

The mechanism of Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Abstract. Autosomal Dominant Polycystic Kidney Disease (ADPKD) has a long history, and it was first discovered after the death of King Stephen Bathory. Until now, the mechanisms are still unclear, but some hypotheses are supported by most people, such as the third hit, termination signal, cilia of pathogenic, and helix-helix interaction. Among all hypotheses, the one called “the third-hit” is the most widely accepted. In addition, recent studies found that germ-line mutations, somatic mutations, and ischemic or toxic damage will lead to ADPKD. Although ADPKD is incurable, some ways can lower the progress of the disease and maintain most of the kidney functions. The most general way of treatment is to adjust lifestyle, such as the ketogenic diet (KD) or time-restricted diet (TRD). Another popular way is symptomatic treatment. The article mainly introduced the mechanisms of ADPKD. To better understand the mechanisms, the basic structure and functions of the kidney will first be introduced.

Keywords: Autosomal Dominant Polycystic Kidney Disease (ADPKD), Mechanism, The Third Hit, Termination Signal, Cilia of Pathogenic.

1. Introduction

ADPKD is one of the most common autosomal dominant diseases, and the incidence rate of ADPKD is 1:1000 [1]. It has affected up to 12 million individuals in 2015 and is the fourth most common cause of renal replacement therapy worldwide [1]. Age of onset varies in patients, concentrated in periods from 30 to 60 years old. Normally, onset first occurs in 35 to 45 years old, however, there are still some people who have their first onset from 70 to 80 years old [1]. After the occurrence of onset, the state of illness can develop rapidly, and it is one common reason for mid-aged people to have uremia. The disease can be divided into three stages: the first stage with no symptoms, in the second stage onset, occurs, and in the third stage uremia takes place.

Autosomal Dominant Polycystic Condition (ADPKD) is a hereditary disease that causes increasing kidney enlargement, as well as hypertension, abdominal fullness, and pain, as well as episodes of cyst bleeding, gross hematuria, nephrolithiasis, cyst infections, and a lower quality of life. With the driving of the disease process, the structure and function of the kidney is been damaged, which leads to end-stage renal disease (ESRD). In ESRD, the majority of nephrons have been destroyed so renal function decline. PKD is a multi-system disease, with a lesion of the kidney, there is a high probability for other symptoms to take place, like cysts in other organs, and cardiovascular, muscular, and bone diseases. The complications increase the difficulty of curing PKD.

ADPKD is caused by mutations in the PKD1 or PKD2 gene, and these two genes produce polycystic 1 (PC1) and polycystic 2 (PC2). According to statistical reports, more than 85% of ADPKD cases result from a mutation in PKD1. According to another study, ADPKD is genetically diverse, and the disease gene is a primary driver of severity; PKD1 is linked to ESRD 20 years earlier on average than PKD2. Researchers have discovered that a mutation in the GANAB gene can also cause ADPKD. GANAB is a cystic condition that does not proceed to end-stage renal disease (ESRD).

For nearly 300 years, polycystic kidney disease (PKD) was thought to be an uncommon and incurable condition. More than half of patients need to receive renal dialysis or renal transplant in their sixtieth, leading to a great economic and spiritual burden on their families. With the development of medicine, the diagnosis of ADPKD is more advanced. Ways to diagnose ADPKD vary, including ultrasonography (US), magnetic resonance imaging (MRI), family history, clinical assessment for

external manifestations, and genetic testing in molecular diagnosis. Because of its huge size and complexity, most genetic testing, such as mutation screen by Sanger sequencing for PKD1, is technically demanding, labor-intensive, and expensive. As a result, most patients will not need molecular genetic testing, but it may be considered in cases of equivocal or atypical renal imaging findings; marked discordant disease in the family history; very mild PKD; sporadic PKD with no family history; early and severe PKD or PKD with syndromic features; and reproductive counseling.

