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The Inheritance, Pathophysiology, and Treatment for Polycystic Kidney Disease and Its Effects on the Heart—A Literature Review

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Abstract

Polycystic kidney disease (PKD) is an autosomal dominant genetic disorder that causes the formation of multiple cysts in the kidneys, leading to kidney failure. PKD is a common condition affecting approximately 1 in 500 individuals worldwide. The most prevalent type of PKD is autosomal dominant PKD (ADPKD). ADPKD is caused by mutations in either the PKD1 or PKD2 genes, which encode for proteins involved in cell growth and differentiation. These mutations lead to the formation of fluid-filled cysts in the kidneys, which can eventually lead to kidney failure. In addition to affecting the kidneys, PKD can also cause cysts in other organs, such as the liver, pancreas, and spleen. PKD can also lead to various complications, including high blood pressure, heart valve abnormalities, and brain aneurysms. This review focuses on the inheritance, pathophysiology, and treatment of PKD, with a specific emphasis on its effects on the cardiovascular system. Currently, there is no cure for PKD. However, several treatments are available to manage the symptoms and complications of the disease. These treatments include medications to control blood pressure, pain relievers, antibiotics for infections, and dialysis or kidney transplantation for kidney failure. Tolvaptan is the only FDA-approved drug specifically for ADPKD and has been shown to slow disease progression. In addition to summarizing current treatment options, this review will discuss promising future treatments, such as gene therapy and stem cell therapy.

Keywords

Polycystic Kidney Disease, Autosomal Dominant, Autosomal Recessive, End-Stage Renal Disease, Epidemiology, Pathophysiology, Cardiovascular Diseases

1. Introduction

Polycystic kidney disease (PKD) is a hereditary disorder characterized by the progressive development of fluid-filled cysts in the kidneys, ultimately leading to end-stage renal disease (ESRD) [1] [2]. This growth of cysts causes enlargement of the kidneys and renal dysfunction, with potential extrarenal manifestations [3]. Clinical consequences include hypertension, renal failure, and increased risk of infection [4].

PKD is classified into two primary types based on inheritance patterns: autosomal dominant polycystic kidney disease (ADPKD) and the less common autosomal recessive polycystic kidney disease (ARPKD). ADPKD is a systemic condition involving multiple organs. In 93% of cases, it is caused by sequence variations in the PKD1 and PKD2 genes, leading to cyst formation in the kidneys, liver, and pancreas [5]. ADPKD is frequently associated with gastrointestinal, cardiovascular, and connective tissue disorders. In contrast, ARPKD typically presents in childhood or early infancy with symptoms such as hypertension, enlarged kidneys, and fluid-filled cysts [1].

2. Background

Polycystic kidney disease (PKD) is a disorder characterized by the formation of fluid-filled cysts in the kidneys, leading to a gradual decline in kidney function over time. The earliest documented case of PKD dates back to the 16th century, with the autopsy report of King Stephen Bathory of Poland in 1576. The report described the presence of "vesicular cysts" in the kidney, referred to as "false hydatids of kidney" by Dr. Matthew Baillie in the late 18th century. The clinical picture of PKD was subsequently detailed by Pierre Rayer, who attributed King Stephen Bathory's death to significant functional changes in various organ systems, notably the central nervous system. The term "polycystic kidney" was coined by Felix Lejars in his 1888 doctoral thesis, and the genetic basis of PKD was first identified by Steiner in 1899 [1].

PKD is categorized into two primary types based on inheritance patterns: autosomal dominant polycystic kidney disease (ADPKD) and the less common autosomal recessive polycystic kidney disease (ARPKD). ADPKD is the most prevalent form of PKD, affecting millions worldwide. It is estimated that 1 in 400 to 1 in 1,000 individuals are affected with ADPKD, accounting for 5-10% of end-stage renal disease (ESRD) cases globally. The prevalence of ADPKD varies across different populations, with reported incidences ranging from 1 in 2,459 in the United Kingdom to 1 in 4,000 in some European and Japanese populations [1].

