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Autosomal Dominant Polycystic Kidney Disease-A Review

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ABSTRACT

Autosomal dominant polycystic kidney disease (ADPKD) is the most prevalent, potentially lethal, monogenic human disorder. It is associated with large interfamilial and intrafamilial variability, which can be explained to a large extent by its genetic heterogeneity and modifier genes. It is also the most common of the inherited cystic kidney diseases - a group of disorders with related but distinct pathogenesis, characterized by the development of renal cysts and various extra renal manifestations, which in case of ADPKD include cysts in other organs, such as the liver, seminal vesicles, pancreas, and arachnoid membrane, as well as other abnormalities, such as intracranial aneurysms and dolichoectasias, aortic root dilatation and aneurysms, mitral valve prolapse, and abdominal wall hernias. Over 50% of patients with ADPKD eventually develop end stage kidney disease and require dialysis or kidney transplantation. ADPKD is estimated to affect at least one in every 1000 individuals worldwide, making this disease the most common inherited kidney disorder with a diagnosed prevalence of 1:2000 and incidence of 1:3000-1:8000 in a global scale.

Key Words PCOD, ADPKD, Kidney

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INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is a genetic disorder characterized by the growth of numerous cysts in the kidneys. The cysts are noncancerous round sac containing fluid. Cyst varies in size and they can grow very large. Development of large cysts may damage kidneys. Polycystic kidney disease can also develop cysts in liver or other body parts. ADPKD symptoms vary in severity and age of onset, but usually develop between the age of 30 to 40. Some affected children can eventually develop end stage renal disease. In some patients, symptoms do not develop until adolescence or adulthood.

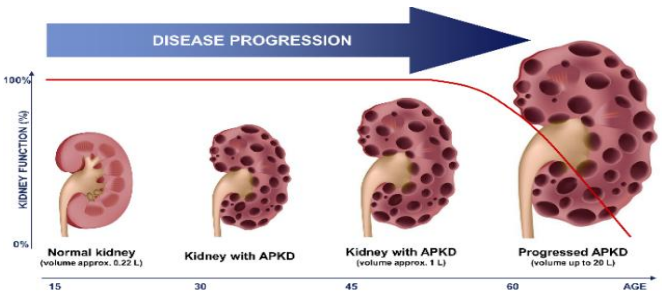

Figure 1 Figure showing progression of ADPKD

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ADPKD is a progressive disease and symptoms tend to get worsen over time. The most common symptoms are kidney cysts, back pain and headaches. Other symptoms include liver and pancreatic cysts, urinary tract infections, abnormal heart valves, high blood pressure, kidney stones and brain aneurysms. ADPKD is most often caused by changes in the *PKD1* and *PKD2* genes, and less often by changes in the *GANAB* and *DNAJB11* genes.[1] It is inherited in a dominant pattern.

Treatment for ADPKD involves managing the symptoms and slowing disease progression. The most serious complication of ADPKD is kidney disease and kidney failure. ADPKD is the most common inherited disorder of the kidneys.[1,2]

SIGN AND SYMPTOMS:

The symptoms and severity of autosomal dominant polycystic kidney disease (ADPKD) vary from person to person. Eventually the formation of multiple kidney cysts leads to kidney damage and kidney failure.[3,4]

People with ADPKD may experience the following symptoms:

- Hypertension
- Back pain
- Haematuria
- Urinary Tract Infection
- Liver and Pancreatic cysts
- Abnormal Heart Valves
- Kidney stones
- Brain aneurysm
- Acute loin pain
- Feeling of fullness in abdomen
- Headache
- Subarachnoid haemorrhage
- Uremia due to kidney failure
- Anaemia due CKD
- Increase RBC or erythropoietin secretion

PATHOPHYSIOLOGY:

Polycystin 1 may regulate tubular epithelial cells adhesion and differentiation; polycystin 2 may function as an ion channel, with mutations causing fluid secretion into cyst. Mutation in these proteins may alter the function of renal cilia, which enable tubular cells to sense flow rate. A leading hypothesis proposes that tubular cell proliferation and differentiation are linked to flow rate and that ciliary dysfunction may thus leads to cystic transformation.

