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Review of Treatments for ADPKD on Tolvaptan and ketogenic Dietary Intervention as a Novel Therapy

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Abstract. Autosomal dominant polycystic kidney disease (ADPKD), the most prevalent genetic kidney disease, affected millions of individuals worldwide. And it is also one of the most prevalent causes of kidney failures and transplants. Previously, in many years, mitigating its symptoms had been the only treatment for this disease. After more than a decade after the early clinical studies of medicines for ADPKD began, the first medication that may successfully delay the course of the condition is now on the market. Due to the severe side effects and high cost of tolvaptan, it cannot be considered a full success, but rather the beginning of therapeutic research. More recently, enlightened by the discovery of the defective metabolism of PKD related cells, researchers have been designing dietary plans and new lifestyles for ADPKD patients to slow down or even halt the disease progression. Current outcomes have been promising. This article will address the best practices for treating ADPKD patients, with a focus on medications that have been proved to be beneficial in preserving kidney's function and structure.

Keywords: autosomal dominant polycystic kidney disease, treatment, tolvaptan, metabolism, ketogenic diet

1. Introduction

Affecting millions of individuals worldwide, autosomal dominant polycystic kidney disease (ADPKD) is a widespread, fatal monogenic chronic illness, which affects millions of people worldwide with an incidence of at least one in a thousand [1]. The two-sided cyst formation that causes fibrosis, kidney structural expansion, and a decline in kidney function distinguishes ADPKD from other kidney diseases. In most situations, the patient would eventually need dialysis or a kidney transplant [2]. A heterozygous mutation is the proposed cause of the disease. Slightly above 80% of all cases are triggered by mutations of PKD1 gene, and the rest of the patients are triggered by PKD2 gene mutations. Patients with the mutated PKD1 gene generally have more acute symptoms and faster disease progression than those with the mutated PKD2 gene [3]

Recently, advanced treatment mainly focused on using tolvaptan as the medicine to reduce the decline of kidney function by reducing the growth of cysts. This medication for ADPKD was authorized by FDA. However, only a small number of patients have access to tolvaptan, a vasopressin receptor antagonist. Moreover, it has serious side effects, is expensive, and only slows the illness's development rather than stopping or reversing it [4]. Owing to adverse events and other side effects, Tolvaptan treatment was also linked to a higher dropout rate [5]. As a result, there is a critical need for treatment choices that are more broadly available, more efficient, and safer.

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According to recent research, the physiological state of ketosis may help diet limitations function more effectively. To be more specific, according to a recent study, cyst cells involved in ADPKD exhibit a modified metabolism marked by faulty construct and function of the mitochondria, a dependency on glucose and glycolysis, and malfunctioning fatty acid oxidation. Furthermore, ketogenic dietary interventions (KDI) were found to initiate ketosis that can significantly inhibit kidney fibrosis, growth of cysts, and signaling pathways associated with ADPKD [6]. This paper gives an overview of general measures for ADPKD management and those two treatments and mainly discusses the research process, mechanisms, and outcomes of the treatments.

2. Current therapies

Some critical innovations in the treatment decelerate the decline of kidney function by reducing the development speed of cysts. General guidelines for all those afflicted by or at risk for ADPKD include a balanced diet and lifestyle, maintaining of bodyweight, everyday workout, quitting smoking, and avoiding nonsteroidal anti-inflammatory drugs [7]. In early-stage ADPKD, excess weight and obesity are linked to increases in total kidney volume as well as decreases in estimated glomerular filtration rate (eGFR). It is also well known that elevated water consumption is effective in preventing and reducing the formation of kidney stones. Individuals suffering from ADPKD are recommended to have a salt intake of 5g per day. Such amount is approximately equal to the recommendation in the overall patient population with other chronic kidney diseases [7]. Furthermore, post-hoc analysis of the HALT-PKD demonstrates high salt intake and secretion result in rapid expansion in total kidney capacity in early-stage ADPKD may lead to deterioration in eGFR specifically in later-stage ADPKD [8]. And it is generally recommended to protect enlarged kidneys from abdominal damage. Early management of hypertension is a crucial part of ADPKD. Educating patients this morning to improve their lifestyle should be a routine part of clinical practice for ADPKD management [9].

3. Vasopressin V2 receptor antagonism

More recently, Tolvaptan (a highly selective vasopressin V2 receptor antagonist) was found to have the effect of delaying the progression of ADPKD disease and has been authorized for treatment of ADPKD. It has been demonstrated to retard the advancement of cysts and the gradual reduction in eGFR. Initially, preclinical investigations have shown that arginine vasopressin-mediated cAMP drives fluid secretion and cyst development in ADPKD. In disease models in rodents, reduction of vasopressin secretion by increased water consumption, antagonism of vasopressin V2 receptors, or genetic deletion of vasopressin reduced cyst burden [4]. Using vasopressin V2 receptor antagonists, ADPKD patients were evaluated in light of these results. Lasting over 3 years, a phase 3 study of Tolvaptan managed to include 1445 ADPKD patients, with ages ranging from 18 to 50 [4]. Over the course of a three-year study, tolvaptan suppressed the growth in total kidney volume, and the most substantial medication outcome was observed in the first year. Patients treated with tolvaptan had a 2.8% per year increase in total kidney volume, while patients treated with placebo exhibited an average of 5.5% increase per year [4]. The secondary outcome measure of declining renal function was similarly significant.