ARPKD is a rarer form of PKD, affecting approximately 1 in 20,000 newborns. Unlike ADPKD, which typically manifests in adulthood, ARPKD presents in childhood, often with severe and rapidly progressive kidney dysfunction. More than half of affected individuals develop ESRD by the age of 10, requiring dialysis or kidney transplantation for survival. In addition to kidney involvement, ARPKD

is characterized by congenital hepatic fibrosis (CHF), a condition affecting the liver. Advances in medical care have led to increased recognition of the long-term effects of CHF, which can manifest at various stages of life, from infancy to young adulthood [1].

Despite the long history of PKD and its recognition as a significant health concern, there remains a lack of comprehensive understanding regarding the pathophysiology, genetics, and associated clinical manifestations of the disease [1]. **Table 1** presents a comparison of the key features of ADPKD and ARPKD, including prevalence, age of onset, kidney disease progression, extra-renal manifestations, and ESRD risk.

Table 1. Key epidemiological features of ADPKD and ARPKD.

Feature	ADPKD	ARPKD
Prevalence	1 in 400 - 1 in 1000	1 in 20,000
Age of onset	Adulthood	Childhood
Kidney disease progression	Gradual	Rapid
Extra-renal manifestations	Less common	Congenital hepatic fibrosis
ESRD risk	5% - 10% of cases	>50% by age 10

2.1. Epidemiology and Prevalence

2.1.1. Epidemiology of Polycystic Kidney Disease

Polycystic kidney disease (PKD) is a group of inherited disorders characterized by the formation of fluid-filled cysts in the kidneys, leading to progressive kidney enlargement and decline in function. PKD is broadly categorized into autosomal dominant PKD (ADPKD) and autosomal recessive PKD (ARPKD), with distinct genetic and clinical features.

2.1.2. Autosomal Dominant Polycystic Kidney Disease (ADPKD)

ADPKD is the most common form of PKD, affecting millions worldwide (Rahbari-Oskoui *et al*., 2022). It is estimated that 1 in 400 to 1 in 1,000 individuals are affected with ADPKD, accounting for 5% - 10% of end-stage renal disease (ESRD) cases globally [6] [7]. The prevalence of ADPKD varies across different populations, with reported incidences ranging from 1 in 2,459 in the United Kingdom to 1 in 4,000 in some European and Japanese populations [7]. This variability may be attributed to factors such as genetic background, founder effects, and access to healthcare.

In the United States, ADPKD affects approximately 140,000 [8]. Interestingly, there is a gender difference in the age of diagnosis, with females often diagnosed earlier in adulthood due to increased abdominal imaging during pregnancy, while males tend to be diagnosed later, often after the onset of chronic kidney disease [8].

2.1.3. Autosomal Recessive Polycystic Kidney Disease (ARPKD)

ARPKD is a rarer form of PKD, affecting approximately 1 in 20,000 newborns [9]. Unlike ADPKD, which typically manifests in adulthood, ARPKD presents in childhood, often with severe and rapidly progressive kidney dysfunction. More than half of affected individuals develop ESRD by the age of 10, requiring dialysis or kidney transplantation for survival [10].

In addition to kidney involvement, ARPKD is characterized by congenital hepatic fibrosis (CHF), a condition affecting the liver. Advances in medical care have led to increased recognition of the long-term effects of CHF, which can manifest at various stages of life, from infancy to young adulthood [11].

2.2. Clinical Manifestations

Polycystic kidney disease (PKD) is characterized by the progressive development of fluid-filled cysts in the kidneys, leading to a wide range of clinical manifestations. While the presentation can vary based on the type and severity of PKD, some common symptoms include:

