Clinical Kidney Journal, 2022, vol. 15, no. 6, 1034–1036

https://doi.org/10.1093/ckj/sfac103
Advance Access Publication Date: 21 April 2022
Editorial Comment

EDITORIAL COMMENT

Can ketogenic dietary interventions slow disease progression in ADPKD: what we know and what we don't

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ABSTRACT

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease leading to kidney failure. To date, there is no cure for the disease although there is one approved disease-modifying therapy: tolvaptan. In this context, a common question that ADPKD patients ask in clinical practice is whether there is anything they can do to slow their disease by modifying their diet or lifestyle. Recent evidence from experimental PKD models has shown the potential benefits of caloric restriction, high water intake and especially ketogenic diets in preserving kidney function. Whether these benefits are translatable to humans remains unknown. In this issue of *CKJ*, Strubl *et al*. report results of a self-enrolled survey of autosomal dominant polycystic kidney disease (ADPKD) patients who have self-administered a ketogenic diet [1]. These results provide interesting insights into the tolerability, potential benefits and harms of such an intervention that could inform a future clinical trial.

Keywords: ADPKD, disease progression, fasting, GFR, ketogenic diets

ADPKD is the most common genetic kidney disease with an estimated clinical point prevalence of 1 in 2500 and genetic prevalence of 1 in 1000 [2]. It is a major cause of kidney failure worldwide and is associated with significant renal and extrarenal morbidity, including reduced quality of life. Previously considered untreatable, clinical trials with the vasopressin receptor-2 antagonist tolvaptan have demonstrated that both kidney growth and function can be slowed by 30–50% in patients with rapid disease progression [3, 4]. Tolvaptan is nevertheless associated with significant aquaretic side effects limiting its tolerability, and rare episodes of idiosyncratic hepatotoxicity requiring frequent safety monitoring [5]. Both factors have limited its uptake even in patients predicted to benefit from treatment.

For patients unsuitable, unwilling or unable to take tolvaptan, a question that often arises in clinical practice is whether dietary or lifestyle modification could make a difference in slowing disease progression and thus preserving kidney function. This simple question is however difficult to answer with confidence as the evidence base for dietary and lifestyle interventions in ADPKD is limited. To date, major interventional trials including protein restriction and increasing water intake have provided negative outcomes [6, 7]. Nonetheless, observational studies based on longitudinal patient cohorts have shown

Received: 23.3.2022; Editorial decision: 24.3.2022

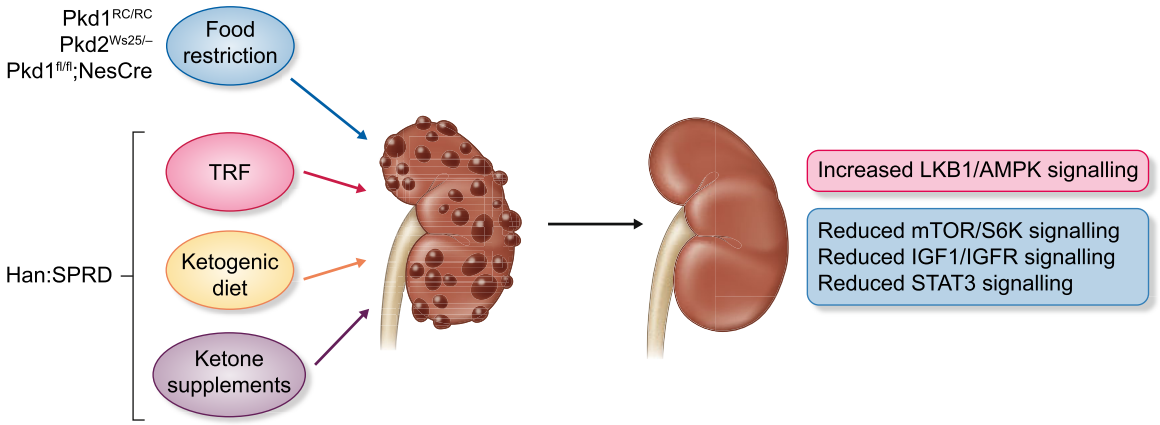

FIGURE 1: Dietary modifications in PKD rodent models. A number of dietary interventions have been shown to reduce cystic disease in rodent models of PKD. Moderate food restriction has been the best studied intervention in three orthologous models [10, 11]. Time-restricted feeding (TRF), ketogenic diets and ketone body supplementation have only been studied in the Han: SPRD rat [12]. The signalling pathways responsive to these interventions are Liver Kinase B1 (LKB1)/Adenosine Monophosphate activated Protein Kinase (AMPK), Mechanistic Target of Rapamycin Complex 1 (mTORC1), Insulin-like Growth Factor-1 (IGF-1) and Signal Transducer and Activation of Transcription 3 (STAT3), depending on the model.

negative associations between daily sodium intake [8] or body mass index (BMI) [9], with the rate of estimated Glomerular Filtration Rate (eGFR) decline implying that sodium or caloric restriction might have beneficial effects on disease progression.

