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Dietary and lifestyle interventions in ADPKD – a review of current literature

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ABSTRACT

Background and aim. Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary nephropathy. The only approved therapeutic option is tolvaptan, which has limited availability. Disease-modifying interventions are a topic of strong interest, and with growing understanding of metabolic pathways that are disrupted in ADPKD, new therapeutic possibilities are being explored. This review discusses the promising role of dietary and lifestyle interventions in management of ADPKD.

Materials and methods. The paper analyzes studies in databases such as PubMed, Google Scholar, ResearchGate, and other scientific databases. Clinical trials, double-blind

randomized controlled trials, meta-analyses, systematic reviews, and other review articles were included in the study.

Conclusions. Among interventions that have established disease-modifying potential in pre-clinical studies are dietary interventions leading to induction of ketosis, which has been shown to slow cyst growth in pre-clinical studies. However, little is known about long term benefits and safety of such interventions. Increased water intake and low salt consumption also have the potential to slow cystogenesis, but current research remains inconclusive regarding their efficacy. Lifestyle interventions such as physical activity and cessation of smoking play an important role in management of common comorbidities and help improve quality of life. Further research is necessary in order to establish optimal dietary treatment that corresponds to ADPKD patients' specific metabolic needs.

KEYWORDS: autosomal dominant kidney disease, dietary intervention, chronic kidney disease, ketogenic diet, physical activity

INTRODUCTION AND OBJECTIVES

ADPKD is the most common hereditary kidney disease, affecting approximately 1 in every 1000 subjects in the general population(1) It manifests clinically through the development of bilateral renal cysts throughout life, resulting in increase in total kidney volume and progressive loss of kidney function, leading to kidney failure commonly during or after the 6th decade of life(2). Other renal manifestations are related to increased kidney volume and cyst formation and include flank pain, kidney stones, cyst rupture and urinary tract infections. Extra-renal manifestations include hepatic and pancreatic cysts and vascular complications such as intracranial aneurysms, which are found 4-5 times more frequently in ADPKD patients than in the general population(3)

At present, there is only one drug that has been registered for treatment of ADPKD. Tolvaptan, a selective nonpeptide antagonist of the arginine vasopressin receptor type 2, has been shown to slow renal cyst formation and subsequent loss of kidney function(4). Unfortunately, access to tolvaptan is limited due to restrictive inclusion criteria and prohibitive cost of the treatment. Besides tolvaptan, management of ADPKD consists of pharmacological treatment of concomitant conditions such as hypertension and kidney

replacement therapy (KRT) after reaching End Stage Renal Disease (ESRD)(5). The research on other therapeutic modalities, such as lifestyle and dietary interventions, remains limited and guidelines are mostly in line with general recommendations for chronic kidney disease (CKD)(5).

Dietary interventions in ADPKD management is especially promising field of research due to the recent discoveries regarding the presence of defective glucose metabolism in cystic cells, suggesting ineffective use of other energy metabolites, such as ketone antibodies(6). Intervetions that lead to induction of ketosis have been of particular interest in the recent years.

Dietary care is a topic of interest in management of many clinical conditions both for patients and healthcare providers, which is also the case for ADPKD. In a recent study of 747 survey responders, including ADPKD patients, carers and healthcare professionals, lifestyle interventions and diet were chosen among the top 10 research priorities(7). Such interventions have the potential to not only improve patient outcomes, but also to give ADPKD patients a sense of control over their health.

ADPKD can vary significantly in severity, age of onset and progression rate even among members of the same family(8,9). This suggests that apart from genetic variability, environmental and dietary factors might contribute to the diversity of phenotypes that are observed in clinical practice. Furthermore, it has been demonstrated that in addition to underlying gene mutation renal injury – which can be caused by dietary factors – acts as a necessary trigger for development of cystic disease(10). Diet also plays an important role in management of CKD regardless of etiology of the disease, with the potential to slow its progression and manage symptoms associated with accumulation of metabolic products due to insufficient kidney function. Additionally, dietary treatment plays an important role in management of concomitant conditions such as hypertension, type 2 diabetes and obesity.

The purpose of this review is to describe the specific dietary interventions that have become objects of research and discuss them as potential parts of multispeciality, holistic management of ADPKD patients and consider potential benefits and risks associated with dietary treatment.