- **Pain:** Abdominal, back, or flank pain is frequently reported, ranging from mild and intermittent to severe and persistent. This pain is often caused by the enlargement of cysts within the kidneys, which can stretch the renal capsule and put pressure on surrounding organs. Pain can also arise from cysts in other organs, such as the liver [12].
- **Hypertension:** Elevated blood pressure is a common early finding in PKD, often attributed to increased pressure on renal blood vessels due to cyst expansion. The compression of renal vasculature can activate the renin-angiotensin-aldosterone system (RAAS), leading to increased vasoconstriction and sodium retention, which contribute to hypertension [12].
- **Hematuria:** Blood in the urine (hematuria) is a prevalent manifestation, resulting from cyst rupture or bleeding. As cysts grow, their walls can become thin and fragile, making them prone to rupture. This can release blood into the collecting system of the kidneys, resulting in hematuria [12].
- **Urinary Tract Infections (UTIs):** The obstruction of urine flow caused by cysts increases the risk of UTIs. The cysts can compress and distort the ureters and bladder, leading to urinary stasis and creating an environment conducive to bacterial growth and infection [13].
- **Proteinuria:** The presence of protein in the urine (proteinuria) signifies impaired renal filtration. The presence of cysts disrupts the normal filtering function of the glomeruli, allowing proteins to leak into the urine [14].
- **Kidney Stones:** Mineral and substance accumulation within the cysts can lead to kidney stone formation. The altered fluid dynamics within the cysts can promote the precipitation of minerals and other substances, leading to the formation of kidney stones [14].
- **Kidney Failure:** Progressive cyst growth and kidney damage can culminate in renal failure, necessitating dialysis or transplantation. The continuous expansion of cysts gradually replaces healthy kidney tissue, leading to a decline in

renal function and eventually kidney failure [14].

In addition to these primary symptoms, PKD can lead to complications like liver cysts, vascular aneurysms, and cardiovascular issues.

2.3. Early Detection and Disease Progression

PKD is often considered a "silent" disease, as symptoms may not become apparent until later stages [15]. Early detection through imaging techniques like CT scans or MRI is crucial for managing symptoms and slowing disease progression. Incidental diagnoses are common during evaluations for unrelated conditions like pregnancy, back pain, or accidents [6].

2.4. Factors Influencing PKD Progression

Several factors can accelerate the progression of PKD, including hypertension, proteinuria, kidney stone formation, gross hematuria, and specific genetic mutations like the PKD1 mutation [6]. In autosomal dominant PKD (ADPKD), parental evaluation is essential due to the hereditary nature of the disease.

2.5. Clinical Manifestations in ARPKD

Autosomal recessive PKD (ARPKD) often presents in the neonatal period with a range of symptoms, including abdominal swelling, respiratory distress due to underdeveloped lungs, decreased kidney function, hypertension, enlarged liver, jaundice, and poor growth [16]. Severe cases can lead to life-threatening complications like respiratory distress syndrome and renal failure, emphasizing the importance of early diagnosis and prompt treatment [17]. **Table 2** shows the clinical manifestations of PKD.

Table 2. Clinical manifestations of PKD.

Symptom	Description	Potential Cause(s)
Pain	Abdominal, back, or flank pain; may be mild to severe, constant or intermittent.	Cyst expansion, pressure on organs, cyst rupture.
Hypertension	Elevated blood pressure.	Increased pressure on renal blood vessels due to cyst growth.
Hematuria	Blood in the urine.	Cyst rupture or bleeding.
Urinary Tract Infections	Increased frequency of infections.	Obstruction of urine flow by cysts.
Proteinuria	Protein in the urine.	Impaired renal filtration.
Kidney Stones	Formation of stones within the kidneys.	Accumulation of minerals and substances within cysts.
Kidney Failure	Gradual loss of kidney function.	Progressive cyst growth and kidney damage.
Other Complications	Liver cysts, vascular aneurysms, cardiovascular problems.	-

3. Polycystic Kidney Disease: A Genetic Overview

Polycystic kidney disease (PKD) is a hereditary disorder characterized by the formation of fluid-filled cysts in the kidneys, and potentially in other organs. While individuals with PKD typically possess two healthy kidneys at birth, the presence of small cysts marks the early stages of the disease. These cysts can progressively enlarge, leading to complications within the kidneys, bladder, and urinary tract. PKD is primarily categorized into two forms: autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD). Table 3 summarizes the key genetic features of ADPKD and ARPKD, including the genes involved, chromosomal location, protein product, inheritance pattern, prevalence, and age of onset.

Table 3. Key genetic features of ADPKD and ARPKD.

