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Title page

Diet and Polycystic Kidney Disease: Nutrients, foods, dietary patterns and implications for practice

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Abstract

Polycystic Kidney Disease (PKD) is a chronic, progressive hereditary condition characterized by abnormal development and growth of cysts in the kidneys and other organs. There is increasing interest in exploring whether dietary modifications may prevent or retard the disease course in people with PKD. While vasopressin receptor agonists have emerged as a novel drug treatment in advancing care for people with PKD, several recent landmark trials and clinical discoveries have also provided new insights into potential dietary related therapeutic strategies. In this review, we summarise the current evidence pertaining to nutrients, foods, dietary patterns and cyst growth and progression of PKD. We also describe existing evidence-based dietary care for people with PKD and outline the potential implications for advancing evidence-based dietary interventions.

Key words

Polycystic Kidney Disease, diet, food, dietary patterns, nutrients, nutrition

Background

Polycystic kidney disease (PKD) is the most common inherited cause of kidney failure globally [1]. The condition is caused by mutations in the PKD1 and PKD 2 gene which result in abnormal prolific irreversible growth of fluid filled cysts in the kidney [2]. Autosomal dominant PKD accounts for up to 10% of patients undergoing kidney replacement therapy[3]. The ongoing growth of cysts causes pain as well as damage to the architecture of the kidney parenchyma leading to kidney failure [4].

Several physiological mechanisms are disrupted in PKD [5]. One of these is in the ability to concentrate urine [6]. With infiltration of the cysts in the kidney parenchyma, the osmotic gradient in the kidney cortex and medulla is disrupted and polyuria develops. In addition, there is increased vasopressin secretion in response to dehydration, with high levels of vasopressin shown to promote cyst growth [7]. An increase in water consumption has been a longstanding recommendation to suppress vasopressin secretion [8]. However, further clinical trials are required to confirm its efficacy in slowing down clinical progression of PKD. More recently, experimental models have observed altered glucose metabolism with a preference for aerobic glycolysis in cyst cells[9,10]. Other distinct metabolic alterations identified in PKD include impaired fatty acid metabolism and mitochondrial β oxidation[11,12]. These metabolic derangements may form potential targets for dietary intervention in PKD.

The vasopressin receptor agonist (V2RA) Tolvaptan, is an approved drug treatment for PKD and has been shown to inhibit cyst growth in experimental data and demonstrated to be effective in slowing the decline of kidney function in PKD [13]. However, its use is associated

with significant aquaretic and other side effects [14] leading to a high discontinuation rate [15]. Further interventions to slow PKD progression are needed.

Lifestyle modification including the manipulation of diet and fluid intake is therefore of great interest to people with PKD [16-18], health professionals [19] and the research community [20,21]. Several reviews have been published in recent years but these have focused on specific elements such as water [22], specific diets such as energy restriction [23] or were published [21,24,25] prior to the release of results from landmark trials such as the PREVENT-ADPKD trial [26]. Given the close link between nutrients, foods and dietary patterns, this review aimed to provide an overview of the current evidence on nutrients, foods, dietary patterns and PKD and describe the implications for clinical practice as well as areas for future research.

Nutrients

Sodium

Excessive intake of sodium has been associated with accelerated cyst growth and hypertension in individuals with PKD. In a post hoc analysis of the HALT PKD study[27], Torres et al reported that each 18 mmol of urinary sodium excretion was associated with a faster decline in eGFR (-0.09ml/min/1.73m^2/ year) and more rapid kidney growth (0.43%/year Total Kidney Volume (TKV) growth) demonstrating the benefit of sodium restriction. However, despite regular support for up to 8 years with the goal of reduced sodium intake (~100mmol salt per day), the mean urinary salt excretion (reflecting dietary intake) was not achieved (mean 178mmol/day) [27]. This underscores the challenge of dietary interventions to reduce sodium intake.

The exact mechanism by which sodium accelerates cyst growth in PKD was explored by Kramers et al [28]. Analysis of an observational cohort of 589 individuals with ADPKD used mediation analyses to determine that the effect on disease progression was primarily due to a salt induced rise in circulating vasopressin, measured by plasma copeptin as a surrogate marker. The authors eloquently translated this into practical terms and suggested that a reduction in salt intake to 5g (2000mg / 90 mmol sodium) per day could postpone dialysis commencement by 4 years but this would require further evaluation in a randomized trial fashion. In a second observational cohort [29], a single session of dietary counselling on sodium restriction was associated with an improvement in tolerance to V2RA medications by reducing polyuria, one of the most bothersome side effects of the medication. This led to the suggestion to consider dietary counselling of a reduced sodium diet in patients treated with V2RAs. A summary of the findings and implications from the small number of human studies exploring dietary sodium intake in PKD are shown in Table 1.

[insert Table 1 here]

Protein

Excessive protein intake in the CKD population is associated with increased glomerular hyperfiltration and worse proteinuria [36]. Higher levels of dietary protein also stimulate renin release, which increases angiotensinogen and raises blood pressure [25]. However, there is limited human evidence as to how or if protein may influence cyst growth. A 2 year follow up of the MDRD study in 200 participants with PKD and GFR of 25-55ml/min per 1.73m^2 found low protein (0.58g/kg/day) diet had no benefit in slowing the rate of decline in GFR

compared to normal protein diet (1.3g/kg/day) [37]. Instead, blood pressure and proteinuria predicted faster decline in kidney function. Similarly, a retrospective analysis of 109 patients with ADPKD also found no effect of lower protein intake (mean intake 0.87g/kg/day) on progression to kidney failure [38], and a 4-year follow-up of patients with ADPKD demonstrated no association between protein intake and annual change in eGFR[30].

Some work in non-orthologous animal models of PKD have demonstrated that protein type may be important. For example, plant proteins (soy) as compared to animal protein (casein) may exert beneficial effects on PKD progression as reviewed in work by Pickel et al [23]. Rats fed soy protein had reduced kidney weight[39-41], cyst volume[39,40,42], and kidney cyst growth[39]. These inhibitory effects were correlated to lower Insulin growth factor -1 (IGF) production [39], as well reduced inflammation due to improvements in long chain polyunsaturated fatty acid (PUFA) intake [41,43]. However, any evidence of benefit from plant protein failed to replicate in multiple orthologous rodent models [23,44]. Moreover, the role of protein source has not been tested in human dietary intervention studies.

Fat

Similar to protein source, there were suggestions from studies in non-orthologous rodent PKD models that the source of dietary fat may impact PKD progression, with dietary long chain PUFA intake positively influencing all stages of cyst pathogenesis including epithelial cell proliferation, oxidation, inflammation, fibrosis and cyst area [25,45-48] (Figure 1). This literature has been reviewed elsewhere [23]. Importantly, results did not replicate in orthologous rodent models [44]. In the only human intervention study to date, 20 Japanese adults with PKD were randomised to supplementation with 2.4g/day of eicosapentanoic acid (EPA) for 2

years or without supplementation [49]. Compared to patients not given supplementation, there was no impact on kidney volume or rate of kidney function decline with EPA supplementation over 2-years. However, the study population was small and did not report dietary intake, which may have seen a higher EPA intake than in Western countries given the high intake of fish and seafood in the Japanese diet. Given the paucity of PKD specific dietary intervention studies, it seems prudent to recommend intake of foods rich in long chain polyunsaturated fats, and the ratio of fat in the diet of PKD subjects according to that for the healthy population (that is a suggested dietary intake of long chain polyunsaturated fats of 610mg for men and 430mg for women, and less than 30% calories from saturated fat)[50].

[insert figure 1 here]

Vitamin D

Observational data suggests an inverse relationship between serum 25 hydroxyvitamin D levels and vitamin D receptor expression with total kidney volume [51]. Furthermore, vitamin D deficiency in rat models of PKD had inhibitory effects on kidney enlargement and adverse effects on interstitial inflammation [52]. To explore this relationship, Vendramini and colleagues[53] randomized 42 vitamin D deficient patients with PKD to receive either monthly cholecalciferol or placebo for 3 months but no difference was found in inflammation, vitamin D receptor expression or blood pressure. Further large-scale human studies are needed to evaluate the role if any of vitamin D supplementation in ADPKD.

