MA, Sanz AB, Ortiz A, Sanchez-Niño MD. Dietary Care for ADPKD Patients: Current Status and Future Directions. Nutrients. 2019 Jul 12;11(7):1576.



Dietary Recommendations in PKD

Dietary Fiber⁵

25-38 g/day

Increase fruits and vegetables³

2-4 cups/d

Diet low in phosphorus^{1,4}

Avoid processed foods

Caloric Restriction to maintain a normal BMI^{1,2,4}

20-25 kg/m²

Consult a Renal Dietician

Plant-Based Diets^{3,4}

(e.g., DASH/PLADO Diet)

Moderate sodium restriction^{1,2,4}

2.3-3 g daily

Moderately enhanced hydration, spread out over 24 hours 1,2

Maintain urine osmolality ≤280 mOsm/kg

Lower protein diet^{1,2}

0.8-1.0 g/kg ideal body weight

Anticipated
Management
Recommendations

Keto Diet, Microbiome

PKD= polycystic kidney disease; BMI=body mass index.

1. Chebib FT et al. (2018). J Am Soc Nephrol. 29(10):2458-2470. 2. Meijer E, Gansevoort RT. Emerging non-pharmacological interventions in ADPKD: an update on dietary advices for clinical practice. Curr Opin Nephrol Hypertens. 2021;30(5):482-492. 3. Joshi S, McMacken M, Kalantar-Zadeh K. Plant-Based Diets for Kidney Disease: A Guide for Clinicians. Am J Kidney Dis. 2021;77(2):287-296. 4. Kalantar-Zadeh K, Jafar TH, Nitsch D, Neuen BL, Perkovic V. Chronic kidney disease. Lancet. 2021;398(10302):786-802. 5. Carriazo S, Perez-Gomez MV, Cordido A, García-González MA, Sanz AB, Ortiz A, Sanchez-Niño MD. Dietary Care for ADPKD Patients: Current Status and Future Directions. Nutrients. 2019 Jul 12;11(7):1576.



Putting Plant Foods into Practice: Strategies to Implement

"Meet patients where they are at" Start with small changes Provide recipes, meal and snack examples Simplify



Interested in Learning More? Check Out These Resources

- <u>NephU Kidney Kitchen Creations Cookbook</u>: The NephU Kitchen Creations for Kidney Health Cookbook from the NephChef provides an assortment of kidney-friendly recipes ranging from appetizers to entrées to kidney-healthy desserts, that are rich in flavor and meet several nutritional guidelines. Download your copy today.
- <u>NephU Nutrition & The NephChefTM</u>: NephU provides a platform to emphasize the importance of proper nutrition and diet for patients with acute and chronic kidney diseases. The NephU Nutrition & The NephChefTM contains evidence-based information, best practices, and insights to help with shared decision-making.
- <u>www.kidney.org/atoz/content/plant-based</u>: An informative series of webpages created by the National Kidney Foundation to help educate patients and physicians alike on plant-based diets for the prevention and treatment of kidney disease, its causes, and its complications
- <u>www.nutritionfacts.org</u>: A not-for-profit website offering evidence-based information in the form of videos and articles on timely aspects of plant-based nutrition and other dietary issues
- <u>www.PCRM.org</u>: A not-for-profit organization focused on improving patient and societal health through the consumption of plant-based diets, offering free physician education, including CME, and patient education materials, such as starter kits and brochures
- https://vegetariannutrition.net/: The consumer/patient website of the Vegetarian Nutrition Dietetic Practice Group, a dietetic practice group of the Academy of Nutrition and Dietetics, offering patient-level information on plant-based diets
- <u>www.vndpg.org</u>: The professional website of the Vegetarian Nutrition Dietetic Practice Group, a dietetic practice group of the Academy of Nutrition and Dietetics, offering professional information for health care professionals, including registered dietitians



23

^{1.} Joshi S, McMacken M, Kalantar-Zadeh K. Plant-Based Diets for Kidney Disease: A Guide for Clinicians. Am J Kidney Dis. 2021;77(2):287-296.