Feature	ADPKD	ARPKD
Gene(s) Involved	PKD1, PKD2	PKHD1
Chromosomal Location	PKD1: 16p13.3 PKD2: 4q21.2	6p12
Protein Product	Polycystin-1, Polycystin-2	Fibrocystin
Inheritance Pattern	Autosomal dominant	Autosomal recessive
Prevalence	More common (approximately 1 in 500 to 1 in 1000 individuals)	Less common (approximately 1 in 20,000 to 1 in 40,000 individuals)
Age of Onset	Variable, often adult-onset	Can present in newborns, children, or adults

To understand these inheritance patterns, it's essential to grasp the concept of genes and chromosomes. Humans have two copies of each gene, one inherited from each parent. These genes are located on chromosomes, which are thread-like structures found in the nucleus of our cells. Each chromosome carries many genes. In autosomal dominant inheritance, only one copy of the mutated gene is necessary to cause the disease. This means that if one parent has ADPKD, there is a 50% chance that their child will inherit the mutated gene and develop the disease [7]. In autosomal recessive inheritance, two copies of the mutated gene are required to cause the disease. This means that both parents must carry a copy of the mutated gene, even if they don't have the disease themselves. If both parents are carriers, there is a 25% chance that their child will inherit two copies of the mutated gene and develop the disease.

The terms "autosomal dominant" and "autosomal recessive" are used to describe how a particular trait or disease is inherited. "Autosomal" refers to the fact that the gene responsible for the trait or disease is located on one of the 22 pairs of autosomes, which are the non-sex chromosomes. "Dominant" means that only one copy of the mutated gene is necessary to cause the disease, while "recessive" means that two copies of the mutated gene are required.

3.1. Autosomal Dominant Polycystic Kidney Disease (ADPKD)

ADPKD, the most prevalent form of PKD, arises from genetic alterations on chromosomes 16 and 4. Specifically, mutations in the PKD1 and PKD2 genes, encoding polycystin-1 and polycystin-2 proteins respectively, are implicated in the disease pathogenesis [18]. The PKD1 gene resides on chromosome 16p13.3, while PKD2 is located on chromosome 4q21.2 [19]. Notably, mutations in PKD1 account for approximately 85% of ADPKD cases, with the remaining 15% attributed to PKD2 mutations [20].

ADPKD follows an autosomal dominant inheritance pattern, meaning an individual has a 50% chance of inheriting the mutated gene from an affected parent. Inheriting a single copy of the altered gene is sufficient to cause the disease [21]. Although the genetic defect is present from birth, the onset of symptoms can vary, with some individuals remaining asymptomatic until middle age or later.

3.2. Autosomal Recessive Polycystic Kidney Disease (ARPKD)

ARPKD, also recognized as ciliopathy-associated polycystic kidney disease, is a less common form of PKD. It results from mutations in the PKHD1 gene on chromosome 6, which encodes fibrocystin, a protein crucial for the structure and function of primary cilia [22].

Unlike ADPKD, ARPKD follows an autosomal recessive inheritance pattern. This implies that an individual must inherit two copies of the mutated PKHD1 gene, one from each parent, to develop the disease [16]. Consequently, ARPKD is less prevalent than ADPKD. The clinical presentation of ARPKD can manifest in newborns, children, or adults [11].

4. Pathophysiology of ADPKD

Autosomal dominant polycystic kidney disease (ADPKD) is characterized by the progressive development of fluid-filled cysts in the kidneys, leading to a gradual decline in renal function. This process is primarily driven by mutations in the PKD1 or PKD2 genes, which encode polycystin-1 and polycystin-2 proteins, respectively. These proteins are crucial for maintaining the structural integrity and functional regulation of primary cilia in renal tubular cells [19].

4.1. Ciliary Dysfunction and Cyst Formation

Mutations in PKD1 or PKD2 disrupt the normal function of these proteins, leading to abnormal ciliary signaling and intracellular calcium dysregulation. This disruption triggers a cascade of cellular events, including increased fluid secretion, cell proliferation, and extracellular matrix remodeling, ultimately resulting in cyst formation [23] [24].