Caffeine

Animal models of ADPKD demonstrated that cyclic adenosine monophosphate (cAMP) promotes growth of human polycystic kidney epithelial cells [54]. A murine model of ADPKD extended this observation and found that caffeine may stimulate the production of cAMP[55]. However, there are so far no randomised trials testing the effects of reducing caffeine intake in humans with ADPKD. A small case control study in 102 adults with ADPKD did not find any association between caffeine intake and kidney volume [56]. Instead, kidney volume was associated with hypertension and the stage of CKD. Given the uncertainty, it would be reasonable to follow current guidance on caffeine intake for healthy population [19] in ADPKD, i.e., 200mg caffeine daily equivalent to 2 cups coffee / 4 cups of tea per day.

Oxalate

Nephrolithiasis is common in ADPKD, with a reported prevalence of up to 58% in some studies [57,58]. The most common composition of stones are uric acid and/or calcium oxalate [59]. Animal studies have shown that oxalate stones are associated with cyst formation[60]. Several factors may contribute to the high prevalence of kidney stones in ADPKD including anatomical (such as cyst obstruction, or dilated lumens causing urine stasis) and metabolic derangements (low urine citrate[61], low urine pH and hyperuricemia). Urinary citrate is an inhibitor of calcium oxalate crystal formation[60]. Treatments to increase urinary citrate could be achieved via dietary means. Daily intake of lemon or lime juice would result in enhanced urinary citrate excretion in addition to providing additional variety in fluid intake for people with PKD [62]. Approximately 60mEq of potassium citrate is provided in 85ml lemon or lime juice [62,63]. Advice to avoid high intake of vitamin C rich foods (juices, smoothies) and supplements is also recommended as ascorbic acid is the precursor to oxalate.

Foods

Water

There is a clear relationship between cAMP and stimulation of epithelial cell proliferation and increased cyst fluid accumulation in PKD[64]. Vasopressin stimulates cAMP production in the collecting ducts and the distal nephron, a common site for cyst formation [54]. Maintaining fluid intake that is adequate to reduce vasopressin secretion was recently tested in the PREVENT-ADPKD trial[26]. This trial tested ad libitum intake vs individualised intake to reduce urine osmolality to ≤270mOSm/kg for 3 years. Despite intensive, structured, evidence-based support, both groups had similar outcomes for total kidney volume and kidney growth although only a proportion (52.3%) in the intervention group successfully maintained the target urine osmolality. The authors concluded that detailed self-monitoring in enhanced fluid intake was challenging to persevere with over 3 years. A higher fluid intake may still be beneficial in ADPKD patients who can excrete the extra volume of fluid (usually GFR >60ml/min)[64] to reduce the formation of kidney stones and the incidence of urinary tract infections. Water is the preferred fluid as it is low in kilojoules and electrolyte free.

Turmeric and Stevia

Turmeric is a rhizomatous plant from the ginger family, and has been used as a traditional medicine for many years[65]. The active ingredient is curcumin, and there is in-vivo evidence that curcumin inhibits cyst production[66]. There are ongoing trials using curcumin to manage vascular health in chronic and polycystic kidney disease (NCT03475017; NCT03223883; and NCT02494141) On the other hand, Stevia is a plant from the chrysanthemum family that contains steviol glycosides. Stevia may be used as an alternative to sugar but without calories as the body does not metabolise the glycosides[67]. Murine evidence suggested that renal cyst

growth is retarded with stevia ingestion [68-70]. However, neither have been tested in humans with PKD, so their value beyond culinary purposes is unknown.

Dietary patterns

There are significant challenges translating nutritional science findings from the basic sciences to the bedside [71]. This is in part because people eat food and not isolated nutrients. The interconnected nature of nutrients within a food matrix is also highly complex, and may influence the bioavailability of nutrients and biological responses[72]. Given these complexities, it is important to examine the evidence about known dietary patterns in the PKD population.

Low acid diets

Taylor et al conducted a small pilot study of a low osmolar low acid diet in 20 adults with PKD with a mean eGFR 84ml/min/1.73m^2 [73]. The diet was designed to halve endogenous acid production and was low in urea (protein 0.8-1.0g/kg body weight per day), sodium (1-1.5mEq/kg), dietary acids and a high-water intake (urine osmolality ≤285mosm/kg water per day). The premise of the intervention was based on evidence in animal studies showing that increased urine acid excretion accelerates cyst growth [74]. Detailed instruction was provided by a dietitian and dietary points were awarded to specific foods, including a target of consuming 40 points per day from base inducing fruits and vegetables (such as raisins, apricots, kiwifruit, spinach, cauliflower, zucchini). The relatively complex dietary intervention resulted in a tripling of fruit and vegetable intake, and significant improvements in protein, fibre, sodium, dietary acid load, and urine osmolality. However due to the short-term nature of the intervention (4 weeks) it is unclear if this dietary pattern is sustainable and

effective in the longer term and the impact on kidney cyst volume was not measured. In people with PKD, this approach of increasing fruit and vegetable intake, and reducing potential renal acid load is consistent with evidence-based nutrition care for CKD and is unlikely to harmful [75] - but whether it may ameliorate growth of cysts or PKD progression require further evaluation. Caution may be necessary for those with advanced CKD or undertaking dialysis where potassium control and increased protein intake may be required.

High fruit and vegetable / Mediterranean style diets

The 2020 Kidney Disease Outcomes Quality Initiative guidelines for nutrition management in CKD recommended a dietary pattern high in fruit and vegetables in people with CKD [75] including a Mediterranean diet for those with CKD stage 1-5 not on dialysis or post-transplant. This was based on epidemiological evidence that dietary patterns high in fruit and vegetables are associated with reduced mortality and morbidity in the CKD population [76]. So far, only a small cross-sectional study from Korea has examined DASH (Dietary Approaches to Stop Hypertension) and Mediterranean style patterns in 68 ADPKD patients[77]. Those who followed a DASH style of eating (that is a diet high in vegetables, legumes, fruit, nuts, wholegrains and low-fat dairy) had a reduced risk of low muscle strength and sarcopenia compared to those adopting a Mediterranean style eating pattern (high in vegetables, legumes, fruit, nuts, wholegrains, fish and monounsaturated oils). However, cyst growth and kidney volume were not examined.

Caloric restriction

Animal studies have found that a reduction in calorie intake may inhibit cyst growth and disease progression [78,79]. Kipp et al[78] and Warner et al[79] found that reducing calories by up to

40% could be a potential treatment to slow disease progression in humans with ADPKD. Numerous possible mechanisms for this effect have been proposed, notably inhibition of the mTOR signalling pathway, and are reviewed in detail in Pickel et al [23]. Alterations in metabolic programming are also observed in animal models of PKD including defective glucose metabolism, dysregulated lipid and amino acid metabolism, impaired autophagy and mitochondrial dysfunction[9]. For an excellent overview of evidence on metabolic reprogramming and dietary interventions in PKD readers are referred to Pickel et al [23]. This is also outlined in Figure 2. Human studies exploring daily caloric restriction in PKD (NCT04907799) are currently underway or are completed but not yet published (NCT03342742). These include strategies to test time restricted feeding to studies examining reduction in energy intake by >30%. These are shown in more detail in Table 2. Advice to patients to adopt this dietary pattern is premature, and not appropriate for those who have a healthy weight.

Intermittent fasting and time restricted diets

While caloric restriction shows promise to reduce cyst volume, fibrosis and inflammation in animal studies[78,79], examination of other dietary approaches to reduce cell proliferation pathways and which may be more tolerable and safer than pharmacological strategies is underway. These include intermittent fasting (NCT03342742, Table 2) and time restricted feeding (NCT04534985, Table 2). Both dietary strategies may theoretically reduce caloric intake, though their mechanism of action may not rely on caloric restriction [23]. For example, time restricted diets limit eating to a specific time such as an 8-hour window, and intermittent fasting involves fasting for specific meals or alternate days. Interestingly, observations of patients with ADPKD who follow time restricted diets during Ramadan showed a reduction

in proteinuria and no negative impact on kidney function [80]. Preclinical evidence showed that time restricted feeding compared to ad libitum feeding reduced kidney weight, cyst size and epithelial proliferation[81] in animal models.