As anticipated, thirst, nocturia, polyuria, polydipsia, and pollakiuria are common undesirable aquaretic symptoms associated with the medicine's mechanism of action [5]. In the phase 4 extension trial of the previously mentioned research (TEMPO 4:4), researchers observed that 9 percent of those who converted to tolvaptan terminated therapy because of aquaresis. During the 5-week single-blind portion of the REPRISE study, polyuria was the most prevalent side effect (31.7%), and 4.6% of patients stopped tolvaptan owing to aquaretic episodes. Torres et al. suggested that included patients from all randomized trials. They found that thirst and polyuria were more widespread amongst people who received tolvaptan for a shorter duration, implying that aquaretic adverse effects might diminish quickly [5].

However, clinically significant elevations in liver enzyme values were unanticipated, with the value reaching 4.4% in the tolvaptan group while it was only 1% in the placebo group [5]. Three cases of

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hepatotoxicity reaching the required Hy's Law criteria were identified in this population of patients (an elevation of liver function tests and bilirubin); hardly any of them displayed with organ failure, and all three patients recovered completely [5]. Likewise, the duration of the REPRISE trial was comprised of monthly testing. However, there are no serious cases. As a result, only one case of sudden liver failure requiring organ transplantation in a patient with ADPKD receiving tolvaptan has been documented so far. To present, only a single instance of ADPKD patients treated with tolvaptan requiring an organ transplant due to abrupt liver failure has been documented [5].

Via lowering its renal clearance, tolvaptan is very likely to increase serum uric acid concentrations, as proposed. Recent research found that the tolvaptan treatment was linked with a substantially greater incidence of hyperuricemia. Its commonality rose to 3.9 percent, whereas the value was only 1.9 percent in the placebo group, while gout also rose to 2.9% from 1.4% [4]. Despite this, no medicine was discontinued as a result of an increase in uric acid. The long-term follow-up of TEMPO and REPRISE trial participants revealed that 2.8% of Tolvaptan-treated patients had hyperuricemia [5]. Concerning the likelihood of nephrolithiasis, new study discovered that tolvaptan lead to lower supersaturation ratios of brushite, calcium oxalate and uric acid, along with decreased urine net acid output, resulting in a more significant lithogenic profile [10].

In addition, two instances of suspected tolvaptan-induced increase of blood creatine kinase, which is associated with muscular damage, have been recorded in 2019. The rise was minor, and creatinine kinase levels reverted to normal following medication cessation [10]. Due to the fact that it was not re-administered to test for recurrence, a definite association cannot be established at this time.

FDA has authorized the drug for the indication of lowering the decline in GFR in individuals having progressive ADPKD. Clearly, tolvaptan does not stop the disease's course. Unfortuitously, just a fraction of individuals qualifies for tolvaptan, and its usage is additionally impeded by toxicities and adverse side effects, as well as a relatively high price, rendering it inaccessible to the more significant part of afflicted persons throughout the globe [7].

4. Ketogenic dietary intervention

A recent study has shown that ADPKD cyst cells have an abnormal metabolism defined by faulty mitochondrial function and structure, impaired fatty acid oxidation, and dependence on carbohydrates and glycolysis [6]. These traits resemble the Warburg effect, which is eminent in several types of cancer and is believed to promote cellular survival and development [11]. Using the glycolysis inhibitor 2-deoxy glucose, carbohydrate dependence has been exploited for pharmacological intervention in PKD animal models [8]. New evidence shows that pharmaceutical intervention might not always be required, but dietary therapies that influence metabolism may be highly successful and manageable in animal models of PKD.

As part of their roadmap of translational projects, a retrospective study series research was planned for 2021 to gather the first in-person observations from ADPKD patients about the feasibility, safety, and advantages of ketogenic dietary interventions (KDIs) in ADPKD [2]. The researchers were successful in obtaining 131 qualified PKD individuals, the majority of whom were located in the USA, for this trial, of whom 74 followed a KD and 52 a TRD. Surprisingly, according to the study, 80% of patients said their quality of life had improved. In addition, 67% of patients with other chronic health conditions also reported benefits after using KDIs. Quantitative data also supported their statement; individuals in the study cohort experienced an average reduction of BMI by 3.1 points and reported an average weight reduction of 9.1 kg. However, none of the patients had a BMI that indicated they were underweight [2]. The patients in this research did, however, experience other health issues, much like many other people who follow a ketogenic diet. On average, 2.6 additional mild KDI symptoms were reported by 66% of the subjects [2]. Despite HDL cholesterol levels and triglycerides levels seeming essentially unaffected, cholesterol levels were rising [2]. The Weimbs lab also particularly created a ketogenic diet for those with ADPKD towards the conclusion of the trial series, including dietary adjustments based on current research findings [9]. The overwhelming majority of participants

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believed that their involvement in This approach brought about major changes in their physical condition and welfare [9].