Though ADPKD is an incurable disease, there are some methods to slow down the progression of the disease. The treatment should start early before the kidney parenchyma is damaged severely. Tolvaptan was licensed by the US Food and Medication Administration as the first drug treatment to halt kidney function deterioration in persons at risk of fast advancing ADPKD in recent years. Some doctors stated that when prescribing tolvaptan, doctors should take into account the patient's age, htTKV, and eGFR to determine who is at the most risk of rapid advancement. Another important therapeutic option is to change their diet to a ketogenic or time-restricted diet (TRD). Ketosis means reducing eating carbohydrates Keto diet or fasting, lowering blood glucose and insulin. So, the consumed and stored fat burning increases, and liver will break down fat into ketones. At last, ketones are released into the bloodstream.

Until now, a better understanding of the genetic, molecular, and cellular pathways underpinning ADPKD has resulted in the development of some new results and speculations about the disease's pathophysiology.

2. The basic structure and function of the kidney

The kidney plays a significant role in the urinary system, which filters the plasma and forms urine. Also, it is the most important organ in the human body for osmotic adjustment and excretion, and it has secreting function as well, which can synthesize renin.

The kidney has two parts: the medulla and the cortex. Collecting tubule, the loop of Henle, blood vessel, and supporting tissue are all in the medulla and glomerulus, proximal and distal convoluted tubule, supporting tissues, and nerves are in the cortex.

The nephron is the functional unit of the kidney, with roughly 1 million nephrons in each kidney. Nephrons include renal corpuscles and tubules. Corpuscles can be divided into glomerulus and capsules. The glomerulus is a capillary net that plays the first part in filtering blood in the kidney. Tubules have two types of convoluted tubules: proximal convoluted tubule and distal convoluted tubule. The collecting tube is related to the distal convoluted tubule; however, it is not a member of the tubules. The collecting tube, on the other hand, plays a function in reabsorption.

Urine is synthesized in the kidney, and the mechanism of synthesis is complex, including 3 steps: ultrafiltration, reabsorption, and secretion. An experiment in 1924 proved that the original urine (fluid in capsule) is ultra-filtrate of blood. The second step is reabsorption. In the proximal convoluted tubule, 67% of sodium ions are transported out by active transportation [2]. With the change of concentration gradient, substances like water, glucose, amino acids, vitamin, and other nutrients are reabsorbed. At the end of the proximal convoluted tubule, the volume of fluid become 1/4 of the original one [2]. The final stage is secretion. The proximal convoluted tubule and distal convoluted tubule will secrete potassium ions, ammonium, organic acid, base, drugs, and poisons into the fluid. These substances will be transported out of the body by urine.

Patients with ADPKD have problems with their tubules. In most cases, when crystal occludes tubules and disrupts the flow, tubules will dilate to re-establish the flow. After that, normal tubules will get back to normal, on the contrary, tubules with ADPKD will continuously dilate and cysts will grow.

3. History of PKD

Since the animals' internal organs have been exploited for feeding and/or slaughtered for God, PKD is a natural process that can be seen first in their internal organs [3]. In the first stage of observation, dead human bodies were great resources to help living one's boost understanding of cysts in kidneys.

The death of King Stephen Bathory marks the beginning of the recognition of PKD. Symptoms of PKD appeared after the king's last uniting trip and led to death within 9 days. Torres and Watson meticulously documented the progression of the condition, which included exhaustion, chest pain, loss of consciousness, weakness, chattering teeth, difficulty breathing, facial shivers, very pale facial color, and excessive sweating Edith weak and irregular heartbeats.

After 347 years, the real problem was first considered as the cause of death in a meeting called "400th anniversary of King's birth" [3].

4. Mechanism of the disease

Though the causes of the disease have been discussed for many years, there is no evidence for it. However, some hypotheses are supported by most people, including the third hit, termination signal, cilia of pathogenic, and helix-helix interaction. All hypotheses will be discussed below.