4.2. Cyst Growth and Expansion

Once initiated, cysts progressively enlarge due to fluid accumulation and cell proliferation, driven by various signaling pathways, including cAMP and mTOR.

This expansion compresses surrounding renal tissue, leading to ischemia, inflammation, and fibrosis, further contributing to kidney damage [25]. However, this fibrosis contributes to additional kidney damage, eventually leading to chronic kidney disease (CKD) and end-stage renal disease (ESRD).

4.3. Extrarenal Manifestations

Beyond the kidneys, ADPKD can manifest in other organs, notably the cardiovascular system. Ciliary dysfunction in vascular smooth muscle cells is implicated in the development of aneurysms and hypertension, significant contributors to cardiovascular morbidity and mortality in ADPKD patients. Understanding the links between renal cystogenesis and these extrarenal manifestations, particularly those affecting the heart, is crucial for developing comprehensive management strategies for ADPKD.

4.4. Two-Hit Hypothesis

An important hypothesis proposed to explain the development of cysts in PKD is the two-hit hypothesis. According to the two-hit hypothesis, the progress of cysts in the kidneys and other body parts or organs requires two separate genetic mutations, or "hits," to occur [20]. The first hit involves an inherited metamorphosis in one of the PKD genes, PKD1 or PKD2. This initial genetic insult leads to the formation of small cysts in the kidneys, which are typically benign and asymptomatic early in life. However, these cysts can grow and expand with time, leading to the expansion of larger cysts and eventual kidney failure. The second hit in the two-hit hypothesis involves a somatic mutation in one of the residual PKD alleles within a cystic epithelial cell [26].

Various experimental and clinical studies have supported the two-hit hypothesis. For example, patients with ADPKD caused by PKD1 mutations tend to have a more severe disease phenotype and an earlier onset of symptoms than those with PKD2 mutations. This difference may be explained by the fact that PKD1 encodes a more significant protein with more functional domains and is involved in more cellular processes than PKD2 [26] [27]. Therefore, a mutation in PKD1 may have a greater impact on the overall function and may require fewer additional hits to cause cyst formation.

Furthermore, studies have shown that cystic epithelial cells in ADPKD patients exhibit a "second-hit" mutation in the remaining PKD allele, suggesting that this process is necessary for cyst development [28]. Animal models of PKD have also reinforced this idea, which has shown that cyst formation and kidney enlargement require mutations in both PKD1 and PKD2.

5. Treatment

Treatment for polycystic kidney disease (PKD) primarily addresses the symptoms. Doctors recommended managing blood pressure, properly managing pain, taking antibiotics for urinary tract infections, drinking enough fluids, and avoiding foods

and beverages such as caffeine, dairy products, and smoking. As the condition becomes more severe and end-stage renal disease develops, dialysis and kidney transplantation may be necessary [29].

Currently, there is no cure for PKD. However, significant advances have been made in developing potential treatments to slow the progression of the disease and improve the quality of life for affected individuals. Potential therapy options for PKD include drugs, gene therapy, stem cell therapy, lifestyle modifications, dialysis, and kidney transplantation [10] [16] [20] [30]-[32].

5.1. Pharmacological Therapies

a) Tolvaptan: Tolvaptan has shown encouraging outcomes in clinical studies as a treatment option for ADPKD. It works by inhibiting the activity of vasopressin, a hormone that promotes cyst growth. In clinical studies, Tolvaptan's efficacy in decelerating renal cyst growth has been demonstrated [20]. However, Tolvaptan has some side effects, such as thirst, increased urine output, and fatigue, and is not recommended for patients with advanced liver disease.

b) Sirolimus and Everolimus: Sirolimus and Everolimus are immunosuppressant drugs studied to treat PKD. These drugs work by inhibiting the activity of the mTOR signaling pathway, which is a critical part of cyst growth [19]. Clinical trials have shown that both drugs can reduce cyst growth in patients with PKD, but their long-term effects are still under investigation.

c) Metformin: Metformin is an oral medication commonly used to treat diabetes. It has also been studied as a potential therapy for PKD. Metformin obstructs the activity of the AMP-activated protein kinase (AMPK) pathway, which promotes cyst growth in PKD [33] [34]. Research has indicated that metformin can potentially decrease cyst growth and ameliorate kidney function in patients with PKD.