Ketogenic diets

Based on the beneficial effects on cyst growth observed from caloric restriction, Torres et al [81] identified that a key mechanism driving these improvements was ketosis. Cyst cells exhibit defective glucose metabolism and are reliant on aerobic glycolysis and glucose for proliferation[82]. Traditional ketogenic diets are high in fat and low in carbohydrates. The composition of the diet therefore deprives the body of glucose and theoretically could result in lower cell proliferation and higher cell death. Beyond glucose deprivation, multiple interacting mechanisms may contribute to the effect of the ketogenic diet on ADPKD progression, many of which overlap with caloric restriction or intermittent fasting [23]. A clinical trial of ketogenic diets in ADPKD is underway (NCT04680780, Table 2), and commercial plant based ketogenic diet programs have been developed in the United States [83]. No human data yet exists on the impact of ketogenic diets on cyst growth or disease progression.

[insert Table 2 here]

So far, 3 case series have been published [83-85] describing the feasibility of ketogenic diets in ADPKD. The first provided survey feedback on the experiences of 131 patients who had self-initiated ketogenic diets [84]. The second case series reported feedback from the Beta

version of the Ren.Nu commercial program in 24 participants [83]. This remote, dietitian supervised 16-week program which advocates a plant-based low carbohydrate high fat diet that is high in fluid, and low in oxalate, phosphate, sodium and purines. In addition, participants take one sachet of KetoCitra supplement per day to provide exogenous β-hydroxy butyrate (BHB) and citrate. The supplemental BHB provides an energy substrate as well as anti-inflammatory effects [81]. Adverse effects reported include fatigue, hunger, constipation and 'keto flu'. Adherence in the two case series was reported to be 50%[84] and 92% [83] , with issues such as ketone level tracking, cost, eating out and time taken to prepare meals as barriers to sustainability. The third case series tested the feasibility of a 3-day water fast (n=5) or 14-day ketogenic diet (n=5). All but one participant successfully reached measurable ketosis and rated the intervention as feasible [85]. While promising, there is still limited human evidence of efficacy to recommend widespread adoption of these dietary patterns in PKD[86]. Further randomized controlled trials are needed to evaluate the efficacy of ketogenic diets in retarding progression of ADPKD Potential side-effects of ketogenic diet include increased kidney stone formation and cardiovascular risk due to increased hypercholesterolemia.

Implications for practice

While dietary modification is of great interest to people with PKD [16], very limited randomized controlled studies have investigated the efficacy and practicalities of various aspects of dietary intervention specifically in patients with PKD. Social listening analysis [16] identified that a strong desire by people with PKD for practical and specific dietary information and a desire for assistance to navigate conflicting information about diet.

The patient perspective

Evaluation of the Re.Nu program (a plant focused ketogenic diet) reported that when provided with weekly support for 12 weeks, participants expressed a high degree of satisfaction with the new eating pattern and enjoyment of food [83]. However, data on the sustainability of the program as well as clinical outcomes are lacking. In another qualitative study, 12 participants who undertook a low osmolar, low acid dietary intervention [87] found that tracking nutrients was challenging and tedious. Eating out was always problematic, with a complex dietary prescription acting as a barrier to social interactions.

It may be disappointing for people with PKD when they are unable to tolerate or are not suitable to take V2RA therapy. In these instances, people with PKD may choose to modify their diet. However, dietary modification must be sustainable for patients for many years if the aim is to, at least slow, if not prevent further kidney function decline. People with PKD require dietary advice to be readily accessible, available and evidence based. Healthy dietary habits are essential for all people with kidney disease. We believe that the earlier children and young people with PKD are introduced to good PKD dietary practices the better their PKD course will be. We also know from our experience that people with PKD want specific advice about foods they can enjoy and whether there are foods they should avoid. Whether there are specific dietary components that could impact cyst growth and progression in PKD needs further evaluation and trials. In the interim, guidance around the suitability of popular diets is recommended, along with plain language explanations of the pathophysiology of their disease.

The answer to the question "what is evidence-based dietary advice for people with PKD?" is summarised in Table 3, below. Currently the recommended diet consists of eating a variety of fruits and vegetables combined with an intake of protein that is appropriate for the stage of CKD; with an emphasis on including some plant-based proteins for good health. The long-term diet should contain adequate water intake and be as low in salt as possible. It is important to advise patients to drink an appropriate amount of fluid for the stage of kidney disease. Further studies examining urine osmolarity and cyst growth are needed to confirm these inferences.

[insert Table 3 here]

Summary and Conclusions

Understanding how diet and lifestyle changes may affect or alter the course of PKD is a research, clinical and patient priority. Currently several dietary approaches including time restricted feeding, ketogenic and fasting regimens are under investigations by randomized controlled trials. However, the benefits of each are yet to be proven and caution is required before widespread use is recommended. Before more quality evidence is available, people with PKD should be advised to follow the dietary recommendations and receive dietary counselling as for patients with CKD, encourage a diet with adequate variety of fruits and vegetables, with protein intake according to the stage of CKD, and with salt restriction. Fluid recommendations are individualised according to the stage of CKD, but water is the preferred choice of fluid at all stages. Other nutrients, foods, and dietary patterns are not supported by sufficient evidence at this stage, though investigations are underway. Further dietary interventions appropriate for the PKD community require evaluation.

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References

1. Yu ASL, El-Ters M, Winklhofer FT. Clinical Trials in Autosomal Dominant Polycystic Kidney Disease. In: Li X, ed. *Polycystic Kidney Disease*. Codon Publications; 2015.
2. Müller R-U, Haas CS, Sayer JA. Practical approaches to the management of autosomal dominant polycystic kidney disease patients in the era of tolvaptan. *Clinical kidney journal*. 2018;11(1):62-69. doi:10.1093/ckj/sfx071
3. Ong ACM, Devuyst O, Knebelmann B, Walz G. Autosomal dominant polycystic kidney disease: the changing face of clinical management. *The Lancet*. 2015/05/16/ 2015;385(9981):1993-2002. doi:https://doi.org/10.1016/S0140-6736(15)60907-2
4. Saini AK, Saini R, Singh S. Autosomal dominant polycystic kidney disease and pioglitazone for its therapy: a comprehensive review with an emphasis on the molecular pathogenesis and pharmacological aspects. *Molecular medicine (Cambridge, Mass)*. 2020;26(1):128. doi:10.1186/s10020-020-00246-3
5. Bergmann C, Guay-Woodford LM, Harris PC, Horie S, Peters DJM, Torres VE. Polycystic kidney disease. *Nature Reviews Disease Primers*. 2018/12/06 2018;4(1):50. doi:10.1038/s41572-018-0047-y
6. van Gastel MDA, Torres VE. Polycystic Kidney Disease and the Vasopressin Pathway. *Annals of nutrition & metabolism*. 2017;70 Suppl 1:43-50. doi:10.1159/000463063
7. Bichet DG. A defect in vasopressin secretion in autosomal dominant polycystic kidney disease. *Kidney International*. 2012;82(10):1051-1053. doi:10.1038/ki.2012.271
8. Chapman AB, Devuyst O, Eckardt KU, et al. *Autosomal-dominant polycystic kidney disease (ADPKD): Executive summary from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference*.
9. Nowak KL, Hopp K. Metabolic Reprogramming in Autosomal Dominant Polycystic Kidney Disease: Evidence and Therapeutic Potential. *Clinical journal of the American Society of Nephrology : CJASN*. 2020;15(4):577-584. doi:10.2215/CJN.13291019
10. Rowe I, Chiaravalli M, Mannella V, et al. Defective glucose metabolism in polycystic kidney disease identifies a new therapeutic strategy. *Nat Med*. Apr 2013;19(4):488-93. doi:10.1038/nm.3092
11. Menezes LF, Lin CC, Zhou F, Germino GG. Fatty Acid Oxidation is Impaired in An Orthologous Mouse Model of Autosomal Dominant Polycystic Kidney Disease. *EBioMedicine*. Mar 2016;5:183-92. doi:10.1016/j.ebiom.2016.01.027
12. Padovano V, Podrini C, Boletta A, Caplan MJ. Metabolism and mitochondria in polycystic kidney disease research and therapy. *Nat Rev Nephrol*. Nov 2018;14(11):678-687. doi:10.1038/s41581-018-0051-1
13. Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease. 2012;367(25):2407-2418. doi:10.1056/NEJMoa1205511
14. Bellos I. Safety Profile of Tolvaptan in the Treatment of Autosomal Dominant Polycystic Kidney Disease. *Ther Clin Risk Manag*. 2021;17:649-656. doi:10.2147/tcrm.S286952
15. Watkins PB, Lewis JH, Kaplowitz N, et al. Clinical Pattern of Tolvaptan-Associated Liver Injury in Subjects with Autosomal Dominant Polycystic Kidney Disease: Analysis of Clinical Trials Database. *Drug Safety*. 2015;38(11):1103-1113. doi:10.1007/s40264-015-0327-3