Recent results from animal studies have led to a resurgence of interest in the role of dietary modification in ADPKD (Fig. 1). First, two groups showed that moderate food restriction was able to slow disease progression in *Pkd1* and *Pkd2* mouse models, potentially in a dose-dependent manner [10, 11]. Next, the benefit of fasting could be reproduced in a non-orthologous PKD rat model (Han: SPRD) not only by time-restricted feeding (compared with *ad libitum*) but also by a ketogenic diet given *ad libitum* [12]. More remarkably, dietary supplementation with ketones, specifically β-hydroxy-butyrate (BHB), in mice otherwise fed *ad libitum*, had the same effect. BHB administration was shown to slow disease progression in both juvenile (week 3–8) and adult (week 8–13) rats by reducing cyst number and cyst size, respectively. Finally, the authors further provided indirect evidence to support their hypothesis in other models (*Pkd1* conditional mice, *PKD1* cat) showing that acute fasting was able to induce increased apoptosis of cyst epithelia leading to shrinkage of individual cysts. The effect of a ketogenic diet or ketone supplementation was not tested in these models.

Ketogenic diets through adherence to a high-fat, very-low-carbohydrate intake have been used for over 100 years in the management of childhood epilepsy [13], and ketone body (BHB) dietary supplements are in widespread popular use in the self-management of obesity. Ketosis can also be induced by fasting or caloric restriction (CR). Fasting results in a metabolic switch to production and utilization of ketone bodies, i.e. β- hydroxybutyrate and acetoacetate. Intermittent fasting (IF) and time-restricted diets (TRD) are alternative dietary interventions that produce similar effects to CR through the periodic activation of fasting-responsive systems, such as the AMPK pathway, without requiring constant restriction [14]. The term IF encompasses repeated fasting periods of a day or more (e.g. alternate-day fasting), while TRF refers to a restricted daily eating window. For example, 16:8 TRF consists of 16 h fasting and 8 h eating *ad libitum*. A hypocaloric ketogenic diet (KD) has been demonstrated to be safe and effective for weight loss in obese individuals with early kidney failure (stage 2 chronic kidney disease), nearly a third of whom, surprisingly, had improved renal function after a 3 month intervention [15]. Although CR holds promise, its implementation is challenging due to side effects [16].

In this study, Strubl *et al.* compiled information volunteered by ADPKD patients who had self-initiated a ketogenic dietary intervention (KDI) for at least 6 months [1]. A total of 131 patients were recruited through PKD patient advocacy groups and social media sites in the USA (88%) and Germany (12%), which included TRD ($n = 52$), KD ($n = 74$) and CR ($n = 5$). The study design was retrospective and uncontrolled, and relied on online self-reporting of symptoms, medical history and investigation results. The median age of the participants was 50 years, with a mean eGFR of 57 mL/min/1.73 m^2 and the patients were mostly women (70%).

Perhaps unsurprisingly, 90% of patients reported significant weight loss (median BMI reduction 3.1) and 64% reported lower blood pressure. Although a validated general or ADPKD-specific quality-of-life questionnaire was not used, 80% reported improvements in their overall health and 64% noted improvement in PKD-associated symptoms. More surprisingly, a mean increase in eGFR of 3.6 mL/min/1.73 m^2 after 6 months of KDI was reported by a subgroup of patients (45/70), although the rest (25/70) had either no change in eGFR or noted a decline. Considerable caution should be applied here since these observations were based on two single values obtained in an uncontrolled, unblinded and unconfirmed fashion.

About 66% reported diet-emergent side effects most commonly fatigue, hunger or 'keto-flu' and 40–42% reported intermittent breaks in their dietary regime every month suggesting that long-term tolerability is an issue even in this highly motivated group. About 17% raised significant safety concerns largely to do with increased cardiovascular risk due to increases in total and Low Density Lipoprotein cholesterol of 13 and 8.5 mg/dl, respectively. Only one patient, however, reported the development of kidney stones, a recognized complication of long-term KD in children [13].