Other potential treatments for PKD, such as gene therapy and stem cell therapy, are still in the early stages of development. Lifestyle modifications, such as following a healthy diet and exercising regularly, can also help to manage the symptoms of PKD and slow the progression of the disease.

5.2. Gene Therapy

The use of gene therapy shows potential as a method of treating genetic conditions such as PKD. Gene therapy aims to restore normal gene function by delivering a functional version of the mutated gene to affected cells. Several approaches have been developed for gene therapy in PKD, including:

a) Antisense Oligonucleotides (ASOs): ASOs are small molecules that can bind to specific RNA molecules and alter their function. In the case of PKD, ASOs can be designed to bind to RNA transcripts of the mutated gene and prevent them from being translated into the protein product [16]. This approach has been successful in preclinical studies and is currently being investigated in clinical trials.

b) CRISPR-Cas9: CRISPR-Cas9 is a powerful gene editing technology that can

directly modify the target gene's DNA sequence. In PKD, CRISPR-Cas9 can be used to correct the mutation in the PKD1 or PKD2 gene [20]. Although this approach is still in the early stages of development, it has shown promising results in preclinical studies.

c) Viral gene therapy: Viral gene therapy involves the use of a virus to deliver the functional gene copy to affected cells. Several types of viruses, including adeno-associated virus (AAV) and lentivirus, have been studied to treat PKD [20]. Although this approach has shown promise in preclinical studies, there are still concerns about the safety and efficacy of viral gene therapy.

5.3. Stem Cell Therapy

Stem cell therapy is another promising approach for the treatment of PKD. Stem cells are a type of unspecialized cell that can differentiate into various cell lineages [35]. The successful generation of disease-specific induced pluripotent stem cells (iPSC) from kidney transplant patients provides a promising avenue for personalized therapy. iPSC-derived kidney cells have demonstrated the ability to reabsorb glucose and secrete renin, lower polycystin-two levels at the ciliary level indicating their potential for repairing and regenerating the kidneys [36] [37].

The use of iPSC eliminates the risk of immune rejection, a significant challenge in the treatment of PKD patients with organ transplants. More studies are necessary to improve the iPSC generation process and evaluate the safety and efficacy of iPSC-based therapy for patients with PKD [36]. However, the generation of disease-specific iPSCs from kidney transplant recipients offers a potential solution to the difficulties of treating PKD and represents a promising direction for personalized regenerative medicine.

5.4. Lifestyle and Diet Modifications

Patients with PKD can manage symptoms and reduce the progression of the disease by making diet and lifestyle modifications. Patients should follow a balanced diet that is low in sodium, protein, and fat. Sodium restriction is essential to control blood pressure, a significant risk factor for the progression of PKD [38]. Lowering protein intake can also slow the growth of cysts in the kidneys. In addition, excessive intake of caffeine and alcohol should be avoided and patients should quit smoking [22]. Regular exercise can also benefit PKD patients by controlling blood pressure and improving overall health

5.5. Dialysis

Hemodialysis and peritoneal dialysis are two distinct therapeutic modalities used to eliminate toxins and surplus fluids from the bloodstream when the renal system has lost its ability to carry out this vital function [39].

a) Hemodialysis: Hemodialysis is a medical procedure that involves the use of a machine to remove waste products and excess fluids from the blood by filtering it outside the body. Vascular access is created, usually in an arteriovenous fistula,

allowing blood to be withdrawn from the body and returned to the body after filtration [17]. The process typically takes 3-4 hours per session and is usually performed three times a week.

b) Peritoneal dialysis: Peritoneal dialysis is a type of dialysis that uses the peritoneum, which is a membrane that covers the abdominal cavity, to filter the blood. It involves the insertion of a catheter in the abdomen, followed by the infusion of a solution into the peritoneal cavity [19]. This solution remains in the peritoneal cavity for several hours, during which time it removes waste products and excess fluids. Then, the solution is drained from the body, and a new solution is infused.

