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Polycystic Kidney Disease Diet

What is Known and What is Safe

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Abstract

Autosomal dominant polycystic kidney disease (ADPKD) is a genetic disorder characterized by kidney cyst formation and progressive kidney function loss. Dietary interventions such as caloric restriction, intermittent fasting, and ketogenic diet have recently emerged as potential strategies to induce metabolic reprogramming and slow ADPKD progression. We review the available evidence supporting the efficacy and safety of these interventions in ADPKD. Dietary interventions show promise in managing ADPKD by improving metabolic health and reducing oxidative stress. However, while preclinical studies have shown favorable outcomes, limited clinical evidence supports their effectiveness. In addition, the long-term consequences of these dietary interventions, including their effect on adverse events in patients with ADPKD, remain uncertain. To optimize ADPKD management, patients are advised to follow a dietary regimen that aims to achieve or maintain an ideal body weight and includes high fluid intake, low sodium, and limited concentrated sweets. Caloric restriction seems particularly beneficial for patients with overweight or obesity because it promotes weight loss and improves metabolic parameters. Supplementation with curcumin, ginkgolide B, saponins, vitamin E, niacinamide, or triptolide has demonstrated uncertain clinical benefit in patients with ADPKD. Notably, β-hydroxybutyrate supplements have shown promise in animal models; however, their safety and efficacy in ADPKD require further evaluation through well-designed clinical trials. Therefore, the use of these supplements is not currently recommended for patients with ADPKD. In summary, dietary interventions such as caloric restriction, intermittent fasting, and ketogenic diet hold promise in ADPKD management by enhancing metabolic health. However, extensive clinical research is necessary to establish their effectiveness and long-term effects. Adhering to personalized dietary guidelines, including weight management and specific nutritional restrictions, can contribute to optimal ADPKD management. Future research should prioritize well-designed clinical trials to determine the benefits and safety of dietary interventions and supplementation in ADPKD.

Keywords: ADPKD, nutrition, polycystic kidney disease

Introduction

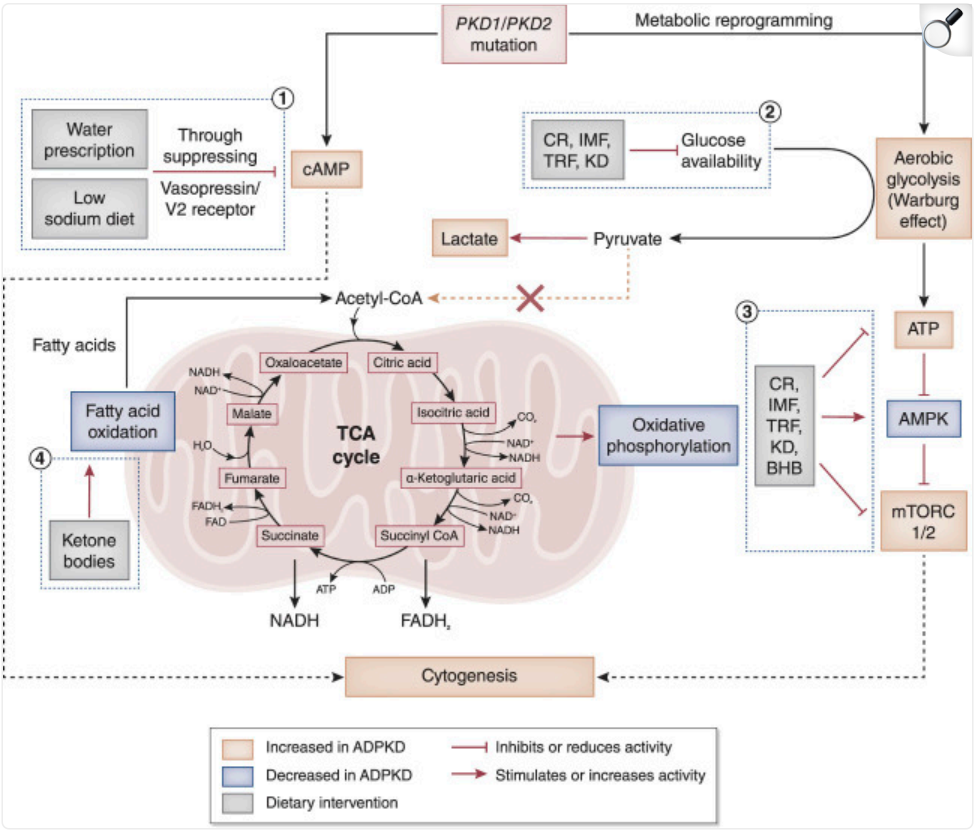
Autosomal dominant polycystic kidney disease (ADPKD) is the fourth most common cause of kidney failure leading to potentially life-threatening kidney and extrarenal manifestations.[1–3] Dietary interventions have emerged as a strategy to slow progression and improve outcomes. In 2018, experts recommended moderate sodium restriction, increased hydration, moderate caloric restriction, and moderate protein restriction for patients with kidney function decline.[4] Since then, additional preclinical and clinical studies have focused on dietary

manipulation. This review summarizes current evidence and provides expert opinion for dietary interventions and nutritional supplementation in ADPKD while considering safety and efficacy.

Metabolic Reprogramming and Rationale of Dietary Interventions in ADPKD

ADPKD is caused by a gene mutation affecting the function of polycystin 1 or 2, proteins that localize to mitochondria.[5] Loss of functional polycystin 1 or 2 alters mitochondrial structure and function, leading to metabolic changes in ADPKD, such as a shift to aerobic glycolysis and defective fatty acid β-oxidation, glutamine metabolism, mechanistic target of rapamycin (mTOR), and adenosine monophosphate–activated protein kinase (AMPK) regulation (Figures 1 and 2).[6–8] Ketogenic dietary interventions (*e.g.*, caloric restriction, intermittent fasting, and classic ketogenic diet) can activate AMPK pathways, improve cellular metabolism, and reduce cyst growth in preclinical models.[9–12] This section summarizes the rationale, benefits, and safety concerns of these interventions for ADPKD.

Figure 1.