Early in the disorder, tubules dilate and slowly fill with glomerular filtrate. Eventually, the tubule separate from the functioning nephron and filled with secreted fluid rather than filtered fluid, forming cysts.[5,6,7,8,9,10,11,12,13]

CAUSES:

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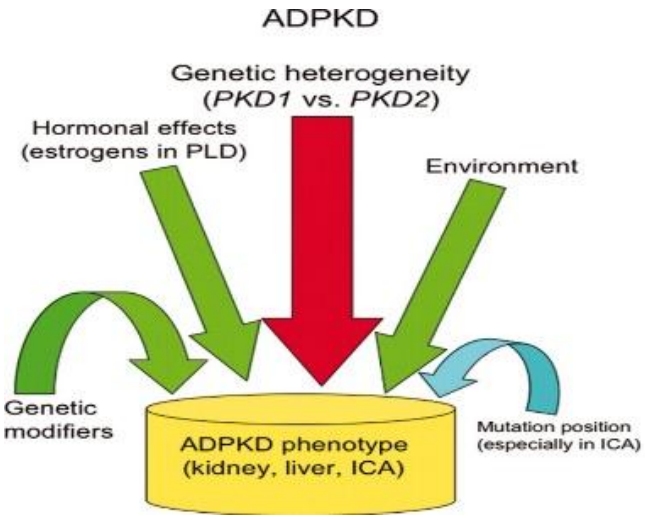

Figure 2 Diagram showing the relative contributions of various factors to the resulting phenotypes in ADPKD. Strong factors are shown red, moderate are in green and lesser effects are shown blue

ADPKD is caused by genetic defect that disrupts the normal development of some cells in the kidneys and causes cysts to grow. The genes responsible for ADPKD are:

- PKD1, which is responsible for 85% of cases
- PKD2, which is responsible for 15% of cases

COMPLICATIONS:

Complications associated with polycystic kidney disease include:

- **High blood pressure.** Elevated blood pressure is a common complication of polycystic kidney disease. Untreated, high blood pressure can cause further damage to kidneys and increase the risk of heart disease and strokes.
- **Loss of kidney function.** Progressive loss of kidney function is one of the most serious complications of polycystic kidney disease. Nearly 50% of patients suffering from ADPKD may have kidney failure by age 60.

PKD can interfere with the ability of the kidneys to filter the wastes from the blood, which leads to the condition called uremia. As the disease worsens, end-stage kidney (renal) disease.

- **Chronic pain.** Pain is a common symptom for people with polycystic kidney disease. It often occurs on side or back, the pain can also be associated with a urinary tract infection, a kidney stone or a malignancy.
- **Growth of cysts in the liver.** The likelihood of developing liver cysts for someone with polycystic kidney disease increases with age. While both men and women develop cysts, women often develop larger cysts. Female hormones and multiple pregnancies might contribute to liver cyst development.
- **Development of an aneurysm in the brain.** A balloon-like bulge in a blood vessel (aneurysm) in the brain can cause bleeding (haemorrhage) if it ruptures. Patient with polycystic kidney disease have a higher risk of aneurysms. People with a family history of aneurysms seem to be at highest risk.
- **Pregnancy complications.** Pregnancy is successful for most women with polycystic kidney disease. In some cases, however, women may develop a life-threatening disorder called preeclampsia. Those who are at risk have high blood pressure or a decline in kidney function before they become pregnant.

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- **Heart valve abnormalities.** As many as 1 in 4 patient with polycystic kidney disease develops mitral valve prolapse. When this happens, the heart valve no longer closes properly, which allows blood to leak backward.
- **Colon problems.** Weaknesses and pouches or sacs in the wall of the colon (diverticulosis) may develop in patient with polycystic kidney disease.[14-31]

DIAGNOSIS:

The following are the tests which determines the size, shape, number of kidney cysts and evaluate the amount of healthy kidney tissue:

1. Ultrasound
2. CT Scan
3. MRI Scan
4. Urinalysis detects mild proteinuria and microscopic or macroscopic haematuria.
5. Genetic testing
6. GFR Blood Tests[33,34,35]

DIAGNOSTIC CRITERIA:

Age (years)	*Number of cysts*
Ultrasonography (at-risk of ADPKD type 1)	
< 30	≥ 2 in one or both kidneys
30 to 59	≥ 2 in each kidney
≥ 60	≥ 4 in each kidney
Ultrasonography (at risk and unknown genotype)	
15 to 39	≥ 3 in one or both kidneys
40 to 59	≥ 2 in each kidney
≥ 60	≥ 4 in each kidney
Magnetic resonance imaging (at risk)	
< 30	≥ 5 in each kidney
30 to 44	≥ 6 in each kidney
45 to 59 (females)	> 6 in each kidney
45 to 59 (males)	> 9 in each kidney

Figure 3 Figure showing Radiographic Diagnostic Criteria for ADPKD

PROGNOSIS:

By age 75, 50 to 75% of patients with autosomal dominant polycystic kidney disease (ADPKD) require renal replacement therapy (dialysis or transplantation). On average, glomerular filtration rate (GFR) declines by about 5 mL/min/year after the fourth decade of life. Predictors of more rapid progression to renal failure include the following:

- Earlier age at diagnosis
- Male sex
- Sickle cell trait
- PKD1 genotype
- Larger or rapidly increasing kidney size
- Gross haematuria
- Hypertension
- Being black
- Increasing proteinuria

Cyst and kidney volume measurements predict risk of progression to chronic kidney disease and end-stage renal disease, often before changes in routine laboratory studies. For example, cyst size and kidney size predict 8-year risk of chronic kidney disease more accurately than age, degree of proteinuria, or serum blood urea nitrogen (BUN) or creatinine. Kidney size is the most important predictor for progression, particularly total kidney volume >1500 mL.