16. Ma T, Lambert K. What are the information needs and concerns of individuals with Polycystic Kidney Disease? Results of an online survey using Facebook and social listening analysis. *BMC nephrology*. 2021;22(1):1-12. doi:10.1186/s12882-021-02472-1
17. Tran W-C, Huynh D, Chan T, Chesla CA, Park M. Understanding barriers to medication, dietary, and lifestyle treatments prescribed in polycystic kidney disease. *BMC nephrology*. 2017;18(1):214. doi:10.1186/s12882-017-0641-3
18. Harris T, Sandford R, De Coninck B, et al. *European ADPKD Forum multidisciplinary position statement on autosomal dominant polycystic kidney disease care: European ADPKD Forum and Multispecialist Roundtable participants*. 2018.
19. Campbell KL, Rangan GK, Lopez-Vargas P, Tong A. KHA-CARI Autosomal Dominant Polycystic Kidney Disease Guideline: Diet and Lifestyle Management. *Seminars in nephrology*. 2015;35(6):572. doi:10.1016/j.semnephrol.2015.10.008
20. Tong A, Tunnicliffe DJ, Lopez-Vargas P, et al. Identifying and integrating consumer perspectives in clinical practice guidelines on autosomal-dominant polycystic kidney disease. *Nephrology (Carlton, Vic)*. Feb 2016;21(2):122-32. doi:10.1111/nep.12579
21. Meijer E, Gansevoort RT. Emerging non-pharmacological interventions in ADPKD: an update on dietary advices for clinical practice. *Current opinion in nephrology and hypertension*. Sep 1 2021;30(5):482-492. doi:10.1097/mnh.0000000000000734
22. Wang CJ, Grantham JJ, Wetmore JB. The medicinal use of water in renal disease. *Kidney Int*. Jul 2013;84(1):45-53. doi:10.1038/ki.2013.23
23. Pickel L, Iliuta I-A, Scholey J, Pei Y, Sung H-K. Dietary Interventions in Autosomal Dominant Polycystic Kidney Disease. *Advances in nutrition (Bethesda, Md)*. 2021;doi:10.1093/advances/nmab131
24. Carriazo S, Perez-Gomez MV, Cordido A, et al. Dietary Care for ADPKD Patients: Current Status and Future Directions. *Nutrients*. Jul 12 2019;11(7)doi:10.3390/nu11071576
25. Maditz KH, Gigliotti JC, Tou JC. Evidence for a role of proteins, lipids, and phytochemicals in the prevention of polycystic kidney disease progression and severity. *Nutrition reviews*. 2013;71(12):802-814. doi:10.1111/nure.12085
26. Rangan GK, Wong ATY, Munt A, et al. Prescribed Water Intake in Autosomal Dominant Polycystic Kidney Disease. *NEJM Evidence*. 2022;1(1)doi:10.1056/evidoa2100021
27. Torres VE, Abebe KZ, Schrier RW, et al. Dietary salt restriction is beneficial to the management of autosomal dominant polycystic kidney disease. *Kidney international*. 2017;91(2):493-500. doi:10.1016/j.kint.2016.10.018
28. 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*. Oct 2020;98(4):989-998. doi:10.1016/j.kint.2020.04.053
29. Côté G, Asselin-Thompstone L, Mac-Way F, et al. Sodium and urea excretion as determinants of urine output in autosomal dominant polycystic kidney disease patients on V2 receptor antagonists: impact of dietary intervention. *International urology and nephrology*. Feb 2020;52(2):343-349. doi:10.1007/s11255-020-02384-3
30. Kramers BJ, Koorevaar IW, Drenth JP, et al. Salt, but not protein intake, is associated with accelerated disease progression in autosomal dominant polycystic kidney disease. 2020;98(4):989-998.
31. Torres VE, Abebe KZ, Schrier RW, et al. Dietary salt restriction is beneficial to the management of autosomal dominant polycystic kidney disease. Journal Article; Randomized Controlled Trial; Research Support, N.I.H., Extramural; Research Support, Non-U.S. Gov't. *Kidney international*. 2017;91(2):493-500. doi:10.1016/j.kint.2016.10.018

32. Chapman AB, Torres VE, Perrone RD, et al. The HALT Polycystic Kidney Disease Trials: Design and Implementation. *Clinical Journal of the American Society of Nephrology*. 2010;5(1):102-109. doi:10.2215/cjn.04310709
33. Torres VE, Grantham JJ, Chapman AB, et al. Potentially Modifiable Factors Affecting the Progression of Autosomal Dominant Polycystic Kidney Disease. *Clinical Journal of the American Society of Nephrology*. 2011;6(3):640-647. doi:10.2215/cjn.03250410
34. Doulton TW, Saggar-Malik AK, He FJ, et al. The effect of sodium and angiotensin-converting enzyme inhibition on the classic circulating renin-angiotensin system in autosomal-dominant polycystic kidney disease patients. *Journal of hypertension*. May 2006;24(5):939-45. doi:10.1097/01.hjh.0000222765.30348.0d
35. Schmid M, Mann JF, Stein G, et al. Natriuresis-pressure relationship in polycystic kidney disease. *Journal of hypertension*. 1990;8(3):277-283.
36. Kalantar-Zadeh K, Fouque D. Nutritional Management of Chronic Kidney Disease. *The New England journal of medicine*. Nov 2 2017;377(18):1765-1776. doi:10.1056/NEJMra1700312
37. Klahr S, Breyer JA, Beck GJ, et al. Dietary protein restriction, blood pressure control, and the progression of polycystic kidney disease. Modification of Diet in Renal Disease Study Group. *Journal of the American Society of Nephrology : JASN*. 1995;5(12):2037-2047. doi:10.1681/ASN.V5122037
38. Choukroun G, Itakura Y, Albouze G, et al. Factors influencing progression of renal failure in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol*. Dec 1995;6(6):1634-42. doi:10.1681/asn.V661634
39. Aukema HM, Housini I. Dietary soy protein effects on disease and IGF-I in male and female Han:SPRD-cy rats. *Kidney international*. 2001;59(1):52-61. doi:10.1046/j.1523-1755.2001.00465.x
40. Aukema HM, Gauthier J, Roy M, Jia Y, Li H, Aluko RE. Distinctive effects of plant protein sources on renal disease progression and associated cardiac hypertrophy in experimental kidney disease. *Molecular nutrition & food research*. 2011;55(7):1044-1051. doi:10.1002/mnfr.201000558
41. Fair DE, Ogborn MR, Weiler HA, et al. Dietary soy protein attenuates renal disease progression after 1 and 3 weeks in Han:SPRD-cy weanling rats. *The Journal of nutrition*. Jun 2004;134(6):1504-7. doi:10.1093/jn/134.6.1504
42. Ogborn MR, Nitschmann E, Weiler HA, Bankovic-Calic N. Modification of polycystic kidney disease and fatty acid status by soy protein diet. *Kidney international*. 2000;57(1):159-166. doi:10.1046/j.1523-1755.2000.00835.x
43. Peng CY-C, Sankaran D, Ogborn MR, Aukema HM. Dietary soy protein selectively reduces renal prostanoids and cyclooxygenases in polycystic kidney disease. *Experimental biology and medicine (Maywood, NJ)*. 2009;234(7):737-743. doi:10.3181/0811-RM-315
44. Yamaguchi T, Devassy JG, Monirujjaman M, Gabbs M, Aukema HM. Lack of Benefit of Early Intervention with Dietary Flax and Fish Oil and Soy Protein in Orthologous Rodent Models of Human Hereditary Polycystic Kidney Disease. *PloS one*. 2016;11(5):e0155790. doi:10.1371/journal.pone.0155790
45. Ogborn MR, Nitschmann E, Bankovic-Calic N, Weiler HA, Aukema H. Dietary flax oil reduces renal injury, oxidized LDL content, and tissue n-6/n-3 FA ratio in experimental polycystic kidney disease. *Lipids*. 2002;37(11):1059-1065. doi:10.1007/s11745-002-1001-4
46. Ogborn MR, Nitschmann E, Bankovic-Calic N, Weiler HA, Aukema HM. Effects of flaxseed derivatives in experimental polycystic kidney disease vary with animal gender. *Lipids*. Dec 2006;41(12):1141-9. doi:10.1007/s11745-006-5064-z