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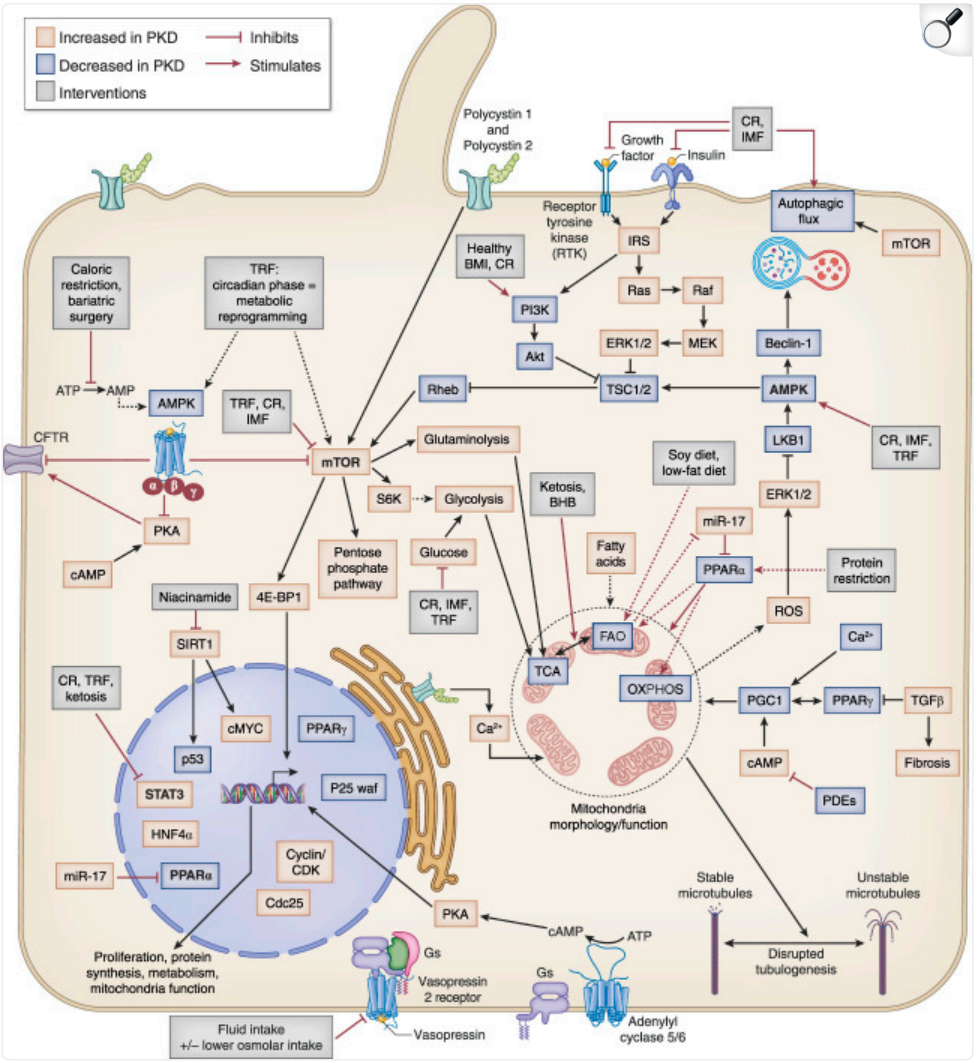
Simplified graphic of impaired metabolic pathways in ADPKD and mechanisms of actions of dietary interventions. Mutations in the *PKD1* and *PKD2* genes lead to higher cAMP levels, which promote cystogenesis. Dietary interventions that reduce osmolar intake and suppress vasopressin secretion, such as water prescription and low-sodium diet, may reduce cystogenesis by inhibiting cAMP formation (box 1). *PKD1* and *PKD2* mutations directly affect mitochondrial function through mitochondrial dynamics, OXPHOS, and FAO. In ADPKD, altered cellular metabolism results in increased aerobic glycolysis and extracellular lactate accumulation. Reduced OXPHOS in mitochondria stimulates glycolysis and results in increased ATP, reduced AMPK activity, and increased mTORC1 activity. Ketosis, a metabolic state in which the body primarily relies on fat-derived ketone bodies for energy, may be induced by dietary interventions reducing carbohydrates, such as caloric restriction, intermittent fasting, time-restricted feeding, and ketogenic diet. Dietary interventions inducing ketosis, including caloric restriction, intermittent fasting, time-restricted feeding, and ketogenic diet, may reduce glucose availability (box 2). This could increase AMPK activity and reduce mTORC1 activity, ultimately reducing cystogenesis in ADPKD (box 3). During ketosis, the body increases the rate of FAO to produce more acetyl-CoA, which is used as an alternative energy source (box 4). As fatty acids are broken down into acetyl-CoA, the levels of NADH and FADH2 also increase, providing more substrates for OXPHOS. The increased production of NADH and FADH2 from FAO during ketosis boosts the electron transport chain's activity, leading to an increased rate of OXPHOS. In summary, ADPKD is a complex disorder that affects cellular metabolism and energy production. Dietary interventions that target metabolic reprogramming, such as reducing osmolar intake and inducing ketosis, may offer potential therapeutic benefits. Further research is needed to determine the safety and efficacy of these interventions in ADPKD management. Brown shapes or red arrows indicate increased activity or level in ADPKD; blue shapes indicate decreased activity or level in ADPKD; gray shapes indicate dietary intervention; red blunted arrows indicate inhibits or reduces activity. ADPKD, autosomal dominant polycystic kidney disease; AMPK, adenosine monophosphate–activated protein kinase; β-hydroxybutyrate; cAMP, cyclic adenosine monophosphate; CR, caloric restriction; FADH2, flavin adenine dinucleotide; FAO, fatty acid oxidation; IMF, intermittent fasting; KD, ketogenic diet; mTORC1, mammalian target of rapamycin complex 1; NADH, nicotinamide adenine

dinucleotide; OXPHOS, oxidative phosphorylation; PKD, polycystic kidney disease; TCA, tricarboxylic acid cycle; TRF, time-restricted feeding.

Figure 2.



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Comprehensive operative molecular pathways in ADPKD with emphasis on dietary interventions. ADPKD is characterized by a complex interplay with multiple nutrient metabolism pathways, disrupting key cellular pathways, such as autophagy, glycolysis, fatty acid metabolism, and mitochondrial function. Crucial signaling intermediaries, including mTOR, AMPK, SIRT-1, IGF-1, and PPAR*α/γ*, exhibit significant roles in ADPKD pathology and metabolic response. PC1 and PC2 proteins modulate calcium ion influx and mitochondrial dynamics, directly influencing mitochondrial function. PC1 C-terminal tail suppresses cystic disease in a mitochondrial enzyme NNT-dependent fashion. PC2 is critical for uncoupling mitochondria from the endoplasmic reticulum. Therefore, it is conceivable that manipulation of mitochondrial bioenergetics through diet modifications (*e.g.*, caloric restriction) may modulate PC1/2 effects on mitochondrial function. The overactivity of the miR-17 microRNA cluster, coupled with PC-1 deficiency, contributes to mitochondrial dysfunction by repressing PPAR*α*. The figure expands on Nowak and Hopp,[81] highlighting additional complexities, including disrupted tubulogenesis; interstitial inflammation; fibrosis; and the implication of metabolic pathways, such as glutaminolysis and the pentose phosphate pathway. These complexities underscore the intricate link between ADPKD progression and metabolic dysregulation. Brown shapes indicate increased activity or level in ADPKD; blue shapes indicate decreased activity or level in ADPKD; gray shapes indicate dietary intervention; red blunted arrows indicate inhibits activity; red arrows indicate stimulates activity. AKT, protein kinase B; BHB, *β*-hydroxybutyrate; BMI, body mass index; CFTR, cystic fibrosis transmembrane conductance regulator; cMYC, cellular myelocytomatosis; 2-DG, 2-deoxyglucose; 4E-BP1, eukaryotic translation initiation factor 4E (eIF4E)-binding protein 1; ERK1/2, extracellular signal–regulated kinase; HNF4*α*,

hepatocyte nuclear factor 4*a*; IRS, insulin receptor substrate; GLP-1, glucagon-like peptides; MEK, mitogen-activated protein kinase; mTOR, mechanistic target of rapamycin; NNT, nicotinamide nucleotide transhydrogenase; PC1, polycystin-1; PC2, polycystin-2; PI3K, phosphoinositide 3-kinase; PKA, protein kinase A; PPAR*a/γ*, peroxisome proliferator-activated receptor-*a/γ*; Rheb, ras homolog enriched in the brain; ROS, reactive oxygen species; S6K, ribosomal protein S6 kinase; SGLT1/2, sodium glucose cotransporter-1/2; SIRT-1, sirtuin-1; STAT3, signal transducer and activator of transcription 3; TCA, tricarboxylic acid cycle; TSC1/2, tuberous sclerosis 1 and 2; V2R, vasopressin-2 receptor miR: micro ribonucleic acid (RNA).

Caloric Restriction/Food Restriction in ADPKD

Rationale and Preclinical Studies

Caloric restriction involves reducing daily caloric intake and has been investigated as a potential intervention to slow ADPKD progression in preclinical studies (Table 1).[9–11] Mild-to-moderate caloric restriction (10%–40%) slowed disease progression and cyst growth in *Pkd1*$^{RC/RC}$ and *Pkd1*$^{cond/cond}$:Nes^{cre} mouse models, mediated in part by suppressed mTOR signaling and/or activation of the AMPK pathway.[9–11] However, intermittent fasting and time-restricted feeding (introduced below) did not show similar benefits.[9] Interestingly, intermittent fasting and time-restricted fasting groups did not have a decrease in body weight, suggesting that weight loss may be necessary for caloric restriction to be effective in ADPKD.[9] Caloric restriction also reversed the ADPKD-associated increase of hexokinase 2, a key mediator of aerobic glycolysis, suggesting metabolic reprogramming.[11] Further investigation is required to understand the mechanisms underlying the potential benefits of caloric restriction in ADPKD.

Table 1.