Phosphaturic hormone fibroblast growth factor (FGF) 23 elevation was associated with

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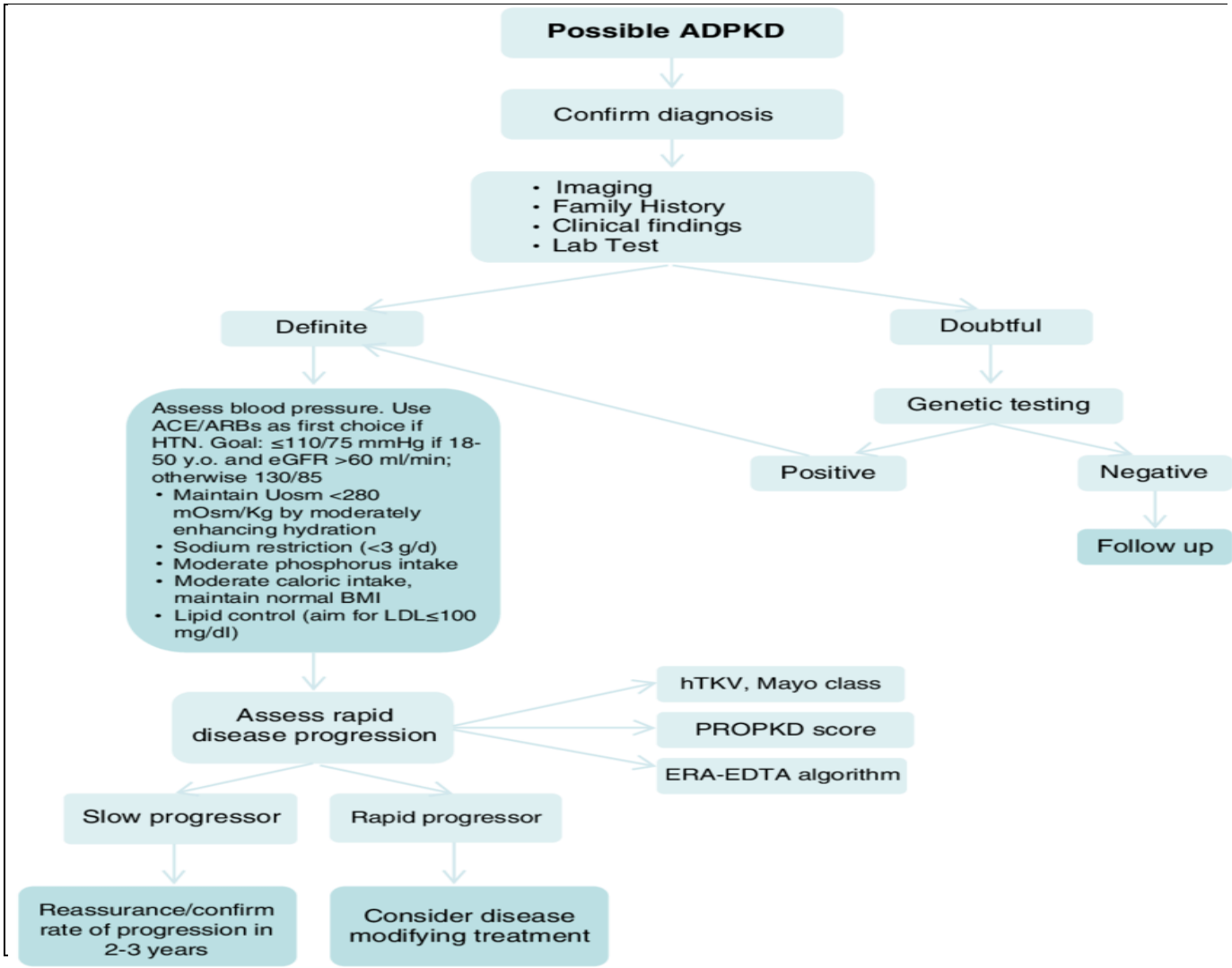
increased kidney size and annualized rate of estimated glomerular filtration rate (eGFR) decline but interestingly did not enhance risk prediction for disease progression.