The most widely accepted hypothesis is the third hit. The hypothesis was originally dubbed "second hit," with the first hit being a germ-line mutation in a polycystic gene and the second hit being mutations in the remaining polycystic allele, resulting in the growth of Genoa's often diverse clinal cysts. However, other researchers have conducted tests that appear to show that a second hit mutation is unimportant. They used an inducible-gene null mouse model. They discovered that removing polycystic from mature kidneys had no immediate effect on the kidneys for months [4]. While interruption of polycystic or cilia in embryonic or early postnatal mice resulted in immediate, substantial renal cyst formation, the same disruption in fully developed kidneys resulted in cyst growth many months later. Polycystic and primary cilia appear to govern proliferation and cyst formation in developing and growing kidneys, but they have no effect on healthy adult kidneys.

So how can this problem be explained? Recent results from several groups provide important insights to explain the findings [4]. The explanation was that loss of polycystin or cilia in mature kidneys does not always result in the formation of renal cysts. The third hit has to be important to the progression. Ischemic and nephrotoxic injuries have lately been identified as major stressors that cause the third hit. Polycystin 1 was knocked out in mature mice via inductive gene knockdown in these experiments [4]. Following kidney damage, cyst development took occurred instead of normal tissue regeneration and repair. The experiments proved that simple mutation in polycystic or cilia may not be the reason for cysts formation, the third hit which is renal injury is needed to cause ADPKD.

To summarize, in the "third-hit" paradigm, three events must occur for the disease to be triggered. A germ-line mutation in the PKD1 or PKD2 gene is the first strike; the second is a random somatic mutation in a single tubule that affects the other PKD1 or PKD2 allele; and the third hit is an insult to the affected kidney, such as ischemia or toxic damage, which initiates a repair response.

Supersaturated solutes, such as calcium oxalate (CaOx), calcium phosphate (CaP), uric acid, and others, are present in the urine filtrate and may precipitate while traveling through the tubular system, posing a persistent challenge to the kidneys. Though millions of crystals may be formed in the tubule, most of them will be excreted out with urine. If too much crystal is stored in the tubule, it can lead to nephrolithiasis. Several correlative observations support that there is a correlation between PKD and Rena crystal burden. Patients with ADPKD are more likely to develop symptomatic nephrolithiasis (up to 20% to 28%), and those with nephrolithiasis had more severe PKD than those without [5]. Other diseases which resulted from crystal formation also occur in many ADPKD patients, including hyperoxaluria (18%), gout (24%), and hyperuricemia (>60%) [5]. All these statistical results indicate that crystal formation in tubules may be one of the results of causing PKD.

A group of researchers explored the probable impact of renal crystal exposure in changing the rate of progression of PKD in a molecular model to better understand this process [5]. In the previous study, they know that the excretion of micro crystal is accomplished by tubule dilation. They found that inducing CaOx crystal deposition in normal rats and mice resulted in rapid activation of the mTOR and SRC/STAT3 signaling pathways, as well as rapid tubule width dilatation throughout the tubular and collecting duct system. The same signaling mechanisms that lead to renal cyst development are known to be active in ADPKD. The CaOx crystals were removed by dilated lumen space after around 7 days of acute oxalate therapy, the signaling pathway was inactivated, and the tubule diameter was restored to normal. Tubule dilation is a mechanism that is initiated to flush out micro crystals, according to the findings. However, in PKD patients, after flushing out the micro crystals, there is persistent activation of mTOR or STAT3 pathways. So, there will be a continuous dilation of the tubule, leading to proliferation. To conclude, ADPKD kidneys are caused by persistent activation of mTOR/STAT3 and other pathways that lead to continuous tubule dilation and cyst growth.

In the process of improving the third-hit hypothesis, some others put forward another theory called the termination signal hypothesis. The epithelial structure originates from interstitial precursor cells. The cells accumulate and form a small lumen, and when the small lumen reaches a specific diameter, the sensor will send a termination signal to it to stop expanding [6]. In diseased kidneys, due to mutations in PKD1 and PKD2 genes, somatic cells will mutate as well and sensors will be unable to work. As a result, the tubule will continue expanding and form a cyst.

The third hypothesis is called cilia of pathogenic. It considers that the abnormal function and structure of cilia will directly lead to the formation of cysts. Non-mobile cilia in the kidney are a kind of primary cilia, it can directly touch the urine, but it pushes urine fluid to move. The damage to cilia function will lead to failure in transferring termination signal to tubule cells, resulting in uncontrolled expansion of the tubule, and forming cysts at last [7].