47. Sankaran D, Bankovic-Calic N, Cahill L, Yu-Chen Peng C, Ogborn MR, Aukema HM. Late dietary intervention limits benefits of soy protein or flax oil in experimental polycystic kidney disease. *Nephron Experimental nephrology*. 2007;106(4):e122-e128. doi:10.1159/000104836
48. Lu J, Bankovic-Calic N, Ogborn M, Saboorian MH, Aukema HM. Detrimental effects of a high fat diet in early renal injury are ameliorated by fish oil in Han:SPRD-cy rats. *The Journal of nutrition*. 2003;133(1):180-186. doi:10.1093/jn/133.1.180
49. Higashihara E, Nutahara K, Horie S, et al. The effect of eicosapentaenoic acid on renal function and volume in patients with ADPKD. *Nephrology Dialysis Transplantation*. 2008;23(9):2847-2852. doi:10.1093/ndt/gfn144 %J Nephrology Dialysis Transplantation
50. Nutrient reference values for Australia and New Zealand including recommended dietary intakes. (NHMRC;) (2006).
51. Vendramini LC, Dalboni MA, de Carvalho JTG, Jr., Batista MC, Nishiura JL, Heilberg IP. Association of Vitamin D Levels With Kidney Volume in Autosomal Dominant Polycystic Kidney Disease (ADPKD). *Frontiers in medicine*. 2019;6:112. doi:10.3389/fmed.2019.00112
52. Rangan GK, Schwensen KG, Foster SL, Korgaonkar MS, Peduto A, Harris DC. Chronic effects of dietary vitamin D deficiency without increased calcium supplementation on the progression of experimental polycystic kidney disease. *American journal of physiology Renal physiology*. 2013;305(4):F574-F582. doi:10.1152/ajprenal.00411.2012
53. Vendramini LC, Rodrigues FG, Dalboni MA, et al. Effects of cholecalciferol supplementation in Autosomal Dominant Polycystic Kidney Disease (ADPKD) patients. Journal: Article. *Human Nutrition and Metabolism*. 2021;24doi:10.1016/j.hnm.2021.200121
54. Wallace DP. Cyclic AMP-mediated cyst expansion. *Biochimica et biophysica acta*. Oct 2011;1812(10):1291-300. doi:10.1016/j.bbadis.2010.11.005
55. Belibi FA, Wallace DP, Yamaguchi T, Christensen M, Reif G, Grantham JJ. The effect of caffeine on renal epithelial cells from patients with autosomal dominant polycystic kidney disease. *J Am Soc Nephrol*. Nov 2002;13(11):2723-9. doi:10.1097/01.asn.0000025282.48298.7b
56. Vendramini LC, Nishiura JL, Baxmann AC, Heilberg IP. Caffeine intake by patients with autosomal dominant polycystic kidney disease. *Brazilian journal of medical and biological research = Revista brasileira de pesquisas medicas e biologicas*. Sep 2012;45(9):834-40. doi:10.1590/s0100-879x2012007500120
57. Idrizi A, Barbullushi M, Kasa M, et al. *Nephrolithiasis in polycystic kidney disease: Risk factors, treatment and prevention*.
58. Idrizi A, Barbullushi M, Gjata M, et al. *Prevalence of nephrolithiasis in polycystic kidney disease*.
59. Torres VE, Wilson DM, Hattery RR, Segura JW. Renal Stone Disease in Autosomal Dominant Polycystic Kidney Disease. *American Journal of Kidney Diseases*. 1993/10/01/ 1993;22(4):513-519. doi:https://doi.org/10.1016/S0272-6386(12)80922-X
60. Torres JA, Rezaei M, Broderick C, et al. Crystal deposition triggers tubule dilation that accelerates cystogenesis in polycystic kidney disease. *The Journal of clinical investigation*. Jul 30 2019;129(10):4506-4522. doi:10.1172/jci128503
61. Borrego Utiel FJ, Herrera Contreras I, Merino García E, Camacho Reina MV, Moriana Domínguez C, Ocaña Pérez E. Urinary citrate as a marker of renal function in patients with autosomal dominant polycystic kidney disease. *International urology and nephrology*. 2022;54(4):873-881. doi:10.1007/s11255-021-02953-0
62. Penniston KL, Nakada SY, Holmes RP, Assimos DG. Quantitative Assessment of Citric Acid in Lemon Juice, Lime Juice, and Commercially-Available Fruit Juice Products. *Journal of Endourology*. 2008;22(3):567-570. doi:10.1089/end.2007.0304

63. Aras B, Kalfazade N, Tuğcu V, et al. Can lemon juice be an alternative to potassium citrate in the treatment of urinary calcium stones in patients with hypocitraturia? A prospective randomized study. *Urological research*. Dec 2008;36(6):313-7. doi:10.1007/s00240-008-0152-6
64. Torres VE, Bankir L, Grantham JJ. A case for water in the treatment of polycystic kidney disease. *Clin J Am Soc Nephrol*. Jun 2009;4(6):1140-50. doi:10.2215/cjn.00790209
65. Prasad S AB. Turmeric, the Golden Spice: From Traditional Medicine to Modern Medicine. In: Benzie IFF, Wachtel-Galor S, editors. Herbal Medicine: Biomolecular and Clinical Aspects. 2nd edition ed. CRC Press/Taylor & Francis; 2011. :chap Chapter 13. .
66. Leonhard WN, van der Wal A, Novalic Z, et al. Curcumin inhibits cystogenesis by simultaneous interference of multiple signaling pathways: in vivo evidence from a Pkd1-deletion model. *Am J Physiol Renal Physiol*. May 2011;300(5):F1193-202. doi:10.1152/ajprenal.00419.2010
67. Ashwell M. Stevia, Nature's Zero-Calorie Sustainable Sweetener: A New Player in the Fight Against Obesity. *Nutrition today*. May 2015;50(3):129-134. doi:10.1097/nt.0000000000000094
68. Yuajit C, Chatsudthipong V. Nutraceutical for Autosomal Dominant Polycystic Kidney Disease Therapy. *Journal of the Medical Association of Thailand = Chotmaihet thangphaet*. Jan 2016;99 Suppl 1:S97-103.
69. Yuajit C, Muanprasat C, Gallagher AR, et al. Steviol retards renal cyst growth through reduction of CFTR expression and inhibition of epithelial cell proliferation in a mouse model of polycystic kidney disease. *Biochemical pharmacology*. Apr 1 2014;88(3):412-21. doi:10.1016/j.bcp.2014.01.038
70. Yuajit C, Homvisasevongsa S, Chatsudthipong L, Soodvilai S, Muanprasat C, Chatsudthipong V. Steviol reduces MDCK Cyst formation and growth by inhibiting CFTR channel activity and promoting proteasome-mediated CFTR degradation. *PloS one*. 2013;8(3):e58871. doi:10.1371/journal.pone.0058871
71. Tapsell LC, Neale EP, Satija A, Hu FB. Foods, Nutrients, and Dietary Patterns: Interconnections and Implications for Dietary Guidelines. *Advances in Nutrition*. 2016;7(3):445-454. doi:10.3945/an.115.011718 %J Advances in Nutrition
72. Aguilera JM. The food matrix: implications in processing, nutrition and health. *Critical reviews in food science and nutrition*. 2019;59(22):3612-3629. doi:10.1080/10408398.2018.1502743
73. Taylor JM, Hamilton-Reeves JM, Sullivan DK, et al. Diet and polycystic kidney disease: A pilot intervention study. *Clinical Nutrition*. 2017/04/01/ 2017;36(2):458-466. doi:https://doi.org/10.1016/j.clnu.2016.01.003
74. Cowley BD, Jr., Grantham JJ, Muessel MJ, Kraybill AL, Gattone VH, 2nd. Modification of disease progression in rats with inherited polycystic kidney disease. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. 1996;27(6):865-879. doi:10.1016/s0272-6386(96)90525-9
75. Ikizler TA, Burrowes JD, Byham-Gray LD, et al. KDOQI Clinical Practice Guideline for Nutrition in CKD: 2020 Update. *Am J Kidney Dis*. Sep 2020;76(3 Suppl 1):S1-s107. doi:10.1053/j.ajkd.2020.05.006
76. Kelly JT, Palmer SC, Wai SN, et al. Healthy dietary patterns and risk of mortality and ESRD in CKD: a meta-analysis of cohort studies. 2017;12(2):272-279.
77. Ryu H, Yang YJ, Kang E, Ahn C, Yang SJ, Oh KH. Greater adherence to the dietary approaches to stop hypertension dietary pattern is associated with preserved muscle strength in patients with autosomal dominant polycystic kidney disease: a single-center cross-sectional study. *Nutrition research (New York, NY)*. Sep 2021;93:99-110. doi:10.1016/j.nutres.2021.07.006