Preclinical studies investigating dietary interventions in polycystic kidney disease animal models

Dietary Interventions	Authors, Year of Publication	Study Design	Animal Model Used	Duration of Intervention	Key Findings	Safety Signals/Concerns
Food restriction	Warner *et al.*,[11] 2016	10–40% restriction versus *ad libitum*	Pkd1$^{RC/RC}$ mice, Pkd2$^{WS25/-}$ mice	From 6 wk to 7.5 mo	Reduced cyst area, kidney fibrosis, inflammation, and injury in a dose-dependent manner	None noted
Food restriction	Kipp *et al.*,[10] 2016	23% food restriction versus *ad libitum*	*Pkd1*$^{cond/cond}$:Nes^{cre} mice	Postnatal weeks 5–12	Reduced cyst area, maintained kidney function	None noted
Food restriction	Hopp *et al.*,[9] 2021	30% food restriction versus *ad libitum*	Pkd1$^{RC/RC}$ mice	From 3 to 6 mo of age	Reduced cyst area, reduced body weight	Reduced lean mass, spleen mass, and femur length
Intermittent fasting	Hopp *et al.*,[9] 2021	80% food restriction 3 d/wk, *ad libitum* other days versus *ad libitum* every day	Pkd1$^{RC/RC}$ mice	From 3 to 6 mo of age	No reduction in cyst area, no reduction in body weight	None noted
Time-restricted feeding	Torres *et al.*,[12] 2019	Restricted food access to 8-h during the 12-h dark cycle versus *ad libitum*	Han:SPRD rat	Postnatal weeks 3–8	Reduced cyst area, improved kidney function, reduced proliferation, reduced fibrosis	None noted
Time-restricted feeding	Hopp *et al.*,[9] 2021	Restricted food access to 8-h during the 12-h dark cycle versus *ad libitum*	Pkd1$^{RC/RC}$ mice	From 3 to 6 mo of age	No reduction in cyst area, no reduction in body weight	None noted
Ketogenic diet	Torres *et al.*,[12] 2019	Multiarm preclinical trial	Han:SPRD rat, juvenile and adult and male versus female	5 wk (age 3–8 wk) (age 8–12 wk)	Ketogenic diet attenuated kidney cystic disease progression (kidney weight and cystic indices) and the rise in serum creatinine in the juvenile model, and kidney weight and cystic indices in the adult model	Ketogenic diet–associated lower body weight

Dietary Interventions	Authors, Year of Publication	Study Design	Animal Model Used	Duration of Intervention	Key Findings	Safety Signals/Concerns
Oral BHB	Torres *et al.*,[12] 2019	Multiarm preclinical trial	Han:SPRD rat, juvenile and adult and male versus female	5 wk	BHB attenuated kidney cystic disease progression (kidney weight and cystic area indices and the rise in serum creatinine)	None noted
Caffeine	Belibi *et al.*,[51] 2002	Caffeine (10–50 μM), other nonselective phosphodiesterase (PDE) inhibitors (1-methyl-3-isobutyl xanthine and theophylline), specific PDE IV inhibitor (rolipram)	ADPKD-mural epithelial cells versus normal human cortex cells		Increased cAMP levels in both cell lines Increase in chloride secretion in ADPKD cells Increased P-ERK level	None noted
Caffeine	Tanner and Tanner,[78] 2001	Solution of caffeine versus tap water	Heterozygote Han:Sprague–Dawley rats	1–6 mo of age	No effect of caffeine on inactin GFR Higher BP in PKD rats, and even higher in the caffeine arm	None noted
Curcumin	Leonhard *et al.*,[55] 2011	Diferuloylmethane (curcumin)	Tamoxifene-induced iKsp-*Pkd1*^{del} mouse	23 wk (to reach kidney failure)	Reduced STAT3 activation Reduced proliferation index Reduced cystic index Reduced kidney weight/body weight ratios	None noted
Curcumin and ginkgolide B	Li *et al.*,[56] 2020	Mice exposed to 2 μM curcumin 0.5 μM ginkgolide Or 2 μM curcumin+0.5 μM ginkgolide	1—*In vitro:* MDCK cyst model 2—*In vivo:* *Pkd1*$^{flox/-}$ mice and *Ksp-Cre*	10 d (these cell lines typically die at 15 d)	In both *in vitro* and *in vivo experiments,* curcumin combined with ginkgolide inhibited cystogenesis more effectively compared with either treatment alone	None noted
Isoflavone (geinstein)	Tomobe *et al.*,[72] 1998	Casein-based diet with or without geinstein (isoflavone)	DBA/2FG-pcy (pcy) mouse	90 d	No effect of isoflavone in kidney outcomes	None noted
Soyasaponin B_b powder with or	Philbrick *et al.*,[73] 2003	Study 1: casein (control) diet versus isoflavone+saponin-	*pcy* mice	3 mo (2–5 mo of age)	Lower plasma creatinine, urea, and kidney weight in SEAE	None noted

Dietary Interventions	Authors, Year of Publication	Study Design	Animal Model Used	Duration of Intervention	Key Findings	Safety Signals/Concerns
without isoflavone		enriched soy supplement, versus control+SEAE Study 2: control diet versus soyasaponin-enriched versus isoflavone-enriched diets or 99.5% pure saponin diet			diet Lower plasma creatinine in isoflavone+soyasaponin supplements compared with controls Lower plasma creatinine, urea, and kidney weight in soyasapoinin Bb diet and the soyasaponin+isoflavone supplements compared with control	
Triptolide (extract of Lei Gong Teng, a Chinese herbal medicine)	Leuenroth *et al.*,[62] 2008	Intraperitoneal triptolide versus dimethyl sulfoxide	*Pkd1*$^{flox/-}$;*Ksp-Cre* mouse (neonatal model with rapid cystic expansion after birth)	Day 8 postnatal	Improved kidney function Inhibition of cyst growth	Weight loss Overall concerns about safety of triptolide Amenorrhea, gastrointestinal, kidney, or hepatic safety concerns in other studies
Vitamin D receptor agonist (Paricalcitol)	Sagar *et al.*,[60] 2021	Experiment 1—vehicle versus paricalcitol Experiment 2—vehicle, paricalcitol, enalapril, or combination of enalapril+paricalcitol	Lewis PKD (n=16) versus Lewis control rats (n=6)	Week 10 Week 20	No effect on cyst growth or kidney function Reduction of proteinuria but less than enalapril Improved cardiovascular outcomes (reduced systolic BP and heart–body weight ratio)	Risk of hypercalcemia and weight loss
Vitamin D deficient diet	Rangan *et al.*,[59] 2013	Normal diet versus vitamin D–deficient diet	Lewis PKD rats versus Lewis control rats	Week 10	Mild reduction in kidney weight Exacerbation of proteinuria Worsening kidney function Worsening hypertension Mild reduction in serum calcium	Cardiac enlargement
Vitamin E (*a* tocopherol)	Torres, *et al.*,[61] 1998	Vitamin E–deficient diet Vitamin E 65 IU/kg	Han:SPRD-*cy* rats	5 wk (from 3 to 8 wk of age)	No difference in kidney cystic burden or kidney function on the basis of	None noted

Dietary Interventions	Authors, Year of Publication	Study Design	Animal Model Used	Duration of Intervention	Key Findings	Safety Signals/Concerns
		of chow Vitamin E 10,000 IU/kg of chow			vitamin E intake Higher *a*-tocopherol levels but lower cystic disease in females	
Soybean oil	Jayapalan *et al.*,[76] 2000	AIN-93G purified rodent diet Soybean oil as the sole lipid source at levels of 5 and 20 g/100 g of diet	Han:SPRD-*cy* rats	6 wk (from 4 to 10 wk of age)	High-fat diet resulted in: 17% higher kidney volume 30% higher cyst score 25% higher BUN 49% higher serum creatinine (only in males)	None noted
Flaxseed oil, corn oil, algal oil	Sankaran *et al.*,[78] 2004	Study 1: adult mice on 4, 10, or 20 g soybean/100 g/diet Study 2: weanling mice on flaxseed oil diet (rich in 18:3*n*−3), or corn oil (rich in 18:2*n*−6), or algal oil (rich in 22:6*n*−3)	CD1-*pcy/pcy mouse*	8 wk	Low-fat diet slows progression of kidney injury in male and female *pcy* mice Flaxseed oil diets rich in 18:3*n*−3 slowed early fibrosis progression compared with diets rich in 18:2*n*−6 (corn oil) or in 22:6*n*−3 (algal oil)	None noted
Soy protein versus casein protein Soy oil versus fish oil versus flax oil	Yamaguchi *et al.*,[77] 2016	Casein protein+soy oil Casein protein+80% fish oil Casein protein+ 80% flax oil Soy protein+soy oil Soy protein+80% flax oil Soy protein+80% fish oil	*Pkd2*$^{WS25/-}$ mice (ADPKD) PCK rats (ARPKD)	13 wk	No effect of dietary protein on kidney function Fish oil resulted in larger kidney size in females Soy oil was associated with lower proteinuria, higher creatinine clearance and urinary pH Lower kidney size in soy oil with casein-based protein diet	Liver was larger in the fish oil group Two rats in the casein+fish oil group terminated due to poor condition (weight loss, enlarged heart)
Sunflower seed oil and *n*−3 fatty acid enriched diet	Yamaguchi *et al.*,[66] 1990	24 mice divided into three groups on three different diets (standard laboratory chow versus sunflower seed oil versus *n*−3 fatty	DBA/2FG-pcy mice	60 d	Lower kidney size, tubular dilatation, and cystic burden in the *n*−3 fatty acid–enriched diet	None noted