METHODS

A literature review was conducted using data bases such as PubMed and Google Scholar with search terms like "dietary modification in ADPKD patients", "lifestyle

interventions in autosomal dominant polycystic kidney disease patients", "ketogenic diet in ADPKD patients", "diet in chronic kidney disease", "water intake" and related variations. The focus was on clinical trials, double-blind randomized controlled trials, meta-analyses, systematic reviews, and other review articles. Priority was given to articles published within the last five years to ensure that the review captured the most up-to-date research in this rapidly evolving field. Case reports were not included in the review.

INDUCTION OF KETOSIS

In recent years, dietary interventions aimed to correct metabolic defects present in ADPKD have become a topic of interest. Various ways of inducing ketosis have shown promising results in pre-clinical studies. Nonetheless, research regarding the long-term impact of ketosis on ADPKD patients and safety of implementation of dietary interventions associated with its induction remains scarce.

There are multiple interventions that can lead to ketosis, including various forms of caloric restriction, e.g. daily caloric restriction, where daily caloric intake is restricted by a certain percentage of caloric needs, time restricted feeding, where caloric intake is limited to a specific time interval each day and intermittent fasting, which implies a substantial reduction of caloric intake for up to three non-consecutive days per week. Another approach is the ketogenic diet, which is defined as any diet which leads to the induction of ketosis. It commonly is a high fat and very low carbohydrate diet. Oral supplementation of beta-hydroxybutyrate (BHB), which is readily available in many countries, is yet another way of inducing ketosis.

Ketosis has been shown to strongly inhibit renal cyst growth and fibrosis in polycystic kidney disease mouse models on which different approaches to induction of ketosis were tested[3] In the study, time restricted feeding, ketogenic diet and acute fasting led to consistently promising results.

Ketogenic diet has a long history as a safe therapy for paediatric epilepsy(12), and has grown in popularity as an effective way of achieving weight loss(13). Very low-calorie ketogenic diet has been shown to be a safe and effective in treatment of obesity in patients with mild kidney failure, with some patients even achieving normalization of glomerular filtration rate after the intervention(14). In a study of 131 ADPKD patients who had self-initiated a ketogenic dietary intervention, 90% of patients reported significant weight loss and

overall health improvement(15). Another clinical trial, where 23 patients were randomized to a ketogenic diet group, found that ketogenic diet lead to significant reduction in body fat and reduced kidney volume compared to the control group(16). Interestingly, in this study ketogenic diet has been associated with improved kidney function at the end of the 3-month-long intervention.

Ketogenic metabolic therapy as a form of medical nutritional therapy may become a therapeutic option in treatment of CKD caused by overnutrition and diabetes mellitus(17) Due to its efficacy in treatment of obesity, ketogenic diet might be especially beneficial in ADPKD patients with high body weight. The prevalence of obesity in ADPKD patients reflects that of general population and continues to rise (18). Overweight and obesity have been associated with faster progression in early-stage ADPKD(19)Accumulation of adipose tissue and resulting chronic inflammation might exacerbate metabolic dysfunction associated with cyst development(18). High BMI has not only been associated with accelerated cyst growth and loss of kidney function, but is also one of the key modifiable cardiovascular risk factors(20). Additionally, obesity is one of the known causes of focal segmental glomerulosclerosis (FSGS), which could lead to further exacerbation of kidney function.

However, ketogenic diet is not without its risk. Notably, it has been associated with an increased risk of nephrolithiasis(21), which remains a particular concern for ADPKD patients. It has also been associated with fatigue, hunger and increase in Low Density Lipoprotein cholesterol(15).

In the most recent guidelines, KDIGO does not recommend ketogenic diet in ADPKD patients due to limited research regarding the efficacy and safety of the diet in this patient population(5). Without further proof of its disease-modifying effect, it appears sensible to remain cautious in introducing ketogenic diet in ADPKD patients, especially those with higher cardiovascular risk or history of nephrolithiasis. Conversely, ketogenic diet might prove to be an especially useful therapeutic measure in ADPKD patients with obesity.

It has been demonstrated that even mildly elevated levels of BHB are associated with less decline in kidney function in ADPKD patients(6). While no association with total kidney volume was observed, the favorable effect of BHB on the eGFR slope is noteworthy.

In animal models, BHB supplementation has been found to ameliorate disease progression and lead to a decrease of markers of cystic disease(22,23). In combination with citrate supplementation, BHB has produced a synergistic effect. The results of this study show

promise, and the potential of BHB and citrate supplementation are an interesting avenue of research, especially due to the wide availability of both compounds.