Another popular hypothesis is called helix-helix interaction. It is said that PKD1 is located on the surface of the cell membrane, connecting with other proteins to form receptors. And PKD2 is located in the endoplasmic reticulum, they interact with each other by helix on the C terminal, sensing stimulation on extracellular ligands, and sending cations as a second messenger to send a signal to the cell nucleus. As a result, any mutations that happen on either the PKD1 or PKD2 gene will lead to problems in signal generation and transduction pathway, resulting in PKD.

5. Treatments of ADPKD

ADPKD cannot be completely cured, so the main idea for treatment is to prevent complications, maintain the function of kidneys and delay the process of PKD. The most general way of treatment is to adjust lifestyle, including quitting smoking, limiting drinking, adjusting the diet structure, and preventing using nonsteroidal anti-inflammatory drugs and nephrotoxic drugs. Recently, the Weimbs Lab has published the first evidence that nutritional ketosis, is induced by the ketogenic diet (KD) or time-restricted diet (TRD). Improves disease progression in PKD animal models [5]. Ketosis means increasing the proportion of fat to 70%-80% as the main part, protein to about 20% to 25%, and a little carbohydrate for about 5% to 10% [5]. In this case, the blood glucose and insulin will lower, so stored fat burning will increase. The liver will break down fat into ketones, and ketones are released into the bloodstream. The brain will use ketones for energy instead of glucose. And there is a retrospective case series study designed to collect the first real-life observation of the safety, feasibility, and possible benefits of using KDIs to treat ADPKD. According to figure 1, about 56% of patients felt that KD improved their ADPKD symptoms, and 86% of patients thought that their health and well-being is improved by diet [5].

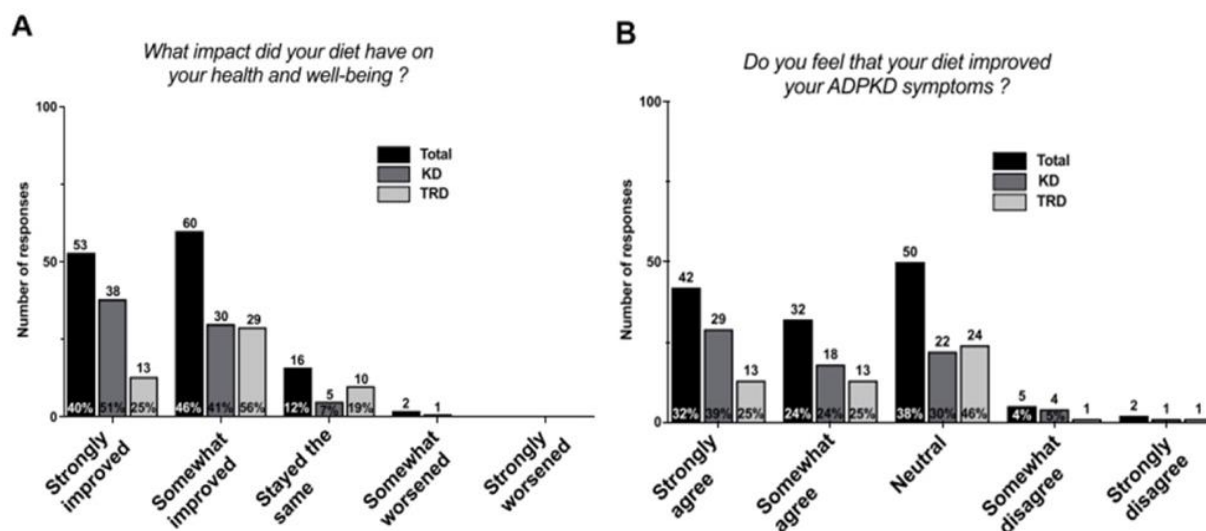


Figure 1. The result of using KDIs to treat ADPKD [5]. A) what impact did the ketosis diet have on patients' health and well-being. B) do patients feel that their ketosis diet improved their ADPKD symptoms.