Dietary Interventions	Authors, Year of Publication	Study Design	Animal Model Used	Duration of Intervention	Key Findings	Safety Signals/Concerns
		acid–enriched diet). Killed after 60 d				
Flax oil versus soy protein	Sankaran *et al.*,[79] 2007	Standard diet (7% corn oil+20% casein) versus 7% flax oil versus 20% soy protein diet	Han:SPRD-*cy* rats	4 mo (from age 2–6 mo)	No difference in serum creatinine, cystic growth, or kidney fibrosis Lower oxidative stress, inflammation, and cell proliferation in the dietary soy protein and flax oil group compared with standard diet	None noted

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Orthologous and nonorthologous animal models have different metabolic profiles; none of the used animal models perfectly mimic the human disease. Orthologous animals have the same gene mutation (but do not necessarily present in a similar way to the human disease), whereas nonorthologous animals have a different gene mutation, but may have a somewhat similar phenotype to the human polycystic kidney disease. Furthermore, some animal models, such as Han:SPRD rat, represent a proximal tubular cystic disorder. BHB, β-hydroxybutyrate; IV, intravenous; ADPKD, autosomal dominant polycystic kidney disease; cAMP, cyclic adenosine monophosphate; PDE, phosphodiesterase; P-ERK, phospho extracellular signal-regulated kinase; PKD, polycystic kidney disease; STAT3, signal transducer and activator of transcription 3; MDCK, Madin–Darby canine kidney; *Ksp-Cre*, kidney-specific cre; SEAE, saponin-enriched alcohol extract; NPHP, nephronophthisis; AIN-93G, American Institute of Nutrition.

Clinical Studies

Daily caloric restriction (approximately 30%) is a standard approach to weight loss in obesity.[13] Clinical studies on caloric restriction in patients with ADPKD are limited (Table 2). Obesity is an independent risk factor of incident CKD and kidney failure in the general population,[14] and weight loss can prevent further decline in eGFR in patients with prevalent CKD.[15] Overweight status or obesity is strongly and independently associated with ADPKD progression in early-stage patients.[16,17] Thus, ADPKD clinical studies have focused on caloric restriction in these patients. A pilot study evaluated two dietary interventions for weight loss in patients with ADPKD and overweight or obesity: daily caloric restriction (34% restriction every day, $n=15$) and intermittent fasting (80% restriction for three nonconsecutive days per week, $n=13$).[9] Participants in the daily caloric restriction group reported higher adherence, better tolerability, and more pronounced weight loss.[9] Both interventions were safe, and annual kidney growth was lower in both groups than in historical controls, correlating strongly with loss of body weight and visceral abdominal adiposity.[9] A phase 2 randomized controlled trial is currently underway to assess the efficacy of daily caloric restriction versus standard dietary care in slowing kidney growth in overweight/obese patients with ADPKD (NCT04907799).

Table 2.

Clinical trials and epidemiologic studies investigating dietary interventions in patients with autosomal dominant polycystic kidney disease

Dietary Intervention and Duration	Authors/Year of Publication	Study Design/Patient Characteristics	Primary/Secondary Outcomes	Key Findings	Safety Signals/Concerns	Limitations
Daily caloric restriction (34%) for 1 yr	Hopp *et al.*,[9] 2021	18–65 yr; BMI 25–45 kg/m^2; eGFR ≥30 ml/min per 1.73 m^2	Primary: feasibility; exploratory: change in htTKV	Daily caloric restriction had high adherence with few side effects and an average weight loss of 9%; annual change in htTKV was qualitatively low versus historical control and correlated with weight loss	Minimal adverse events	Small sample size (pilot)
Intermittent fasting (80% restriction every other day) for 1 yr	Hopp *et al.*,[9] 2021	18–65 yr; BMI 25–45 kg/m^2; eGFR ≥30 ml/min per 1.73 m^2	Primary: feasibility; exploratory: change in htTKV	Adherence was lower than daily caloric restriction with more side effects; annual change in htTKV was qualitatively low versus historical control and correlated with weight loss	Compared with daily caloric restriction, lower tolerability, and more likely to experience hunger, fatigue, cold intolerance, irritability, and insomnia	Small sample size (pilot)

Dietary Intervention and Duration	Authors/Year of Publication	Study Design/Patient Characteristics	Primary/Secondary Outcomes	Key Findings	Safety Signals/Concerns	Limitations
Daily caloric restriction (34%) for 1 yr	Nowak, ongoing (NCT04907799)	18–65 yr; BMI 25–45 kg/m^2; eGFR ≥30 ml/min per 1.73 m^2	Primary: annual change in htTKV; secondary: changes in abdominal adiposity, circulating and adipose tissue markers	To be determined	To be determined	Initial trial (n=126)
Self-initiated ketogenic diet intervention for at least 6 mo	Strubl *et al.*,[33] 2022	Uncontrolled, unbalanced retrospective case series study of self-reported observation and medical data. N=131 patients with ADPKD	Self-reported overall health and ADPKD-related symptoms	Ketogenic diet improved overall and ADPKD-associated health, including the weight loss and improvement of hypertension	81% of patients with ADPKD on ketogenic diet new health issues, most commonly hypercholesterolemia (17%)	Uncontrolled, unbalanced retrospective case series study (no control group), self-reported observation and medical data, selection bias
Ketogenic diet versus water fast (3 of 14 d; water fasting) versus *ad libitum* (no diet; control) in ADPKD; duration 12 wk	Cukoski *et al.*[31] 2022 (Kidney Week poster)	Exploratory, randomized, open, single-center, three-arm dietary intervention study	Feasibility of ketogenic diet (ketone body levels and patient-reported feasibility). Changes in TKV, BMI, IGF-1, hsCRP, SF-12, ADPKD impact scale, adverse events	Interventions were feasible. Potential beneficial effect on htTKV (P = 0.08), htTLV (P = 0.01), and eGFR (P = 0.00) changes	Ketogenic diet–associated higher rates of kidney stones (grade 3), cyst infection uric acid >ULN Triglycerides and cholesterol (grade 2)	Small study (patients with ADPKD: 23 ketogenic diet versus 21 water fast versus 19 control *ad libitum* diet) Short intervention duration (12 wk); small absolute change in htTKV and htTLV
Sodium	Multiple studies[35–37,40,41]	Adult patients		Higher sodium intake correlated with higher TKV growth and faster decline of eGFR		These studies show a correlation but did not test to see if lowering salt intake improved TKV growth or eGFR decline
Potassium	HALT-PKD; V. Torres *et al.*[36] 2018	A *post hoc* analysis of the HALT-PKD data	Changes in urine potassium excretion	A higher potassium intake was associated		This study established a correlation but did not test whether