78. Kipp KR, Rezaei M, Lin L, Dewey EC, Weimbs T. A mild reduction of food intake slows disease progression in an orthologous mouse model of polycystic kidney disease. *American journal of physiology Renal physiology*. 2016;310(8):F726-F731. doi:10.1152/ajprenal.00551.2015
79. Warner G, Hein KZ, Nin V, et al. Food Restriction Ameliorates the Development of Polycystic Kidney Disease. *Journal of the American Society of Nephrology : JASN*. 2016;27(5):1437-1447. doi:10.1681/ASN.2015020132
80. Ekinci I, Erkoc R, Gursu M, et al. Effects of fasting during the month of Ramadan on renal function in patients with autosomal dominant polycystic kidney disease. *Clinical nephrology*. Feb 2018;89(2):103-112. doi:10.5414/cn109102
81. Torres JA, Kruger SL, Broderick C, et al. Ketosis Ameliorates Renal Cyst Growth in Polycystic Kidney Disease. *Cell metabolism*. 2019;30(6):1007. doi:10.1016/j.cmet.2019.09.012
82. Rowe I, Chiaravalli M, Mannella V, et al. Defective glucose metabolism in polycystic kidney disease identifies a new therapeutic strategy. *Nature Medicine*. 2013;19(4):488-493. doi:10.1038/nm.3092
83. Bruen DM, Kingaard JJ, Munits M, et al. 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. doi:10.3390/kidneydial2020020
84. Strubl S, Oehm S, Torres JA, et al. Ketogenic dietary interventions in autosomal dominant polycystic kidney disease—a retrospective case series study: first insights into feasibility, safety and effects. *Clinical Kidney Journal*. 2022;15(6):1079-1092. doi:10.1093/ckj/sfab162
85. Oehm S, Steinke K, Schmidt J, et al. RESET-PKD: A pilot trial on short-term ketogenic interventions in autosomal dominant polycystic kidney disease. *Nephrology Dialysis Transplantation*. 2022;doi:10.1093/ndt/gfac311
86. Ong ACM, Torra R. Can ketogenic dietary interventions slow disease progression in ADPKD: what we know and what we don't. *Clinical Kidney Journal*. 2022;15(6):1034-1036. doi:10.1093/ckj/sfac103
87. Taylor JM, Ptomey L, Hamilton-Reeves JM, et al. Experiences and Perspectives of Polycystic Kidney Disease Patients following a Diet of Reduced Osmoles, Protein, and Acid Precursors Supplemented with Water: A Qualitative Study. *PloS one*. 2016;11(8):e0161043. doi:10.1371/journal.pone.0161043

Figure legends

Figure 1. Conceptual diagram of cyst formation in humans with PKD (Adapted from Maditz et al [25]).

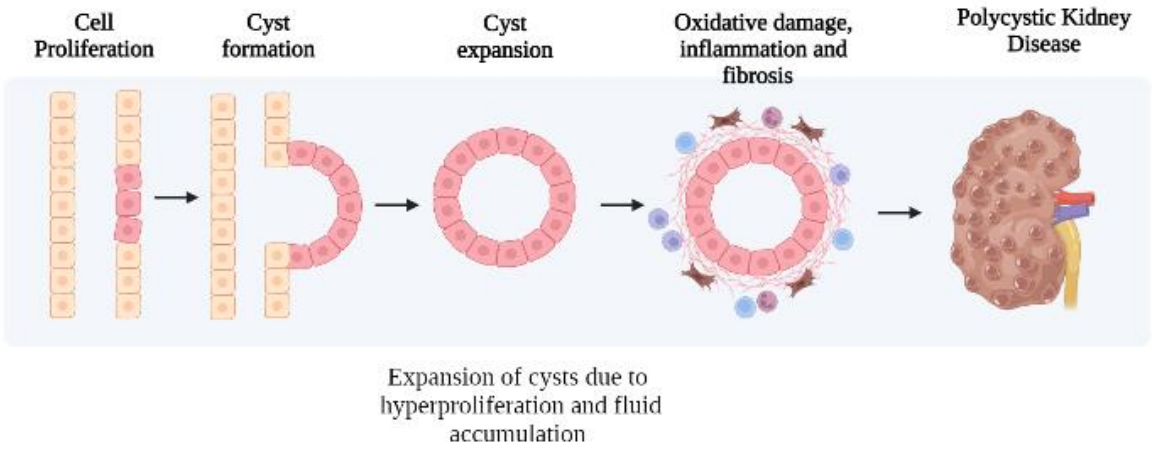
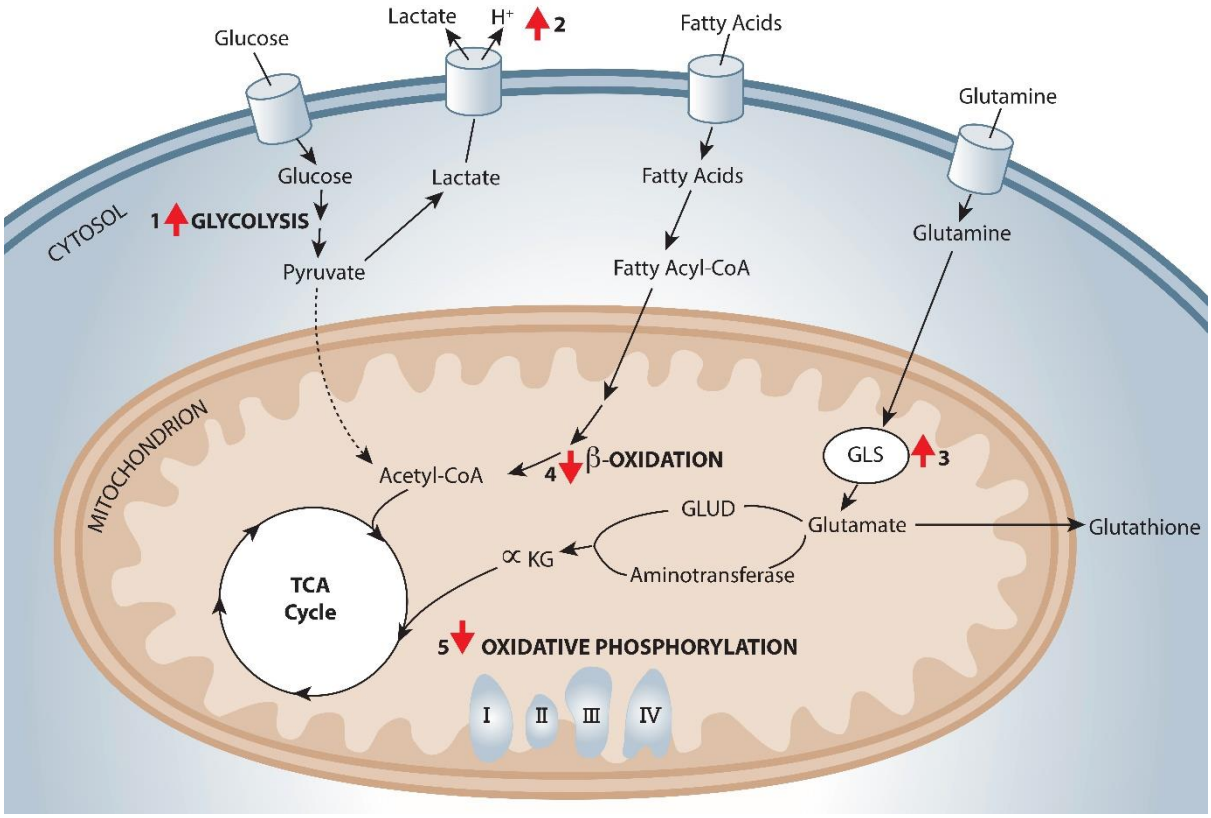


Figure created in Biorender.com

Figure 2.