Another popular way is symptomatic treatment. According to different symptoms, different methods will be used.

5.1. Pain:

The pain can be divided into acute pain and chronic pain. Acute pain is mostly caused by cysts breaking and inflammation. Under this situation, analgesics can be adapted, including acetaminophen and opioid. If the glomerular filtration rate (GFR) of the patient is normal, short-term nonsteroidal anti-inflammatory drugs can be used [8]. Traction of the renal pedicle, oppression of structure nearby, or abnormal activation of the sensory or autonomic nervous system can lead to chronic pain. The first choice is non-drug intervention, including physical intervention (like massage and physical treatment) and mental-educational intervention. Drug analgesia therapy can also be adapted, and it must follow the regulation of the World Health Organization's three-step labor pain: firstly, para-acetyl amino acid; secondly, nonsteroidal anti-inflammatory drugs, it is worth noticing that there is a limitation in ADPKD patients; thirdly, strong opioids. When drug treatments and conservative treatments are of no use, renal denervation, cyst puncture, and radiofrequency ablation can be adapted.

5.2. Hypertension

Cyst oppression can lead to ischemic injury of the kidney, activating the renin-angiotensin-aldosterone system (RAAS), leading to hypertension. Abnormal activation fa RAAS will worsen the ischemic injury, speeding the growth of cysts and forming a vicious spiral. The main point of ending the vicious spiral is the regulation of blood pressure. The treatment of hypertension includes non-drug intervention, like losing weight, sports, and diet limitations. In terms of drugs, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) can be considered [9]. If the patients do not have contraindication like renal artery stenosis, ACEIs are the first choice. It can slow down the progression of PKD and prevent left ventricle hypertrophy, lowering the mortality of cardiovascular disease.

5.3. Hematuria

Gross hematuria can take place when cysts in PKD patients connect with the collective system. Most hematuria is self-limiting, so conservative treatments can be adopted, like bed rest, and drinking the proper amount of water to prevent blood clots from blocking ureters. When cysts break which leads to massive hemorrhage, it is proper to adopt blood transfusion therapy. When conservative therapy and blood transfusion therapy are of no use, embolization therapy and surgical nephrectomy

can be considered. To dialysis patients with recurrent hematuria, small molecule heparin or non-molecule heparin dialysis should be used, and consider transcatheter selective renal artery embolization (forbidden for patients with intrarenal infection).

5.4. Urinary tract and cysts inflammation

When urinary tract and cysts inflammation happen, bacterial culture and drug sensitivity test should be completed, and adjust proper antibiotics. Liposoluble antibiotics can penetrate gradient cysts and water-soluble antibiotics can penetrate non-gradient cysts. So, in choosing antibiotics, antibiotics that can penetrate both gradient cysts and non-gradient cysts should be taken into consideration firstly, for instance, fluoroquinolone. Avoid using nephrotoxic antibiotics like sulfonamides, aminoglycoside antibiotics, and cephalosporins I / II to prevent damage to the kidney. The time of treatment cannot be less than 1 week.

5.5. Crystal

Increasing the intake of fluid is the main way to prevent crystals. If the crystal is not large enough and there are no obvious symptoms, conservative treatments can be adopted, including taking in more water and using sodium bicarbonate and vitamin D to correct metabolic abnormalities. Thiazide diuretics may work with hypercalciuria in recurrent renal calculi. If symptoms take place, extracorporeal shock wave lithotripsy or percutaneous nephrolithotomy can be adapted.

6. Other therapy

6.1. Working on calcium ions signal pathway

Targeted therapy can work efficiently on target organs, and significantly ease the symptoms of PKD. Tripterygium wilfordii is one of the most widely used Chinese herbal medicine. The triptolide can slow down the formation of cysts by promoting PC2-mediated intracellular calcium release. According to clinical research, proteinuria can be reduced by the intake of Tripterygium glycoside tablets among ADPKD patients with proteinuria, lowering the progress of the disease [10].