5.6. Kidney Transplantation

A kidney transplant, including PKD, is considered the most efficient treatment for end-stage kidney disease. The procedure involves replacing damaged kidneys with a healthy kidney from a donor or a living or deceased donor [16]. Living donors are usually family members or close friends of the recipient and they undergo a thorough medical evaluation to ensure that they are healthy enough to donate a kidney. Deceased donors are individuals who have died and donated their organs for transplantation. After a kidney transplant, patients will need to take immunosuppressant drugs for the rest of their life to prevent rejection of the transplanted kidney [19].

6. The Effects on the Heart

Patients with PKD are at significantly higher risk of developing additional disease processes, for example, hypertension, left ventricular hypertrophy, myocardial infarction, and other cardiovascular abnormalities. Among the associated effects on organs such as the heart, liver, thyroid, and brain, cardiovascular diseases have been observed to have the highest incidence rate compared to the other organs or systems compromised by PKD [40].

Although the disease is generally considered a kidney disorder, the heart is increasingly recognized as a target organ in PKD. Cardiovascular disorders constitute the second most common cause of mortality among patients diagnosed with PKD, trailing only renal failure in frequency.

The exact mechanisms that cause the cardiac symptoms associated with PKD are not entirely clear, but multiple factors are thought to play a role [41]. These include hypertension, left ventricular hypertrophy, fibrosis of the heart, heart valves, and abnormal heart rhythms.

PKD is commonly associated with hypertension, a notable risk factor for cardiovascular disease. Renin-angiotensin-aldosterone system (RAAS) stimulation is responsible for hypertension in patients with PKD, resulting in increased vascular resistance and salt retention. RAAS activation in PKD is caused by the cystic expansion of the juxtaglomerular apparatus, a specialized group of cells in the kidney that produces renin, an enzyme that initiates the RAAS cascade. Elevated blood pressure in PKD can lead to LVH, a condition in which the muscle mass of

the left ventricle increases in response to pressure overload [42].

In individuals with PKD, the prevalence of left ventricular hypertrophy (LVH) is high and it has been correlated with poor cardiovascular outcomes such as heart failure, sudden cardiac death, and myocardial infarction [41]. The mechanisms underlying LVH in PKD are multifactorial, but hypertension and increased afterload are the main drivers. Additionally, LVH in PKD is associated with diastolic dysfunction, a condition in which the heart has difficulty relaxing during diastole, the filling phase of the cardiac cycle. Diastolic dysfunction can lead to pulmonary congestion, dyspnea, and edema, further exacerbating heart failure symptoms [41].

Cardiac fibrosis is a condition exemplified by an excessive buildup of collagen and other extracellular matrix proteins in the heart, which is also a common feature of cardiovascular disease in PKD patients. It is believed to be the result of the activation of pro-fibrotic pathways, such as TGF-β, angiotensin II and CTGF [43]. The accumulation of collagen and other proteins can lead to reduced compliance, increased stiffness, and the development of arrhythmias, all of which can have a negative impact on cardiac function.

Valvular abnormalities, including mitral valve prolapse and aortic root dilation, are frequently observed in PKD and can contribute to the development of cardiac dysfunction [44]. Mitral valve prolapse denotes the pathological phenomenon in which mitral valve leaflets undergo displacement towards the left atrium during the systolic phase, culminating in the development of mitral regurgitation [44]. The latter refers to the retrograde blood flow from the left ventricle to the left atrium. Aortic root dilatation involves enlargement of the aortic root, the portion of the aorta connected to the heart, and can lead to aortic regurgitation, in which there is a retrograde movement of blood from the aorta into the left ventricle [43].

PKD patients commonly experience arrhythmias, including atrial fibrillation, ventricular tachycardia, and sudden cardiac death [43]. These complications can further increase the probability of the risk of adverse cardiovascular outcomes in PKD patients. The mechanisms underlying arrhythmogenesis in PKD are not well understood, but may involve altered ion channels.

7. End-Stage Renal Disease and Its Mortality Rate

ADPKD is an inherited pathological condition that affects the renal system, triggering the proliferation of multiple cysts that gradually diminish kidney function. Eventually, this process culminates in end-stage renal failure between the fifth and sixth decade of life [45]. Despite its low prevalence, with an incidence rate estimated to be around 1 in 800 to 1,000 individuals, it represents 2.5% of all cases of end-stage renal disease [45].