ADPKD does not increase risk of renal cancer, but if patients with ADPKD develop renal cancer, it is more likely to be bilateral. Renal cancer rarely causes death. Patients usually die of heart disease (sometimes valvular), disseminated infection, or ruptured cerebral aneurysm.[38]

TREATMENT:



The aim of ADPKD treatment is to treat both kidney and non-kidney symptoms and also to slow down the progression of kidney failure.

Treating polycystic kidney disease involves dealing with the following signs, symptoms and complications in their early stages:

- **Kidney cyst growth.** Tolvaptan, a vasopressin receptor 2 antagonist, is a drug

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that can be recommended for those who are at risk of rapidly progressive ADPKD. Tolvaptan appears to slow increase in renal volume and decline in renal function, but it can cause adverse effects via free water diuresis (e.g, thirst, polydipsia, polyuria) that can make adherence difficult. Tolvaptan has been reported to cause severe liver failure and is hence contraindicated in patients with significant liver impairment or injury. Tolvaptan may be especially beneficial for patients at higher risk for rapid progression of kidney disease.

There's a risk of serious liver injury when taking tolvaptan, and it can interact with other medicines you take. It's best to see a doctor who specializes in kidney health (nephrologist) when taking tolvaptan, so that the patient can be monitored for side effects and possible complications.

- **High blood pressure.** Controlling high blood pressure can delay the progression of the disease and slow further kidney damage. Combining a low-sodium, low-fat diet that's moderate in protein and calorie content with not smoking, increasing exercise and reducing stress may help control high blood pressure.

However, medications are usually needed to control high blood pressure. Medications called angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) are often used to control high blood pressure.

- **Declining kidney function.** To help your kidneys stay as healthy as possible for as long as possible, experts recommend maintaining a normal body weight (body mass index). Drinking water and fluids throughout the day may help slow the growth of kidney cysts, which in turn could slow down a decline in kidney function. Following a low-salt diet and eating less protein might allow kidney cysts to respond better to the increase in fluids.
- **Pain.** You might be able to control the pain of polycystic kidney disease with over-the-counter medications containing acetaminophen. For some people, however, the pain is more severe and constant. The doctor might recommend a procedure using a needle to draw out cyst fluid and inject a medication (sclerosing agent) to shrink kidney cysts. Or you may need surgery to remove cysts if they're large enough to cause pressure and pain.
- **Bladder or kidney infections.** Prompt treatment of infections with antibiotics is necessary to prevent kidney damage. The doctor may investigate whether you have a simple bladder infection or a more complicated cyst or kidney infection. For more complicated infections, the patient may need to take a longer course of antibiotics.
- **Blood in the urine.** The patient needs to drink lots of fluids, preferably plain water, as soon as you notice blood in your urine to dilute the urine. Dilution might help prevent obstructive clots from forming in urinary tract. In most cases, the bleeding will stop on its own. If it doesn't, it's important to contact the doctor.
- **Kidney failure.** If your kidneys lose their ability to remove waste products and extra fluids

from your blood, you'll eventually need either dialysis or a kidney transplant. Seeing your doctor regularly for monitoring of PKD allows for the best timing of a kidney transplant. You may be able to have a pre-emptive kidney transplant, which means you wouldn't need to start dialysis but would have the transplant instead.

- **Aneurysms.** If the patient have polycystic kidney disease and a family history of ruptured brain (intracranial) aneurysms, the doctor may recommend regular screening for intracranial aneurysms.

If an aneurysm is discovered, surgical clipping of the aneurysm to reduce the risk of bleeding may be an option, depending on its size. Nonsurgical treatment of small aneurysms may involve controlling high blood pressure and high blood cholesterol, as well as quitting smoking.[5,15,32,36,37]

LIFE MODIFICATION:

Certain lifestyle modifications may be beneficial in the patients with ADPKD. Lifestyle modifications includes:

- Avoid food and drinks containing caffeine.
- Limit the amount of protein in diet.
- Consume low sodium rich diet.
- Diet should be enriched in fruits and vegetables to provide sufficient potassium and reduce the intake of acid forming foods.
- Exercise regularly.
- Drink 3 litres of water everyday.[5,19,22]

Autosomal dominant polycystic kidney disease (ADPKD) is a genetic disorder. It affects about 1 in 500 to 1000 people. Currently there is no cure for ADPKD, and it is not possible to stop the cysts forming in the kidneys. But there are some potentially useful medications, such as tolvaptan, that can sometimes be used to reduce the growth rate of cysts.

CONCLUSION

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