6.2. Working on cyclic adenosine monophosphate(cAMP) signal pathway

There are three possible therapeutic targets for the cAMP signal pathway. The first one is vasopressin V2 receptor antagonist—Tolvaptan. It can greatly inhibit the growth of cysts and lower the process of deterioration of renal function, and it is the first drug to intervene progress of ADPKD admitted by the FDA. However, the side effects of using tolvaptan are also severe, with symptoms like hematuria, renal pain, and liver injury. So, the drug is not recommended for long-term use. The second one is somatostatin analog—octreotide. Inhibiting adenylate cyclase (AC) lowers the concentration of cAMP, and promotes the secretion of vesicular fluid, lowering the progress of PKD. The third one is the phosphodiesterase (PDE) agonist. Promoting the degradation of cAMP can inhibit the formation of cysts. Effects of octreotide and phosphodiesterase did not have clinical tests yet.

6.3. Inhibitor of cell reproduction

By inhibiting cell reproduction, the formation of cysts can also be lowered. So, in the therapy process, drugs that can inhibit cell reproduction can also be taken into consideration. Tyrosine kinase inhibitor: bosutinib can postpone the formation of ADPKD cysts and growth in kidney size, but its long-term effects are needed to ensure. Immunosuppressant: by inhibiting the mammalian target of the rapamycin(mTOR) signal pathway, rapamycin can inhibit epithelial proliferation of cysts, revascularization, and fibroplasia. mTOR inhibitor can delay PKD progress, and improve kidney function, but it did not reach the expected effects in clinical tests. Cyclin-dependent kinase (CDK) inhibitor: by inhibiting cell reproduction, delay the deterioration of renal function. This drug is still clinically tested.

6.4. Renal replacement therapy (RRT)

Not only drugs but also other methods can play a role in ADPKD therapy, including renal replacement therapy (RRT) and surgeries. RRT includes hemodialysis, peritoneal dialysis, and renal transplant. Hemodialysis is one of the RRT treatments for both chronic and acute renal failure patients. By drainage of blood out of the body into the dialyzer, substance exchange takes place between dialysate and blood. Metabolic waste can be cleared, and electrolyte and acid-base balance can be maintained. Small molecule toxins like creatinine and urea ammonia can be eliminated by hemodialysis. However, due to the large change in blood volume, heart function may be damaged in the process and cardiovascular complications may happen.

The principle of peritoneal dialysis is similar to that of hemolysis. But in peritoneal dialysis, dialysate is injected into patients' peritoneal cavity, and solutes exchange down the concentration gradient. Peritoneal dialysis has an easier operation and a relatively stable internal environment. So, blood pressure can be better controlled and renal function can be reserved. However, small toxins cannot be eliminated by peritoneal dialysis, worse than hemodialysis. Depending on different situations of patients, different dialysis can be chosen. If permitted, allograft kidney transplantation can be adapted.

Surgeries include cyst decapitation decompression, trans renal arterial embolization, and nephrectomy. Cyst decapitation is the most widely used. Genetic therapy can be the most ideal way to treat ADPKD. Some researchers combine multiple annealing and looping-based amplification cycle (MALBAC) with third-generation IVF technology, enabling ADPKD patients to give birth to normal babies.

7. Conclusions

Knowing the basic structure and functions of the kidney first, it is easier to understand the mechanisms and therapy of ADPKD. ADPKD has been companied by humans for such a long time and has brought massive difficulties to the society, families, and individuals. ADPKD is a complicated genetic disease, although there are still no precise mechanisms to explain the happening of PKD, with the development of clinical technologies, the treatments of PKD have gained great achievement. Based on traditional symptomatic treatment, new medicine and new methods have appeared, including genetic treatment, and targeting treatment. What is more, by adjusting the diet structure, the progress of ADPKD can be lowered. Some Chinese herbal medicines also have great effects in improving the functions of the kidney and easing the symptoms. However, more clinical tests are needed to test the functions of these methods and medicines. There is still a long way to go to discover the most proper therapy. Researchers should not only put their efforts into developing new drugs but also notice the joint synergy between different drugs.

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