The development of ESRD in people with PKD depends on several factors such as age, gender, disease severity, and family history of ESRD [45]. Those who are older, male, and have a family history of ESRD are at greater risk of developing ESRD compared to those who do not have these risk factors. Furthermore, the

severity of the disease is also a crucial factor, as patients with severe PKD are more likely to develop ESRD.

In addition to these risk factors, hypertension is also a key risk factor for ESRD in PKD. Hypertension can cause damage to kidney tissue, leading to decreased kidney function [45]. High blood pressure can also accelerate the expansion of cysts in the kidneys, causing additional damage to kidney tissue

Mortality Rate Associated with ESRD in PKD

ESRD is a life-threatening disease and patients with ESRD have a higher mortality rate than the general population [46]. The fatality rate associated with end-stage renal disease in patients with PKD surpasses that observed in individuals diagnosed with other kidney pathologies. The mortality rate for patients with PKD with ESRD is approximately 14% per year, compared to approximately 8% per year for individuals with other forms of kidney disease [47].

The increased mortality rate in PKD patients with ESRD is due to several factors. First, PKD patients with ESRD are more likely to have other comorbid conditions, such as hypertension, cardiovascular disease, and diabetes, which can further increase the risk of mortality. Second, patients with PKD with ESRD may be less likely to receive a kidney transplant than individuals with other types of renal disease due to the complex nature of the disease and the difficulty in finding suitable donors [46].

8. Conclusions

PKD is a hereditary disease characterized by the formation of numerous cysts in the kidneys, primarily due to ciliary dysfunction. This leads to progressive kidney impairment and eventual failure, with significant implications for the cardiovascular system. It is a relatively common condition, with ADPKD being the most prevalent form. ADPKD exhibits an autosomal dominant inheritance pattern and arises due to mutations in the PKD1 or PKD2 genes. These genes produce polycystin-1 and polycystin-2 proteins, respectively, which regulate cell growth and differentiation. The disruption of these proteins is responsible for developing cysts in the kidneys.

On the other hand, ARPKD is a less common form of PKD that follows an autosomal recessive inheritance pattern. It is caused by alterations in the PKHD1 gene, which encodes the fibrocystin/polyductin protein. This protein plays a crucial function in the formation and preservation of kidney tubules. ARPKD is characterized by the growth and formation of fluid-filled cysts in the kidneys. These cysts develop from renal tubules and collecting ducts, and their growth is attributed to changes in the equilibrium between cell proliferation and cell death. In addition, there are irregularities in the secretion and reabsorption of fluids.

This disease can have significant impacts on the cardiovascular system, especially in individuals with ADPKD. Studies indicate that individuals with ADPKD are more likely to develop cardiovascular diseases, including hypertension, left

ventricular hypertrophy (LVH), valvular abnormalities, and aortic dilatation. The precise mechanisms causing the increase in cardiovascular risk in ADPKD are unclear. However, the risk is believed to be related to the progression of chronic kidney disease (CKD) resulting from kidney failure.

Treatment for PKD focuses on managing the complications of the disease, including hypertension, CKD, and end-stage renal disease. While no cure exists, Tolvaptan has emerged as a key drug therapy for ADPKD. Promising future treatments include gene therapy and stem cell therapy, which hold the potential to correct underlying genetic defects and regenerate damaged tissues. In addition, ACE inhibitors and ARBs can be used to decelerate, inhibit or retard the progression of renal disease and reduce the risk of cardiovascular impediments in patients with PKD.

In summary, PKD is a genetic condition that affects the kidneys and can result in renal failure. It is inherited in an autosomal dominant or recessive pattern and is caused by gene alterations. PKD is characterized by the development and enlargement of kidney cysts, leading to renal failure. This can also adversely affect the cardiovascular system, particularly in those with ADPKD. The primary approach to managing PKD is to address the complications of the disease, which include hypertension, CKD, and end-stage renal disease.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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