Dietary Intervention and Duration	Authors/Year of Publication	Study Design/Patient Characteristics	Primary/Secondary Outcomes	Key Findings	Safety Signals/Concerns	Limitations
				with less TKV increase (study A) and less eGFR decline (study B)		increasing potassium intake would improve outcomes
Fluid intake	Water (Rangan *et al.*,[41] 2022)	3-yr prospective study assessing a water prescription versus *ad libitum* intake	htTKV	No difference in htTKV between the two groups, but only 53% of the study group achieved the target urine osmolarity	More hyponatremia in the study group	Only a subset of patients was able to achieve water prescription and goal Uosm, indicating the challenges of inhibiting vasopressin by nonpharmacologic interventions. The challenge to achieve this goal is consistent with other disease entities, such as nephrolithiasis prevention
EPA: EPA (a subtype of omega-3 fatty acids)	Higashihara *et al.*,[67] 2008	Multicenter, prospective, randomized $n=21$ on EPA and 20 controls Ages 18–60 yr Follow-up: 2 yr	Plasma creatinine TKV Urinary albumin excretion	No difference in any of the outcomes	None	Small sample size Relatively short follow-up Late initiation of EPA
a-lipoic acid	Lai *et al.*,[68] 2020	Prospective, controlled, longitudinal study Age >18 yr Without cancers, psychiatric disorders, heart failure, and acute coronary syndrome $n=59$ (33 active versus	Serum creatinine Serum CRP Serum uric acid FMD (%) Depression (BDI-II and HAM-D scales) Cognitive function (Mini Mental State Examination) Glucose metabolism (insulin, HOMA)	No difference in serum creatinine Lower serum glucose, HOMA, serum uric acid, and CRP in the a-lipoic group Higher serum CO_2, FMD Improved depression	None	Small sample size Short duration No report of hard kidney or cardiovascular outcomes Lack of adjustment to the effect of concomitant medications

Dietary Intervention and Duration	Authors/Year of Publication	Study Design/Patient Characteristics	Primary/Secondary Outcomes	Key Findings	Safety Signals/Concerns	Limitations
		26 controls) Outcomes at 3 and 6 mo		and cognition tests		
Niacinamide (inhibitor of surtuins)	El Ters *et al.*,[58] 2022	Two safety and efficacy studies: (*1*) Open-label, single-arm, phase 2a trial (n=10) (*2*) Randomized, double-blinded, placebo-controlled trial (n=36) 12 mo 30 mg/kg oral dose divided into two equal daily doses Age 18–60 (or 55 for study 2) eGFR >60 ml/min	Ratio of acetylated p53 to total p53 protein in PBMCs htTKV	No difference in primary or secondary outcomes	C-reactive protein increased consistently during the study on nicotinamide	Small sample size Short follow-up Uncontrolled trial (study 1) Questionable reliability of Western blot assay for acetyl p53
Curcumin	Nowak *et al.*,[57] 2022	Placebo-controlled randomized clinical trial n=68 (34/arm) Age 6–25 yr eGFR >80 ml/min per 1.73 m^2 Follow-up 1 yr	Brachial artery FMD Aortic pulse-wave velocity Urinary 8-iso-prostaglandin, serum CRP, IL-6, IFN-γ htTKV	No difference in any of the cardiovascular or kidney outcomes	None	Small sample size Short follow-up Not powered to assess changes in TKV or eGFR over 1 yr
Caffeine	Vendramini *et al.*,[79] 2012	Case-control, cross-sectional study (102 patients with ADPKD and 102 healthy volunteers) in Brazil	TKV eGFR	Lack of correlation between caffeine intake and TKV or eGFR	Higher BP	Retrospective; based on 3 d recall (recall bias) Much lower caffeine intake in patients with ADPKD compared with controls

Dietary Intervention and Duration	Authors/Year of Publication	Study Design/Patient Characteristics	Primary/Secondary Outcomes	Key Findings	Safety Signals/Concerns	Limitations
						TKV measured by ultrasound
Caffeine	Girardat-Rotar *et al.*,[52] 2018	Prospective, longitudinal analysis of the Suisse PKD cohort (n=151) Median follow-up 4.38 yr	TKV eGFR	Coffee intake was not associated with either TKV or eGFR	None	Self-reported Ignored other sources of caffeine Relatively short follow-up
Caffeine	McKenzie *et al.*,[53] 2018	Retrospective, *post hoc* analysis of the CRISP cohort N=239 (188 coffee consumers and 51 nonconsumers) Median follow-up 12.5 yr	mGFR htTKV	Mildly positive interaction of coffee consumption with htTKV No association between caffeine intake or caffeine dose with mGFR, time to kidney failure or death	None	Self-reported Ignored other sources of caffeine Only effect of baseline coffee consumption was analyzed

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BMI, body mass index; htTKV, height-adjusted total kidney volume; ADPKD, autosomal dominant polycystic kidney disease; TKV, total kidney volume; CRP, C-reactive protein; hsCRP, high-sensitivity C-reactive protein; SF-12, Short Form 12-Item Health Survey; TLV, total liver volume; htTLV, height-adjusted total liver volume; ULN, upper limit of normal; HALT-PKD, The HALT Progression of Polycystic Kidney Disease trial; Uosm, urine osmolality; EPA, eicosapentaenoic acid; FMD, flow-mediated dilation; BDI-II, Beck Depression Inventory, second edition; HAM-D scale, Hamilton rating scale for Depression; HOMA, homeostatic model assessment; CO_2, carbon dioxide; PBMC, peripheral blood mononuclear cell; PKD, polycystic kidney disease; CRISP, Consortium for Radiologic Imaging Studies in Polycystic Kidney Disease; mGFR, measured GFR.

Benefits, Safety, Potential Risks, and Special Considerations in ADPKD

Caloric restriction may slow ADPKD progression, but its safety and efficacy in humans are uncertain. However, moderate caloric restriction combined with exercise is a standard approach for weight loss in patients with obesity outside the context of ADPKD, and weight loss has known health benefits. Nevertheless, caution is needed in patients with an ideal body mass index (BMI, 18.5–24.9 kg/m^2). The Comprehensive Assessment of Long-Term Effects of Reducing Intake of Energy, a 2-year study on healthy, nonobese adults implementing 25% daily caloric restriction, demonstrated that sustained caloric restriction was feasible, safe, and well tolerated.[18] However, long-term caloric

restriction may have potential risks of bone loss and anemia.[18] *Pkd1*$^{RC/RC}$ mice showed a reduced lean mass, spleen mass, and femur length, suggesting that long-term caloric restriction could promote health complications in adult mice; thus, caution may be needed when counseling children, young adults, and lean patients.[9] Patients with ADPKD should not restrict water intake and must maintain an adequate intake of micronutrients while restricting calorie intake. Weight loss through caloric restriction is a reasonable recommendation in patients with ADPKD who are overweight or obese. It should be implemented under medical supervision and in consultation with a registered dietitian. Long-term caloric restriction may not be feasible or advisable. Caloric intake should be monitored to avoid weight gain in individuals who already have an ideal BMI.

Intermittent Fasting and Time-Restricted Feeding in ADPKD

Rationale and Preclinical Studies

Intermittent fasting involves restricting calories (by 80%) for 1–3 nonconsecutive days per week, while time-restricted feeding limits caloric intake to a narrow feeding window of 8–10 hours per day. Preclinical studies have shown that intermittent fasting improves insulin sensitivity, reduces BP and heart rate, and promotes metabolic reprogramming in nonpolycystic kidney disease (PKD) murine models.[19] Time-restricted feeding prevents weight gain, improves body composition, and increases insulin sensitivity in non-PKD murine models.[12,20] However, few preclinical studies on time-restricted feeding and intermittent fasting have been conducted in orthologous PKD models. Limiting feeding to an 8-hour window in the nonorthologous Han:SPRD rat model of PKD reduced cystic index and improved kidney function by induction of ketosis, partially mediated by changes in mTOR and signal transducer and activator of transcription 3 signaling.[12] By contrast, time-restricted feeding had no benefit in the orthologous *Pkd1*$^{RC/RC}$ mouse model of PKD.[9] Time-restricted feeding is referred to the dietary intervention implemented in preclinical studies, whereas time-restricted eating is the term used in human clinical trials. Moderate daily caloric restriction can effectively facilitate weight loss without the requirement of inducing ketosis. In addition, both intermittent fasting and time-restricted eating have a higher likelihood of inducing ketosis.[21]

Clinical Studies

Clinical studies have demonstrated that intermittent fasting is generally safe and feasible in healthy overweight or obese adults, with potential benefits in body weight, BP, lipid profiles, oxidative stress, and inflammation.[22] However, data on intermittent fasting in ADPKD are limited to the single pilot study listed above, which compared daily caloric restriction (34% restriction daily) to intermittent fasting (80% caloric restriction for 3 nonconsecutive days per week) and found more adverse effects with intermittent fasting.[9] The recommended macronutrient content in this study was 55% carbohydrate, 15% protein, and 30% fat in both groups. Patients undertaking intermittent fasting were encouraged to consume noncaloric fluids freely during the fasting period. In comparison with the daily caloric restriction group, participants randomized to intermittent fasting had lower self-reported adherence and lower tolerability and were more likely to experience hunger, fatigue, cold intolerance, irritability, and insomnia. This study was not powered to evaluate the efficacy, but an annual change in total kidney volume (TKV) was similar in the daily caloric restriction group and highly correlated with the change in body weight. By contrast, randomized controlled trials of time-restricted eating in individuals without ADPKD suggest the feasibility and potential health benefits, including reduced body weight, insulin sensitivity, lipids, and BP.[23] A pilot study on the feasibility of time-restricted eating in patients with ADPKD is completed, with results expected by the end of 2023 (NCT04534985).

