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ADVANCING POLYCYSTIC KIDNEY DISEASE (PKD) TREATMENT: EXPLORING EMERGING THERAPIES AND BREAKTHROUGHS

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ABSTRACT

The most common sign of Autosomal dominant polycystic kidney disease (ADPKD) is the development of multiple kidney cysts over time, which eventually lead to end-stage kidney disease (ESKD) and require renal replacement therapy. To treat ADPKD, several treatments have been developed. However, not all these remedies have been effective in preventing the development of the disease. It is essential to have a thorough knowledge of the mechanisms leading to cyst formation and growth before diving into specific therapy for controlling ADPKD. Numerous clinical trials are undergoing over the past two decades aiming to treat ADPKD as a result of significant research efforts. Tolvaptan is the only pharmaceutical agent found to be successful in delaying the deterioration of kidney function in ADPKD, even though Tolvaptan has several undesirable side effects, including thirst, polyuria, and liver damage when used for an extended period. In this review, we have covered the detailed pathophysiology and molecular mechanisms of PKD, as well as the possibility of emerging therapies in the clinical development of PKD.

KEYWORD:- Autosomal dominant polycystic kidney disease, End-stage kidney disease, Emerging therapies

1. INTRODUCTION

1.1 Overview of Autosomal dominant polycystic kidney disease (ADPKD)

Patients with ADPKD gradually progress to end-stage kidney disease (ESKD) and renal insufficiency, requiring dialysis or kidney transplants.[1] The condition is characterized by the development and growth of kidney cysts that are filled with fluid. Urinary tract infections, hematuria, and hypertension are all related to the growth of disease. Tolvaptan is the sole medication for ADPKD that the Food and Drug Administration (FDA) has approved.[2-4] Tolvaptan does have several undesirable side effects, including polyuria, liver damage, and excessive thirst. Therefore, there is an urgent need to better understand the molecular causes of ADPKD in order to design more efficient and secure treatments.

1.2 Prevalence and Impact of ADPKD

ADPKD, the most common genetic kidney disease, affects 1 in 1000 people worldwide and is one of the leading causes of end-stage renal disease (ESRD)1, 2, and 3.[5] Kidney cyst formation is the most prevalent clinical symptom and they get bigger and more numerous as we age. The disease's most severe symptoms—renal failure, lithiasis, arterial hypertension, hematuria, and hematuria—appear between the second and fifth decades of life as a result of the cysts replacing the healthy renal parenchyma. Nearly 50% of ADPKD patients require renal replacement therapy (dialysis or transplantation) at a mean age of 57 years.[6] The two main genes, PKD1 on chromosome 16p13.3 and PKD2 on chromosome 4q21-23.7 are widely known and the disease is diverse. 85% of recorded cases are PKD1 and 15% are PKD27, though this percentage may vary based on the region and the number of individuals examined. Despite significant inter and intra-family heterogeneity, those with PKD1 mutations typically present with a more severe clinical picture.[7, 8] The median age of ESRD is 74.0 years, but more than 50% of individuals with PKD2 mutations had acceptable renal function at that age.[9,10] The average age at which PKD1 mutation carriers develop ESRD is 54.3 years.

1.3 Importance of Advancing ADPKD Treatment

The identification of PKD1 and PKD2 as well as the discovery of the ADPKD proteins polycystin-1 (PC-1) and polycystin-2 (PC-2) has resulted in the discovery of new therapeutic targets, especially in aberrant downstream signaling pathways.[11] However, both proteins have a complicated subcellular distribution, and it is still unclear exactly how each one functions. Both proteins have been found in the endoplasmic reticulum, primary cilia, cell-cell junctions, and focal adhesions. PC-1 interacts with PC2 and possibly other proteins to

form a physiological complex 2+that regulates cell proliferation, cell adhesion, and Ca signaling. TRP superfamily (transient receptor potential) member PC-2 is a non-selective calcium channel.[12] The polycystin complex 2+ controls Ca inflow and cAMP levels in primary cilia as a flow-dependent mechanosensor. In 2+ polycystin deficient or null cells, complex abnormalities in Ca homeostasis have been 2+ observed, including reductions in steady-state calcium, defects in cilia-based Ca influx, store-operated currents, and increased leak currents. This is expected to result in a rise in cAMP 2+ 2+ due to the activation of Ca inhibitable adenylate cyclases (V, VI) and the suppression of Ca activated phosphodiesterases (PDE1). Several other intracellular signaling pathways that are not 2+ regulated by Ca or cAMP have also been reported to be aberrant. A few of these include ATP, Ras/Raf/ERK, mTOR, the cystic fibrosis transduction regulator (CFTR), and AMP-kinase (AMPK). These alterations might be the root of the increases in cell proliferation and fluid secretion observed in ADPKD.[13–16] There are currently no such treatments that can effectively prevent the progression of the disease. The only disease-modifying treatment for ADPKD that has been approved is tolvaptan, a vasopressin V2 receptor antagonist, and it is available in many nations. However, for ADPKD and beyond, there is a critical need for additional and alternative therapeutic options. The current review paper examines the comprehensive pathophysiology and molecular mechanism of ADPKD, as well as the promising pharmacological interventions in ADPKD.[17]