Altered cellular metabolism in PKD. Cyst lining cells exhibit the Altered cellular metabolism in ADPKD. Cyst-lining cells exhibit the Warburg effect; aerobic glycolysis is increased (red arrow 1), resulting in the extracellular accumulation of lactate (red arrow 2). In addition to glucose, highly proliferative cells have increased demands for glutamine, reflected by upregulation of GLS (red arrow 3). At the same time, fatty acid oxidation (red arrow 4) and oxidative phosphorylation (red arrow 5) are impaired. ADPKD, autosomal dominant polycystic kidney disease; GLS, glutaminase; GLUD, glutamate dehydrogenase; TCA cycle, tricarboxylic acid cycle; αKG, alpha-ketoglutarate. Image reproduced with permission from Pickel et al (2022) Adv Nutr;13:652-666 [23]

Table 1. Summary of human studies examining sodium intake in people with PKD

Study	Outcome	Population	Results	Conclusions
Kramers et al 2020 [30] Observational cohort study, 4-year follow-up	Association between dietary salt and protein intake and PKD progression	n=589 patients with ADPKD, mean eGFR 64ml ± 24/min/1.73m^2 Mean age 47 ± 11 yrs Gender: 59% female	High salt intake, but not protein intake was significantly associated with decline in kidney function. Mean salt intake 9.1g/ day, protein intake 84g/day. Results of protein intake not normalised to g/kg/day	Salt intake induces an increase in plasma osmolality, triggering vasopressin secretion which leads to cystogenesis. Reduction of salt to 5g day (2000mg / 90 mmol sodium) could delay kidney failure by 4 years in the model provided.
Cote et al 2020 [29] Retrospective analysis	Effect of pre-medication dietary counselling on sodium and urea excretion rates in patients starting Tolvaptan.	n=30 patients with ADPKD, eGFR 43-74ml/min/1.73m^2 Mean age 47 ± 11 yrs Gender: 59% female	Dietary counselling was associated with a reduction in sodium excretion of 19mmol sodium per day (~1g dietary sodium). Reduction was greatest in those with higher baseline dietary sodium. Those who also reduced protein intake	Reduction in sodium intake and excretion in those on Tolvaptan helps to reduce polyuria, though adherence was temporary (4 months). Multiple interventions to enhance adherence may be required to maintain reduced intake.

			i.e., reduced osmolar load overall, seemed to be more effective and persist over time.	
Torres et al 2017 [31] Post hoc analysis of HALT PKD RCT studies A and B [32]	Effect of salt intake on progression of ADPKD All participants were instructed to follow 6g salt per day diet. Study B also had potassium restriction (60-80mmol/day) and phosphate and protein restrictions individualised.	Study A n=558 aged 15-49 years Study B n=486 aged 18-64 years, eGFR 25-60ml/min/1.73m^2. Follow up varied from 60-94 months Gender: Study A 49.3% female, Study B 51.6% female	Higher salt intake was associated with increased kidney cyst volume and faster decline in eGFR though effects were small. Intake declined during the trial only marginally (Study A: 10g to 9.6g day; Study B: 10g to 8.8g day). Each 1g decrease in salt intake was associated with significantly less kidney growth (0.43% per year)	Sodium restriction is beneficial, but adherence is a challenge. Poor adherence to sodium restricted diets was evident in both groups. According to the authors, intensive counselling and monitoring of food diaries and feedback would have been beneficial
Torres et al 2011 [33] Observational study of 6 year follow up	Identify markers for disease progression in ADPKD.	N=241 patients with ADPKD, mean eGFR 89.1 ± 27.7ml/min/ 1.73m^2 . Mean age 32.4 ± 8.9 yrs at baseline	Baseline urinary sodium excretion was associated with greater increase in kidney volume and GFR decline	Higher sodium intake and excretion was associated with more rapid cyst growth and loss of kidney function.

		Gender: 60.2% female	Protein intake at baseline 71.9 ±22.9g/day. Results not normalised to g/kg/day Baseline urine sodium 193.2 ± 86.1 mEq/24h and urinary potassium 58.9 ± 23.3 mEq/24h. These did not change over 3 years. Protein intake estimated using urinary nitrogen rather than dietary recall or estimation methods	24 hour urine results indicated excessive dietary sodium (~11g salt/ day) and inadequate potassium intake (indicative of low fruit and vegetable intake) While protein intake increased over time, there was no relationship between protein intake at baseline and kidney volume or disease progression
Doulton et al 2006 [34] Double blind RCT	Effects of dietary sodium 50mmol/day vs. 350mmol/day for 11 days on blood pressure and renin angiotensin system (RAS)	n=11 patients with ADPKD and hypertension and n=8 control subjects with essential hypertension Mean age 38 ± 3 yrs Gender: 73% female eGFR not recorded. Creatinine clearance 92 ± 9 ml/min/1.73m^2	Responses of blood pressure and RAS to sodium intake were not different between those with ADPKD and those with essential hypertension A very low sodium diet using low sodium breads and packaged products, as well as cooking methods was sustained for 3 days. A	Activation of the RAS in response to dietary sodium is not unusually high in Caucasian individuals with ADPKD compared to hypertensive controls.

			high sodium diet was achieved by supplementing the low salt diet with 300 mmol salt tablets	
Schmid et al 1990 [35] Non-randomised trial	Effect of very low sodium diet 20mmol/day vs sodium intake of 200mmol/day on blood pressure after 7 days	n=9 patients with ADPKD with hypertension and n=9 normotensive controls Mean age of ADPKD patients: 36 (range 28-53) yrs Gender: 2/9 female eGFR not stated; serum creatinine 113.1 ±15 umol/L	In the ADPKD group, higher salt intake increased blood pressure	A high sodium diet in ADPKD may result in increased blood pressure sensitivity to salt, though the study was small no details on baseline diet were given.

Legend: ADPKD: Autosomal Dominant Polycystic Kidney Disease; RCT: randomised controlled trial; eGFR estimated Glomerular Filtration Rate; RAS: Renin Angiotensin System.

Table 2. Single centre phase 2 human clinical trials relating to PKD and diet in progress and registered with clinialtrials.gov.