Benefits, Safety, Potential Risks, and Special Considerations in ADPKD

The efficacy of intermittent fasting and time-restricted eating for slowing ADPKD progression in humans is unknown. Pilot data suggest that the tolerability of intermittent fasting in patients with ADPKD may pose implementation challenges. Similar concerns regarding daily caloric restriction, including adequate hydration and nutrient intake, and differing caloric needs of lean individuals also apply to intermittent fasting. Other potential risks include hypoglycemia, dizziness, and weakness.[24] Time-restricted eating may have fewer side effects, but can pose lifestyle challenges. In summary, there is insufficient evidence to recommend intermittent fasting or time-restricted eating for patients with ADPKD. Intermittent fasting may be an alternative approach for patients with overweight or obesity, but should only be considered with medical guidance. Time-restricted eating without concurrent caloric restriction is considered safe, regardless of BMI, but efficacy in ADPKD requires further research.

Ketogenic Diet in APDKD

Rationale and Preclinical Studies

Ketogenic diets increase the production of ketone bodies, such as β-hydroxybutyrate (BHB) and acetoacetate. The classic ketogenic diet is a high-fat (55%–65% of dietary macronutrients), adequate-protein (1 g/kg), and low-carbohydrate (5%–10%) diet that leads to a starvation-like metabolic state.[25] AMPK activation and metabolic substrates changes (*e.g.*, increased ketone bodies that fuel cellular metabolism instead of glucose) contribute to the ketogenic diet's beneficial effects on insulin sensitivity, oxidative stress reduction, and cell growth and proliferation.[26–28] Preclinical studies have shown that a ketogenic diet can reduce cystic burden and kidney function loss, making it a promising candidate for managing ADPKD.[12] However, it is unclear whether the benefit is through weight loss or ketosis alone. The ketogenic diet has been used for several decades in the medical management of epilepsy[29] and, more recently, to aid in the treatment of metabolic disorders such as obesity.[16,17] Limited efficacy and safety data are available for ADPKD. Administration of BHB reduces cystic disease in a juvenile ADPKD rat model, suggesting direct disease progression-attenuating effects of ketone bodies.[12] Further details are present in Table 1. While it may still be premature to endorse ketogenic diets or supplements, future research may reveal potential benefits.

Clinical Studies and Benefits

The RESET-PKD pilot trial evaluated short-term ketogenic diet feasibility in five patients with ADPKD.[30] The trial demonstrated feasibility and successful ketogenesis induction.[30] The KETO-ADPKD study investigated 12-week ketogenic diet interventions in patients with ADPKD.[31] The study included three arms: 23 patients with ADPKD on ketogenic diet, 21 patients on water fasting for 3 days every 14 days, and 19 patients on control *ad libitum* food intake. The ketogenic diet was based on a fat:protein:carbohydrate ratio of 10:4:1 (in grams) with advice to consume 20–25 kcal/kg body weight daily.[30] There was no specification on the preference of animal or plant source of protein.[30] The KETO-ADPKD study showed potentially favorable short-term outcomes, including decreased cystic liver growth (-55 ml/m, $P = 0.01$), likely due to glycogen depletion, and an acute improvement in kidney function (ΔeGFR of $+5$ ml/min, $P = 0.01$).[31] The short-term increase in creatinine-based eGFR might be related to decreased animal protein (meat) intake, leading to a decreased creatinine pool size and lowered serum creatinine,[32] rather than true GFR change. Thus, additional measures, such as eGFR by cystatin C and measured GFR, would be essential in future studies involving dietary intervention that might affect muscle mass or protein intake. Long-term efficacy and safety data are still lacking because of limited follow-up. Retrospective case series involved 131 patients with ADPKD practicing ketogenic diet or time-restricted diet for at least 6 months, exploring the effect on overall and ADPKD-related symptoms, feasibility, and safety.[33] Most patients reported improved overall and ADPKD-related health, including weight loss and reduced hypertension severity, with ketogenic diet. Additional details are provided in Table 2.

Safety, Potential Risks, and Special Considerations in ADPKD

In the RESET-PKD trial, significant hyperuricemia was observed with the ketogenic diet.[30] The KETO-ADPKD study reported adverse events such as nephrolithiasis (8%) and hypercholesterolemia (17%).[31] In addition, 17% of patients with ADPKD on ketogenic diet self-reported hyperlipidemia, and 81% experienced new health issues.[33] Further details are provided in Table 2. While there is enthusiasm for plant-based ketogenic diet for ADPKD, its recommendation for patients is not currently supported. Longer-term studies are necessary to determine sustainability and address adverse events. In summary, existing studies show the potential feasibility and short-term benefits of ketogenic diet interventions in ADPKD. However, long-term effects and safety remain unknown, highlighting the need for well-designed clinical trials to address uncertainties.

Brief Overview of Other Dietary Interventions

Low water intake and high salt intake are associated with a higher risk of CKD and a faster decline of eGFR in ADPKD.[34–37] Optimal fluid intake in ADPKD aims to minimize the effect of vasopressin.[38,39] Although a short-term study showed a benefit of matching fluid intake to osmolar load,[40,41] a 3-year study of prescribed (versus *ad libitum*) water intake in patients with ADPKD did not decrease copeptin levels, slow TKV growth, or slow eGFR decline.[40,41] Nonetheless, the observed ineffectiveness might be explained by several factors that only half of the

patients demonstrated the treatment adherence. Therefore, we continue to recommend a high water or fluid intake to achieve hypotonic urine with urine osmolality <280 mOsm/kg. We also support the recommendation for a low-salt diet (2.3 g or 100 mEq of sodium per day), although the benefit of salt restriction has not been established by an interventional trial.[38,39,42]

There are discordant recommendations for protein intake for patients with CKD.[43] Although excess protein intake may contribute to osmolar load and vasopressin release, protein intake was not associated with an annual change in eGFR in the DIPAK (Developing Interventions to Halt Progression of ADPKD) cohort.[37] In the subset of 200 patients with ADPKD in the Modification of Diet in Renal Disease study, there was no beneficial effect of protein restriction.[44] Protein intake should be balanced to avoid intake higher than 1.3 g/kg of protein per day. For patients not on dialysis and with an eGFR of <30 ml/min per 1.73 m^2, it would be prudent to reduce protein intake to 0.8 kg/d per day to avoid uremia.[45,46] Plant-based diets have shown potential benefits in reducing CKD progression. In patients on tolvaptan therapy, a low-solute evening meal is recommended to reduce nocturia and disrupted sleep.

A higher potassium intake has been associated with less TKV increase and less eGFR decline in patients with ADPKD.[36] We recommend a diet rich in fruits and vegetables with high potassium intake for patients with ADPKD with preserved kidney function who are not at risk of hyperkalemia. Potassium-rich foods are typically fruits and vegetables, which likely reduce dietary acid and might also be rich with vitamins, minerals, and fiber. In patients with ADPKD, limiting concentrated sweets helps control serum glucose levels linked to increased TKV.[12] While animal studies suggest that calcium oxalate crystals activate PKD-associated signaling pathways, there is no human evidence to support a low-oxalate diet. Avoiding a high-phosphate diet may help prevent calcium phosphate crystal deposition and disease progression. Given the lack of human data, there is no consensus on restricting dietary phosphate.[38,47,48] Although high serum uric acid is associated with larger TKV and kidney failure risk,[49] it is not an independent risk factor of progression in ADPKD[50]; thus, insufficient evidence exists to recommend a low-purine diet in the absence of hyperuricemia or uric acid stone disease.