Pre-clinical studies on mouse models have demonstrated that mild reductions in food intake significantly inhibit renal cyst growth[4,5]. Torres et al. have demonstrated that TRF in a PKD rat model slows ADPKD disease progression[3]. In adult rats, a single 48-hour-long fast has been observed to significantly reduce the size of kidney cysts(23)

Moderation in caloric intake has been recommanded for the management of ADPKD(26) Dietary interventions are often difficult to implement and maintain for long term. In a year-long study of 28 ADPKD patients, the daily caloric restriction group has achieved greater weight loss than the intermittent fasting group(27). DCR has also been associated with greater adherence, safety and tolerability than intermittent. Additionally, the study found that achievement of clinically significant weight loss and reduced abdominal adiposity were associated with slower kidney growth.

SALT INTAKE

Studies have shown that high salt intake is associated with a faster rate of kidney volume growth and a more rapid loss of kidney function.

In an observational study of 589 ADPKD patients with a wide range of kidney function, Kramers et al. have found that 1 g of salt intake was associated with 0.11 ml/min per 1.73 m^2 annual reduction in eGFR in the cohort(28), which suggests that salt restriction might postpone ESKD and the need for KRT.

In patients treated with tolvaptan, aquaresis-related adverse effects are widely and frequently reported(4). Lower salt intake has been associated with lower urine volume, and thus might improve the tolerability of the therapy(29). Moreover, lower salt intake has been associated with lower vasopression levels, which suggesests it might also amplify the renoprotective effect of tolvaptan(28,29).

Reduction of salt intake is also recommended as a part of nutritional therapy of hypertension(30). Hypertension is a common symptom of ADPKD and is associated with more severe presentation of cystic disease(31). Early onset of hypertension has been linked with increased kidney volume and progression to kidney failure(32). Both ECC hypertension management guidelines and KDIGO guidelines for management of ADPKD patients recommend a maximum salt intake of 5 g per day(5,30).

PROTEIN INTAKE

The role protein intake plays in the development of CKD is controversial, but high protein intake has been linked to hyperfiltration and renal function decline(33). Other studies have disputed this, showing that higher protein intake might have a renoprotective effect(34).

Guidelines for management of CKD recommand a low-protein diet for patients with CKD G3-G5, suggesting a daily intake of 0,8g/kg of body weight(35). High protein intake should be avoided in patients at risk of progression(35), which applies to ADPKD patients as well. Recently published KDIGO guidelines for management of ADPKD recommand a moderate protein intake of 0.8-1.0 g/kg of body weight/day, which is in line with WHO recommendations for the general population(36). In an observational study of 589 ADPKD patients, Kramers et al. have found no association between protein intake and annual change in eGFR(28) which suggests that general recommendations should be followed.

The source of dietary protein is also an important to consider. Multiple studies have demonstrated the protective role of plant-based protein on kidney function, observing a lower risk of development of CKD in patients with greater dietary plant protein intake (34,37,38). Additionally, a healthy plant-based diet has been associated with reduction of inflammation and improved cardiovascular health(39,40). The research on plant-based diets in ADPKD patients is very limited. A study of 106 patients has shown that adherence to a healthful plant-based diet has been associated with lower peripheral inflammatory parameters(41). While dietary plant protein intake has been found to be inversely associated with CKD, the study has also found a positive correlation between animal protein intake and eGFR(41). Therefore, the quantity of protein consumed might be of more importance than it’s dietary source. Further research is needed to assess the safety and possible benefits of different types of diet in ADPKD patients.

Abnormal kidney function and organomegaly are risk factors for malnutrition in ADPKD patients(36). It is important to carefully consider introduction of low-protein diets in patients who are metabolically unstable, frail or with sarcopenia(42), and if such regimen is adopted, it requires careful and frequent monitoring. Higher intake of total, animal and plant protein has been associated with lower mortality in older CKD patients, which highlights the need for careful consideration of risk and benefits of low-protein diet in this group of patients(43).

WATER INTAKE

High water intake causes suppresion of AVP release. Elevated AVP levels are a common finding in ADPKD patients and are associated with cystogenesis and disease progression. It has been theorized that drinking large amounts of water might be an alternative to pharmacological vasopressin blockade, which would be of particular interest for ADPKD patients for whom tolvaptan treatment is unavailable.