Trial	Study Design	Study aim	Study outcomes	Dietetic prescription
NCT04680780 Keto-ADPKD Ketogenic Dietary Interventions in Autosomal Dominant PKD (ADPKD) *Active, not recruiting*	Three arm randomised controlled trial Recruited: 63 (21 patients per arm) Site: University Hospital, Cologne, Germany Duration: 4 months (120 days)	Determine the feasibility of two ketogenic diets in adults with ADPKD vs 'ad libitum' diet control in adults 18-60 with CKD stage G1-3	Primary outcomes: adherence measured using blood ketone and patient reported outcomes (feasibility questionnaire). Secondary outcomes: change in total kidney volume, body mass index, insulin sensitivity, inflammation, QOL, BP and adverse events	Active dietary intervention arm: 'Classic' ketogenic diet – no further details specified OR 3 days water fasting – ie consume only water on 3 consecutive days in the first 14 day period of the month for 3 months. Comparator diet: Eat ad libitum, with low salt intake (5-7g/day) and >3 L water per day.
NCT04534985 Time Restricted Feeding in ADPKD *Recruiting*	Randomised controlled trial Recruitment target: 30 Site: University of Colorado, USA Duration: 12 months Co-sponsor: PKD Foundation	Determine the feasibility of time restricted feeding without energy restriction compared to standard healthy eating advice in adults 18-65 with BMI 25-45kg / m^2 and eGFR ≥ 30ml/min	Primary outcome: adherence, recruitment rate, retention rate Secondary outcomes: safety, tolerability, change in body weight, abdominal obesity, body composition, insulin sensitivity, AMPK expression, kidney volume, mood, pain, energy expenditure,	Active dietary intervention arm: Prescription of 2.3-3g sodium, 0.8-1g/kg protein, <800mg phosphate, 'moderate calorie intake' and 'appropriate hydration' with consumption of daily food intake in 8-hour window from within 3 hours of waking

			energy intake, physical activity	Comparator diet: 2.3-3g sodium, 0.8-1g/kg protein, <800mg phosphate, 'moderate calorie intake' and 'appropriate hydration'
NCT03858439 DIAT Dietary Intervention in ADPKD on Tolvaptan *Recruiting*	Single arm pre-post study Recruitment target: 30 (15 patients per arm) Site: Hamilton Nephrology Clinic, Ontario, Canada Duration: not specified	Determine the effect of a low solute (low sodium, low protein) diet on urine output in adult patients stable on Tolvaptan.	Primary outcome: change in 24 hour urine volume Secondary outcome: QOL, urine total solute load	Low sodium, low protein diet – no further details specified
NCT05228574 TRAMPOLINE Treatment of Vascular Stiffness in ADPKD *Recruiting*	Randomised double blind placebo controlled clinical trial Recruitment target: 54 Site: Erasmus University Medical Centre, Netherlands Duration: 6 weeks	Determine if arterial stiffness is exacerbated by a high salt diet in adults with PKD ≥18 years and an eGFR ≥ 60ml/min	Primary outcome: arterial stiffness measured using pulse wave velocity Secondary outcomes: 24 hour ambulatory BP, salt tasting thresholds, skin sodium levels, vascular inflammation and endothelial dysfunction	Active dietary intervention arm: Low salt diet (3.5g salt per day) for 6 weeks followed by 4 weeks of 6g salt capsule daily + amiloride Comparator Diet: Low salt diet (3.5g day) for 6 weeks followed by 4 weeks of placebo salt capsules + amiloride
NCT03102632 A clinical trial of Water Therapy for ADPKD	Non-randomised clinical trial	Examine if increased consumption of water can slow cyst growth or kidney function decline in	Primary outcome: total kidney volume	Active dietary intervention arm: 6 months of 'high' water intake based on 24 hour

Active, not recruiting	Recruited: 10 (target not specified) Site: Cornell University, USA Duration: 18 months	adults 18-65 years with an eGFR>40ml/min	Secondary outcomes: kidney function (creatinine) change, urine and blood sodium level	urine results. No further details specified Control period: 6 months of usual fluid intake (no further details specified)
NCT04310319 WATER Wishing to Decrease Aquaresis in ADPKD Patients Treated With a V2Ra: the Effect of Regulating Protein and Salt *Recruiting*	Randomised crossover clinical trial Recruitment target: 12 Site: University Medical Centre, Groningen, Netherlands Duration: 8 weeks	Determine if reduced salt and increased water will reduce polyuria in adults 18 years and older with an eGFR>30ml/min	Primary outcome: 24 hour urine volume Secondary outcomes: serum copeptin, eGFR, BP, QOL	Active dietary intervention arms: 6g NaCl tablets per day or placebo; or 6 g NaCl and 40g protein drink per day or placebo; or 40g protein drink and salt placebo; or placebo salt and placebo protein drink. No further details specified.
NCT03342742 Daily Caloric Restriction and Intermittent fasting in Overweight and Obese Adults With ADPKD *Completed*	Randomised clinical trial Recruited: 29 participants Site: University of Colorado, USA Duration: 1 year Co-sponsor: National Institute of Diabetes and Digestive and Kidney Diseases	Determine the feasibility of delivering two behavioural interventions for weight loss in adults with ADPKD.	Primary outcome: feasibility, retention, % change of body weight from baseline Secondary outcomes: QOL, safety, tolerability, mood energy intake, IGF-1, change in kidney volume, change in AMPK expression	The intervention/ treatment target for Group 1 is to reduce energy intake by 34% with caloric restriction and group 2 will reduce energy intake by 34% using 3 days/ week intermittent fasting

NCT04907799 Daily Caloric Restriction in Overweight and Obese Adults With ADPKD *Recruiting*	Randomised double blind controlled clinical trial Recruitment target: 126 Site: University of Colorado, USA Duration: 2 years Co-sponsor: National Institute of Diabetes and Digestive and Kidney Diseases	Compare the efficacy of a daily caloric restriction weight loss intervention in adults 18-65 years with BMI 25-45kg / m^2 and an eGFR ≥ 30ml/min	Primary outcome: total kidney volume Secondary outcomes: abdominal adiposity, insulin sensitivity, adiponectin level, leptin, inflammation, gene expression (pAMPK/ AMPK, pS6K/S6K), safety, tolerability, adherence, physical activity, adverse events.	Group based weight loss intervention with a prescription of 30% reduction in caloric intake and increased physical activity. No other details specified.

Legend: ADPKD: Autosomal Dominant Polycystic Kidney Disease; CKD: chronic kidney disease, QOL : quality of life, BMI: Body Mas Index: BP: blood pressure; L: litres; eGFR: estimated glomerular filtration rate; IGF-1: insulin like growth factor 1; USA:United States of America; p AMPK : phosphorylated cytoplasmic AMP-activated protein kinase; AMPK: cytoplasmic AMP-activated protein kinase; pS6K: phosphorylated ribosomal protein S6 kinase beta-1; S6K: ribosomal protein S6 kinase beta-1;

Table 3. Dietary recommendations for PKD (including those undertaking dialysis)

	People with PKD CKD stage 1-3	**People with PKD CKD stage 4-5**	**People undertaking dialysis**
General advice	Enjoy a wide variety of foods especially fruit and vegetables, and minimal amounts of processed foods.		
Fluid intake	Choose water to drink and drink to satisfy thirst. Seek advice from Doctor on the exact volume but aim for >2L urine volume per day	Choose water to drink. Seek advice from Doctor on the exact volume	Choose water to drink. Seek advice from Doctor on the exact volume if undertaking dialysis
Fruit	Eat 2 cups per day	Eat 2 cups per day Avoid fruit juice	Eat 2 cups per day Avoid fruit juice if on hemodialysis
Vegetables	Eat 2.5 cups per day	Eat 2.5 cups per day Seek individual advice if on low potassium diet	
Breads, cereals, rice, pasta	Choose wholegrain or wholemeal varieties		
Dairy foods (milk, cheese, yoghurt, milk alternatives)	Eat 3-4 cups per day	Limit quantity to control serum phosphate levels. Seek advice from dietitian on exact amount	
Protein rich foods (meat, chicken, fish, eggs, legumes, nuts)	Do not exceed recommended portion of meat / chicken and fish (about palm size or 150g per day) Include at least one meal per week of oily fish Enjoy plant-based proteins (nuts, legumes) often	Do not exceed recommended portion of meat / chicken and fish (about palm size or 150g per day) Include at least one meal per week of oily fish Include plant-based proteins (nuts, legumes) Seek advice from dietitian on exact amount	Ensure adequate protein to replace dialysis losses – aim for protein rich food at each main meal Include at least one meal per week of oily fish Include plant-based proteins (nuts, legumes) Seek advice from dietitian on exact amount
Limit salt	Read food labels on packaged foods to reduce salt intake to ideally <5g (2000mg/ 90mmol sodium /day) Do not add salt to foods or cooking, minimize processed and convenience foods		

Caffeine	Enjoy up to 200mg per day or 2 cups coffee / 4 cups of tea per day. Avoid cola drinks or other drinks containing caffeine	Enjoy small volumes if on a fluid allowance Avoid cola drinks or other drinks containing caffeine