Overview of Nutritional Supplementation

Nutritional supplementation studies in ADPKD are limited, primarily conducted on animal and cell-line models, making translation to human ADPKD challenging without clinical trials. See Tables 1 and 2 for a summary of these studies.

Supplements with Human Data in Patients with ADPKD

Caffeine

Potential risk of caffeine in accelerating cystic kidney disease has been inferred from preclinical models.[51] Although caffeine can independently raise BP, clinical studies on ADPKD showed no significant differences in TKV or eGFR on the basis of caffeine intake.[52,53] Because mild–moderate coffee consumption was associated with metabolic and cardiovascular beneficial effects,[54] patients with ADPKD may benefit from moderate consumption of caffeinated beverages (<200–250 mg per day, equivalent to 2–3 cups of coffee).

Curcumin and Ginkgolide B

Although curcumin and ginkgolide B have shown potential in reducing cystogenesis in animal models of ADPKD,[55,56] there is currently no evidence to support their use in patients with ADPKD. A clinical trial of curcumin in children and young adults with ADPKD did not show any benefit in cardiovascular or kidney outcomes over 1 year of follow-up.[57]

Vitamins

While preclinical studies have shown promising results for the use of specific vitamins in reducing cystogenesis in ADPKD animal models, there is limited clinical evidence to support their use in patients with ADPKD. A clinical trial of niacinamide (vitamin B) in patients with ADPKD showed no significant differences in primary outcomes[58] while studies on the effects of vitamin D and vitamin E have produced mixed results.[59–61]

Supplements without Human Data in Patients with ADPKD

BHB

Given the potential benefits of ketogenic diet and challenges of long-term adherence, BHB combined with other supplements, such as citrate, have been developed. The safety and efficacy of these supplements have not been assessed or validated in patients with ADPKD. Medical foods do not need to undergo premarketing review by the US Food and Drug Administration. Therefore, BHB supplements are not currently recommended for patients with ADPKD because of the absence of safety and efficacy data. It is imperative to conduct well-designed clinical trials to establish the benefits and safety of these supplements before considering their use.

Triptolide

Triptolide, a diterpene derived from a traditional Chinese herbal medicine, has been shown to improve kidney function and inhibit cyst growth in mice.[62] However, its use is limited by toxicity and a narrow therapeutic window.[63]

Saponins

Saponins are bitter-tasting plant-derived organic chemicals found in various foods. Soyasaponin B6 and Saikosaponin d slow cyst growth in animal models and cell lines of PKD.[65,66]

Phytoestrogens (Isoflavones)

Phytoestrogens, found in soybeans as isoflavones and in flaxseed as lignans, mimic estrogen and bind to estrogen receptors, particularly estrogen receptors-beta (ER-β), offering potential benefits in CKD and ADPKD.[69] Isoflavones, flavonoids found in soy products, have been studied for potential benefits in animal models of PKD. However, the results have been conflicting, with some studies showing no improvement and others showing improved kidney function and lower kidney weight.[70,71]

Oils and Seeds (Flaxseed, Flax Oil, Fish Oil, and Soybean Oil)

Several types of oils and seeds have been studied for their effects on PKD progression in animal models. Flaxseed has shown anti-inflammatory properties and improved kidney function in rats because of the enrichment of kidney omega-3 polyunsaturated fatty acids.[72] Fish oil and soybean oil containing high $n-3$ polyunsaturated fatty acid have also shown positive effects in animal models.[64,73] However, soybean oil has resulted in detrimental outcomes in rat models,[74,75] while flax oil and soy protein diet showed lower markers of oxidative stress, inflammation, and cell proliferation in rats.[76,77] The translation of these findings to human ADPKD requires further research.

The PKD Diet

In conclusion, dietary interventions may potentially slow ADPKD progression, but their long-term effects and effect on adverse events are uncertain. Clinical trials are needed to establish the benefits and safety of these interventions. While there is no universally applicable diet for patients with ADPKD, we present specific dietary recommendations on the basis of the available evidence in the scientific literature and authors' expert opinion (Figure 3 and Table 3). All dietary interventions should be implemented under close medical supervision and in consultation with a registered dietitian, with consideration of potential risks and benefits.

– Patients with ADPKD and overweight or obesity should consider caloric restriction aiming to lose weight. Long-term caloric restriction may increase the risk of bone loss and anemia.
– When trying to achieve weight loss, a moderate-energy deficit of around 30% is recommended, which could be calculated using the patient's resting metabolic rate or Mifflin St. Jeor equation and activity level. The patient would receive a daily caloric prescription on

the basis of this calculation.

– Caloric intake should be moderated in patients with normal BMI.

– The recommended macronutrient distribution is as follows: 55% carbohydrate, 15% protein, and 30% fat.

– Promote adequate water intake to achieve dilute urine, with a goal of morning urine osmolality below 280 mOsm/kg.

– Encourage moderate sodium restriction to 2.3 g or 100 mEq of sodium per day. This can be accomplished by avoiding adding salt at the table and limiting processed foods, fast foods, and dining out.

– For patients with preserved eGFR, promote diets rich in fruits and vegetables to increase potassium intake and likely reduce dietary acid.

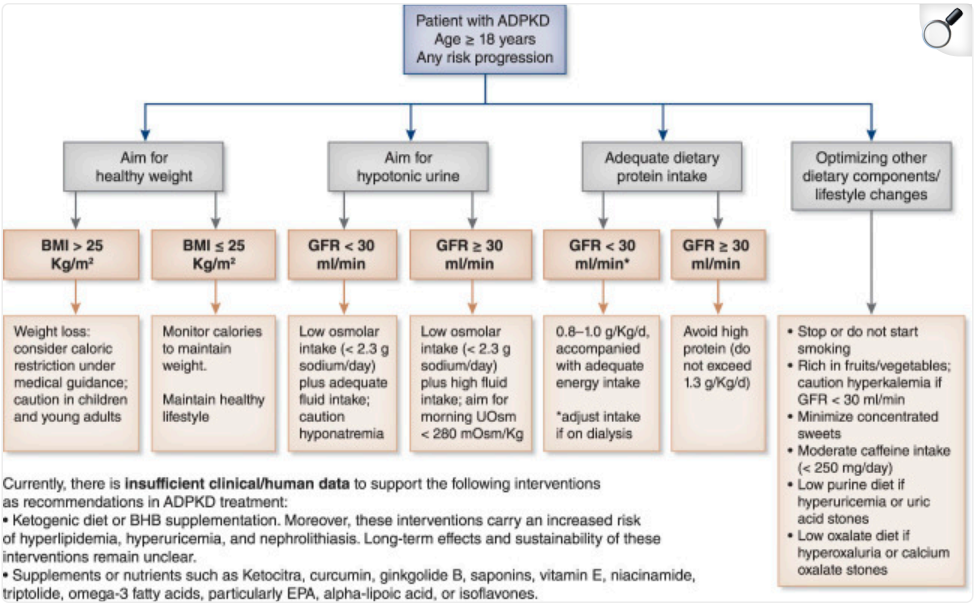
– Encourage adequate dietary protein intake but avoid exceeding 1.3 g/kg per day if GFR ≥30 ml/min per 1.73 m^2. If the patient's GFR is <30 ml/min per 1.73 m^2 and not on dialysis, limit protein intake to 0.8–1.0 g/kg per day. Patients on dialysis should follow dialysis guidelines without restricting protein intake.

– Current data do not support restrictions on dietary oxalate or purine.

– There are insufficient human data to support the recommendation of ketogenic diet or BHB supplementation in slowing ADPKD. Concerns include a higher risk of hyperlipidemia, hyperuricemia, and nephrolithiasis.

– There are currently no or insufficient human data supporting the use of supplements or nutrients in slowing ADPKD, such as Ketocitra, curcumin, ginkgolide B, saponins, vitamin E, niacinamide, triptolide, omega-3 fatty acids, eicosapentaenoic acid, *α*-lipoic acid, or isoflavones.

Figure 3.