Initial evidence indicated that a moderate decrease in food consumption has a significant impact on the course of PKD in mice models. Subsequent study revealed that this effect is regulated by the metabolic ketosis state and several procedures that may induce ketosis, such as fasting beyond 20 hours, time-restricted dining, and keto diets. And these findings were shown to be highly reproducible in a number of other PKD animal models, including cats and rats [8]. By supplementing with high amounts of ketone beta-hydroxybutyrate, almost all of the beneficial effects of ketosis might be reproduced in animal models [8]. The physiological reaction to carbohydrate restriction that enables the body to use fat for energy is called ketosis, both from dietary sources and bodily reserves. Adipose cells produce fatty acids during ketosis, which the liver may then convert into BHB and ketone acetoacetate. Subsequently, fatty acids and ketones overtake carbohydrates as the predominant source of energy for the majority of the human body's organs, tissues, and cells [8]. During ketosis, the liver produces copious levels of BHB, which is considered the main ketone. It also works as a chemical signal with substantial cellular effects, including anti-inflammatory qualities, in addition to being used for energy generation.

In addition, these findings suggest that dietary and lifestyle habits that generate a persistently high blood sugar level could deleteriously accelerate the progression of ADPKD, compared to practices that can trigger the metabolic state of ketosis [12]. This matches clinical relationships. ADPKD patients with type 2 diabetes exhibited a total kidney volume (TKV) that was substantially larger than those who have ADPKD alone [12]. ADPKD patients without diabetes exhibited a significant correlation between fasting blood glucose levels and the rate of disease development, which can be measured from the average yearly TKV change, and the association was proven to be statistically significant [8,13]. In addition, renal stimuli that are mostly determined by diet may exert a devastating effect on the progression of ADPKD. In animal models, the consumption of oxalate or inorganic phosphate may cause the formation of calcium oxalate and calcium phosphate microcrystals, respectively, which are directly involved in the formation of renal crystals and can significantly accelerate the development of PKD [8].

There are continuing efforts to convert these study results into clinical trials. In a recent comprehensive clinical investigation lasted over 6 months and comprised 131 individuals, ADPKD patients that were on a specially designed ketogenic diet, which was later proven to be beneficial. It was discovered that ketogenic dietary interventions for ADPKD were medically safe, were seen by individuals as practical, and reportedly resulted in considerable reductions in pain and other common ADPKD symptoms and complications, in addition to substantial reductions in hypertension and eGFR [2]. Comparing the ketogenic dietary interventions versus intermittent fasting to the placebo group as well as how to effectively combine these two in disease management are the subject of current randomized clinical research seeking a larger sample size and deeper insights. Existing data indicated a correlation between slower kidney disease development and weight loss, indicating that the reported effects may include periods of ketosis [2]. In general, biological justification, animal model studies, and medical evidence strongly imply that a heavy carbohydrate diet resulting in hyperglycemia and prevention of ketosis, which is widespread among developed nations, is not desirable in ADPKD management and likely accelerates disease development [9,12].

With the advancement of diagnosis and treatment technology, more and more researches have been done on the treatment of ADPKD. Diet therapy can be used as the basis for different treatments. Concurrently with other treatments, may better relieve the patient's symptoms and improve the condition while minimizing adverse side effects. Relevant research should be further deepened and not limited to the use of single drugs or single methods. And with the understanding of ADPKD pathology, there are also some new improving drugs under investigation recently. Repurposing of existing drugs and anticipated combination therapy has the potential to improve the efficacy of ADPKD drug therapy.

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5. Conclusion

The inquiry into the molecular etiology and treatment of ADPKD has seen significant advancements in recent years. Significant improvements in biomedical imaging and molecular genetics have greatly enhanced the accuracy of diagnosis as well as prognoses, which are more important for both patients' welfare and future clinical trials. Several extensive clinical studies have yielded new information on the precise control of blood circulation, body mass, and dietary behavior, as well as the discovery of novel disease-modifying pharmaceuticals that target a particular phase in the course of a disease. In addition to the discovery of totally new medications, repurposing of existing pharmaceuticals and prospective combination treatments have the potential to increase the efficacy of pharmacological therapy for ADPKD while minimizing undesirable side effects. Nevertheless, unresolved inquiries and unclear understanding of disease mechanisms still remain. These include the discovery of biological markers of early-stage disease in order to facilitate medical studies; possible use of combination treatment that not only include previously mentioned treatments but more therapies under active development; enhanced comprehension of the advantages and micro-management of current treatment, lifestyle, and nutritional approaches; as well as a better comprehension of the role of modifier genes implicated in the course of the illness. Upcoming clinical trials and case studies will unquestionably enhance our knowledge of treating this acute disease.

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