In summary, just over half of the patients self-enrolled in the study were able to comply with their KDI for at least 6 months. Despite some objectives and subjective health benefits, the study also raises important questions about long-term

tolerability and safety of such interventions. Based on these results, long-term individual compliance is likely to be an issue and thus the ability to detect a clinically meaningful benefit on eGFR or total kidney volume will be limited. Apart from the potential increase in cardiovascular risk, rebound metabolic effects including those on polycystic kidney growth following the cessation of a KDI are presently not known.

A follow-on single centre study in 10 ADPKD patients with rapidly progressive disease to examine the acute effect of a ketogenic state (either 72 h fast or 14 days of a KD) on TKV has been completed (RESET-PKD, NCT04472624). A second open-label single centre randomized study (KETO-PKD, NCT04680780) is currently active, with 63 patients assigned either to a KD for 3 months, acute fasting for 3 days every month or *ad libitum* diet, using TKV growth as an outcome measure. Results of these short-term studies are awaited with interest.

In summary, the results of this study suggest that a long-term trial examining the effect of KDI on ADPKD disease progression could be difficult to execute successfully. One possible intervention not examined in the present study is to trial BHB supplementation in an adequately powered randomized placebo-controlled trial in a representative ADPKD cohort, assuming that clinically relevant levels of ketosis can be safely achieved and well tolerated. Until there is convincing evidence for such a benefit, we should be cautious in recommending KDI or ketone supplementation to our patients, despite the encouraging preclinical findings.

CONFLICT OF INTEREST STATEMENT

A.C.M.O. reports having received consultancy fees from Galapagos, Mironid, ONO, Palladio and Sanofi-Genzyme, companies working in the field of ADPKD. All money is paid to his employing institution. R.T. has received grants and/or remuneration from Otsuka, Ipsen, Sanofi-Genzyme, Galapagos and Reata, companies working in the field of ADPKD. R.T. is member of the *CKJ* editorial board.

REFERENCES

1. 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. *Clin Kidney J* 2022; in press
2. Ong AC, Devuyst O, Knebelmann B *et al*. Autosomal dominant polycystic kidney disease: the changing face of clinical management. *Lancet* 2015; 385: 1993–2002
3. Torres VE, Chapman AB, Devuyst O *et al*. Tolvaptan in later-stage autosomal dominant polycystic kidney disease. *N Engl J Med* 2017; 377: 1930–1942
4. Torres VE, Chapman AB, Devuyst O *et al*. Tolvaptan in patients with autosomal dominant polycystic kidney disease. *N Engl J Med* 2012; 367: 2407–2418
5. Ong ACM. Polycystic kidney disease: tolvaptan slows disease progression in late-stage ADPKD. *Nat Rev Nephrol* 2018; 14: 146–148
6. 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. *J Am Soc Nephrol* 1995; 5: 2037–2047
7. Rangan GK, Wong ATY, Munt A *et al*. Prescribed water intake in autosomal dominant polycystic kidney disease. *NEJM Evidence* 2022; 1: EVIDoa2100021
8. Torres VE, Abebe KZ, Schrier RW *et al*. Dietary salt restriction is beneficial to the management of autosomal dominant polycystic kidney disease. *Kidney Int* 2017; 91: 493–500
9. Nowak KL, You Z, Gitomer B *et al*. Overweight and obesity are predictors of progression in early autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 2018; 29: 571–578
10. Warner G, Hein KZ, Nin V *et al*. Food restriction ameliorates the development of polycystic kidney disease. *J Am Soc Nephrol* 2016; 27: 1437–1447
11. Kipp KR, Rezaei M, Lin L *et al*. A mild reduction of food intake slows disease progression in an orthologous mouse model of polycystic kidney disease. *Am J Physiol Renal Physiol* 2016; 310: F726–F731
12. Torres JA, Kruger SL, Broderick C *et al*. Ketosis ameliorates renal cyst growth in polycystic kidney disease. *Cell Metab* 2019; 30: 1007–1023.e1005
13. Kossoff EH, Zupec-Kania BA, Auvin S *et al*. Optimal clinical management of children receiving dietary therapies for epilepsy: updated recommendations of the international ketogenic diet study group. *Epilepsia Open* 2018; 3: 175–192
14. Pickel L, Iliuta IA, Scholey J *et al*. Dietary interventions in autosomal dominant polycystic kidney disease. *Adv Nutr* 2021; 13: 652–666
15. Bruci A, Tuccinardi D, Tozzi R *et al*. Very low-calorie ketogenic diet: a safe and effective tool for weight loss in patients with obesity and mild kidney failure. *Nutrients* 2020; 12: 333
16. Lee JH, Verma N, Thakkar N *et al*. Intermittent fasting: physiological implications on outcomes in mice and men. *Physiology (Bethesda)* 2020; 35: 185–195