Urine osmolality is highly correlated with AVP and its surrogate's – copeptin – levels in ADPKD patients(44). As such, it is commonly used in clinical trials. In an 8-week long clinical trial, 67% of increased water intake group achieved target 24-hour urine osmolality of 270 mOsm/kg or lower, compared with the ad libitum water intake group where only 24% of patients achieved this result(44), which suggests its feasibility of this intervention. Another study found that increased water intake lead to slower rate of cyst growth in patients at risk of rapid progression of ADPKD(45).

However, a different study by Rangan et al. reported no difference in kidney volume growth between the group prescribed a coached, increased water intake versus the control group(46). In a randomized controlled 3-year clinical trial, the researchers found that only 52,3% of patients achieved the target 24-hour urine osmolality of 270 mOsm/kg and reported no reduction in serum copeptin, which is a surrogate marker of AVP levels. It has also been reported that 20,8% of patients found increased water intake intervention to be impossible to maintain in the long term(46). Appropriate water intake is also an important factor in prevention of kidney stone formation. In patients treated with tolvaptan, increased thirst resulting higher fluid intake lead to lower risk of urinary lithiasis(47), and, consistently, patients who do not receive this treatment should be urged to maintain sufficient hydration.

PHYSICAL ACTIVITY

There is limited published data on physical activity in ADPKD patients. Remaining physically active helps maintain a healthy body weight and contributes to a good QoL. As ADPKD progresses, many patients will become reliant on dialysis as a form of kidney replacement therapy. In dialysis patients, physical inactivity was linked with worse physical functioning and health-related quality of life (48). KDIGO recommands that adults with ADPKD undertake moderate-intensity physical activity for at least 150 minutes per week or

to a level compatible with their physical fitness and undertake at least an hour of strength training twice a week. It is also recommanded that ADPKD patients with large and/or superficial kidney and/or liver cysts avoid contact sports with increased risk of injury and cyst ruptures(5).

SMOKING

Smoking cigarettes is a known risk factor of cardiovascular disease development in CKD patients, and it is linked with higher cardiovascular morbidity and mortality(35). Additionally, it's a known modifiable risk factor of intracranial aneurysm development and rupture(49). Smoking has been shown to exacerbate proteinuria, which could further contribute to a faster rate of disease progression. It has also been associated with kidney function deterioration(50). In ADPKD patients, smoking has been associated with impaired endothelial function and subclinical atherosclerosis(51). In animal models, it has been shown to accelerate development of renal cyst disease(52). Therefore it appears that cessation of smoking can contribute not only to an improvement of overall health, but might also slow ADPKD progression.

CONCLUSION

The impact of dietary factors on progression of APDKD is a promising field of research. Interventions with disease-modifying potential need further research in order to establish the safety of their long-term implementation. Improved understanding of disease pathophysiology and growing body of evidence of dietary intervention efficacy in both animal models and clinical trials involving ADPKD patients might play a role in developing other modalities of disease-modifying therapy, which would be of particular importance to patients who are for various reasons unable to be treated with tolvaptan. Of particular interest are dietary interventions which result in induction of ketosis, such as caloric restriction, intermittent fasting and ketogenic diet. Their role in enhancement of metabolic health and slowing of kidney cyst growth and loss of kidney function requires extensive clinical research to be confirmed.

Additionally to their disease-modifying potential, dietary and lifestyle modifications can contribute to overall improved health and quality of life and lead to lower risk of cardiovascular disease, which is a major cause of morbidity in the general population.

It is important for healthcare practitioners to be able to give well-informed recommendations regarding lifestyle and diet to their patients. At present, the dietary guidelines for individuals with ADPKD are similar to those in CKD. Personalized dietary guidelines which consider the risks and benefits of specific interventions and restrictions and which include weight management, can play a role in ADPKD management and contribute to longer preservation of kidney function. Relatively cheap and simple interventions have the potential to delay the need to rely on RRT and help preserve a higher quality of life of individuals with ADPKD.

Disclosures

Author Contribution Conceptualization, MS, and SP; methodology, MS; software, SP; check, MS, MS; formal analysis, SP; investigation, SP; resources, MS; data curation, SP; writing - rough preparation, MS; writing - review and editing, SP; visualization, MS; supervision, SP; project administration, MS;

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