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Practical approach for nephrologists to guide patients with ADPKD on lifestyle modifications and dietary interventions. The authors recommend the following optimized PKD dietary goals: (*1*) aim for a healthy weight, achieved through sustained weight loss and caloric restriction for overweight or obese patients; (*2*) aim for hypotonic urine by reducing osmolar intake and increasing fluid intake, with caution in advanced CKD, to avoid hyponatremia; (*3*) aim for adequate protein intake, not exceeding 1.3 g/kg per day and restricting to 0.8 g/kg per day in advanced CKD (predialysis); and (*4*) optimize other dietary components, such as increasing dietary potassium unless at risk of hyperkalemia or low GFR, avoiding smoking, minimizing concentrated sweets, moderating caffeine intake, and recommending low-purine or low-oxalate diets only as clinically indicated. Of note, there is insufficient clinical evidence to recommend a ketogenic diet or BHB supplementation with concerns for higher risk of hyperlipidemia, hyperuricemia, and nephrolithiasis. There are also no clinical data supporting the use of supplements or nutrients such as Ketocitra, curcumin, ginkgolide B, saponins, vitamin E, niacinamide, triptolide, omega-3 fatty acids, particularly EPA, *α*-lipoic acid, or isoflavones in slowing ADPKD. While these recommendations are for adult patients with ADPKD, the authors encourage PKD households to adopt a healthy lifestyle for all family members who might be at risk of ADPKD, including the abovementioned goals. EPA, eicosapentaenoic acid.

Table 3.

Nutrients and dietary interventions for polycystic kidney disease management: benefits, risks, and recommended dosages and expert opinion

Nutrients/Dietary Intervention	Proposed Mechanism	Benefits	Evidence of Effectiveness	Risks	Recommended Dosage/Amount	Expert Recommendations/ Conclusion
Daily caloric restriction	Decreased mTOR signaling and increased AMPK activation leading to reduced kidney cystic disease progression, fewer kidney cysts and smaller cyst size. Loss of adiposity may mediate reduction in cystogenesis	Lower BMI associates with slower kidney growth, but trial evidence needed; health benefits of ideal BMI outside the kidney	Preclinical studies; epidemiologic studies; pilot clinical trial	May not be appropriate for lean individuals; long-term adherence may not be feasible or advisable; need to maintain adequate hydration and nutrition	30% restriction to promote weight loss if overweight or obese; maintain healthy weight in patients with ideal BMI	Can be reasonable recommended under medical guidance if overweight or obese; caution needed if normal BMI
Intermittent fasting	Decreased mTOR signaling and increased AMPK activation may also mediate reduction in cystogenesis. In addition, excessive accumulation of oil droplets in cystic tubule cells,[80] leading to apoptosis, which in turn leads to loss of cystic fluid, cystic cell	Health benefits have been reported outside of ADPKD (primarily cardiometabolic health)	Not effective in preclinical study; pilot clinical study showed difficulty with adherence	Need to maintain adequate hydration and nutrition; side effects can include hypoglycemia, dizziness, and weakness	Typical recommendation is 80% restriction, 3 d/wk	There is not enough evidence to specifically recommend intermittent fasting in patients with ADPKD. These may be alternative approaches to daily caloric restriction in patients with overweight or obesity, but should only be considered under physician and registered nutritionist guidance

Nutrients/Dietary Intervention	Proposed Mechanism	Benefits	Evidence of Effectiveness	Risks	Recommended Dosage/Amount	Expert Recommendations/ Conclusion
	death, and disruption of epithelial barrier of cysts					
Time-restricted eating	Decreased mTOR and STAT3 signaling leading to reduced kidney cystic disease progression, fewer kidney cysts and smaller cyst size, and less kidney collagen deposition with fewer myofibroblasts	Health benefits have been reported outside of ADPKD (primarily cardiometabolic health)	Mixed preclinical evidence; clinical pilot study ongoing	Need to maintain adequate hydration and nutrition	Typical recommendation is limiting intake to 8 h/d within 3 h of waking	There is not enough evidence to specifically recommend time-restricted feeding in patients with ADPKD. Time-restricted eating without concurrent caloric restriction is likely safe regardless of BMI, but efficacy of this dietary intervention is currently unknown
Ketogenic diet	Decreased mTOR and STAT3 signaling leading to reduced kidney cystic disease progression, fewer kidney cysts and smaller cyst size, and less kidney collagen deposition with fewer myofibroblasts	Health benefits have been reported outside of ADPKD (metabolic health)	Preclinical data; limited short-term and small clinical studies	Need to maintain adequate hydration and nutrition; side effects can include hyperlipidemia, stone disease, hyperuricemia; questionable long-term sustainability	Typical ketogenic diet: high-fat (55%–65% of dietary macronutrients), adequate protein (1 g/kg), and low-carbohydrate (5%–10%) diet	There is not enough evidence to specifically recommend ketogenic diet in patients with ADPKD. Unclear evidence if ketosis alone or weight loss drives the metabolic reprogramming benefit
Salt intake	In addition to BP control, reduction in sodium and thus osmolar intake allows	Lower intake may reduce eGFR decline and htTKV growth	Clinical correlation noted but no clinical trial	Avoid ultra-low (<2.3 g sodium) to avoid volume depletion	Target 2.3 g sodium (100 mEq) for all patients	In line with current treatment of all CKDs

Nutrients/Dietary Intervention	Proposed Mechanism	Benefits	Evidence of Effectiveness	Risks	Recommended Dosage/Amount	Expert Recommendations/ Conclusion
	reduction of the required water needed to achieve hypotonic urine					
Fluid intake	Suppresses vasopressin and thus downstream effect of activation of V2R	May reduce copeptin levels	No positive trial showing benefit	Monitor for hyponatremia	Aim for hypotonic urine with morning Uosm of <280 mOsm/kg	Adjust fluid intake recommendations as eGFR declines
Potassium intake	Higher potassium intake might be reflecting a healthier diet (possibly other vitamins, minerals, and fiber content of potassium-rich foods); higher fruit and vegetable consumption may reduce dietary acid	Higher intake may reduce eGFR decline and htTKV growth	Clinical correlation but no clinical trial	Monitor for hyperkalemia	Encourage a potassium-rich diet at early stages of ADPKD	In keeping with DASH, Mediterranean or flexitarian diet guidelines in early CKD stages
Phosphate intake	Higher dietary phosphate might limit the renoprotective effect of angiotensin-converting enzyme inhibition, possibly through stimulation of fibroblast growth factor 23. High-phosphate diet might lead to	High phosphate may lead to disease progression; low-phosphate diet slows cystogenesis	Preclinical data	Monitor for hypophosphatemia	No consensus on dietary restriction given lack of human data	Moderate phosphate restriction and phosphate binders as indicated otherwise in CKD management

Nutrients/Dietary Intervention	Proposed Mechanism	Benefits	Evidence of Effectiveness	Risks	Recommended Dosage/Amount	Expert Recommendations/ Conclusion
	calcium phosphate crystal deposition and possible kidney disease progression					
BHB	While the specific mechanism is not reported, BHB administration leads to reduced kidney cystic disease progression, fewer kidney cysts and smaller cyst size, and less kidney collagen deposition with almost no myofibroblasts	Potential benefit of progression-attenuating effects of ketone bodies	Preclinical data only; BHB reduces cystic disease in a juvenile ADPKD rat model, suggesting direct disease progression-attenuating effects of ketone bodies	Monitor for hyperlipidemia, stone disease, hyperuricemia, and cyst infection	Unknown optimal dose in humans because there are no clinical studies in ADPKD	There is no sufficient evidence to recommend BHB in patients with ADPKD. Until adequately designed and powered clinical trials are performed, the risk outweighs the benefit

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Insufficient clinical data to recommend these dietary changes or supplements unless medically indicated outside of autosomal dominant polycystic kidney disease prevention: low oxalate, low purine, curcumin, ginkolide B, niacinamide, vitamin E, triptolide, saponins, eicopentaenoic acid, *a* lipoic acid, isoflavones, flaxseed, flax oil, fish oil, and soybean oil. mTOR, mechanistic target of rapamycin; AMPK, adenosine monophosphate–activated protein kinase; BMI, body mass index; ADPKD, autosomal dominant polycystic kidney disease; STAT3, signal transducer and activator of transcription 3; htTKV: height-adjusted TKV; V2R, vasopressin-2 receptor; Uosm, urine osmolality; DASH, Dietary Approaches to Stop Hypertension; BHB, β-hydroxybutyrate.

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