2. Understanding ADPKD

2.1 Genetics and Inheritance patterns

2.1.1 Gene Mutation and Protein defect

Genetic testing is exceedingly challenging due to the 97-99% similarity between this region and the six PKD1 pseudogenes. The single-copy PKD2 gene spans 68 kb of genomic sequence, has 15 exons, and encodes a 2904 bp open reading frame transcript.[18, 19] PKD2 mutations were shown to account for 15% of patients in community-based research.[20] The extracellular NH2-terminal domain of proteins contains patterns that are essential for protein-protein interactions. The ability of the PC1 protein's GPS site to undergo autoproteolytic cleavage may be essential for the activation of the protein.[22–26] Because it can cleave and enter the nucleus, it has been proposed that the C-terminal tail of PC1 plays a vital function in gene transcription. PC1 resembles an adhesion molecule or a receptor for an unidentified ligand overall. The PC1, PC2, and other proteins connected to different renal cystic disorders have been in the immotile cilia on the renal tubule and other epithelium.[28] In mice, PKD is brought on by mutations in the ciliary assembly genes TG737 and Kif3a. The unexpected suppression of cysts by cilia deletion has been demonstrated in studies using a variety of mutations in mice. According to these findings, Pkhd1 and Cys1 are part of a gene regulatory network for renal epithelial cells that also includes Tfap2b. When this network is disrupted, renal tubular differentiation is impaired, which results in ductal dilatation, the defining feature of recessive PKD.

2.1.2 Epigenetic Mechanism in PKD

2.1.2.1 DNA Methylation

Human cancer and other disorders have been linked to abnormal DNA hypermethylation and hypomethylation patterns, which may be involved in the onset, progression, and treatment of PKD.[30] The PKD2 gene, ADPKD genes, and the genes regulating PKD-associated signaling pathways must be examined to determine whether their methylations contribute to cyst development.[31] Future research should concentrate on the onset and mechanism of modifications to DNA methylation during cyst growth, as well as if correcting DNA methylation differences in the early stages of PKD can prevent cyst growth and the establishment of ESKD.[32]

2.1.2.2 Histone deacetylases (HDACs) in ADPKD

According to the research so far, HDACs play a significant role in controlling ADPKD. HDACs are divided into four groups based on cofactor interactions and sequence similarity.[34] The main cilium, which is a crucial organelle in the development of cystic kidney diseases, is present in practically all eukaryotic cells. The cilium, an organelle made of microtubules, functions as a chemo- and mechano-sensor.[35] The ciliary membrane expresses signaling receptors that mediate external sensory signals and cause a reaction inside the cells. Additionally, cystic kidney disorders are brought on by cilia-related gene alterations or cilia ablation.[36] HDACs control the main cilia shape in ADPKD in addition to the signaling pathways linked to cell proliferation.

According to reports, HDAC6 controls the disassembly of primary cilia by deacetylating -tubulin. Subsequent research found that inhibiting HDAC6 with tubacin stops the disassembly of primary cilia.[37] Primary cilia disintegration was discovered to be regulated by the Class III HDAC SIRT2, and nicotinamide suppression of SIRT2 stopped this process. In addition, it was discovered that SIRT2 suppression decreased cyst formation in Pkd1 mice kidneys.[38] These results suggest that while HDAC6 and SIRT2 are increased in ADPKD. In conclusion, our studies show that HDACs regulate both PKD-mediated and cilia-dependent signaling pathways, which may play a role in the pathophysiology of ADPKD.[39]

2.2 Pathophysiology of PKD

2.2.1 Role of Growth Factors and Hormones in PKD

Growth factors have been identified as potentially significant effectors in various early-stage and experimental studies targeted at revealing unique characteristics of ADPKD pathogenesis.

2.2.1.1 Epidermal Growth Factor (EGF)

EGF can hasten cellular division, fibrosis, inflammation, and fluid secretion.[40] In cpk mice, Gattone et al.[41] investigated the impact of exogenous EGF treatment on the cystic epithelium.

Although there was no discernible change in cystic morphology, renal function was boosted by EGF treatment from postnatal day 3 to 9. This shows that in this paradigm, growth factor and/or reduced apoptosis may enhance renal function. Further research showed that the EGFR tyrosine kinase inhibitor EKI-785 enhanced renal tubular function in mice models of autosomal recessive PKD and markedly decreased the frequency and extent of renal collecting tubule cystic lesions.

These findings provide support to the idea that EGFR regulates the growth of renal cysts.[42]

2.2.1.2 Transforming Growth Factors and Fibroblast Growth Factors

Transforming growth factor 1 (TGF-1) levels in human ADPKD were found to be greater than in the control group. According to a recent study, the Pkd1RC/RC mouse model's overexpression of TGF-1 eventually results in renal function loss. In iKspCre-Pkd1lox, lox animals (conditional Pkd1 deletion causing cystic illness), activin ligands (members of the TGF- family) are expressed more often, as shown by Leonard et al.[43] In this study, cystogenesis in three separate mice PKD models was inhibited by sequestering activin ligands. Studies in 3D cultivation of human kidney ADPKD cells revealed that TGF-2 reduces cyst growth. Another study found that the ARPKD model's bpk mice had abnormally high levels of TGF-, which could hasten the progression of the disease. However, it is unlikely that TGF elevation is the main factor causing the disease to become more severe. In a transgenic mouse model of slowly progressing cystic disease.[44, 45]

2.2.1.3 Endothelin

The family of multifunctional peptides known as endothelins (ET-1, ET-2, and ET-3) has significant impacts on the management of electrolytes by the kidneys as well as fibrosis and inflammation. ET-1 affects renal physiology in several different ways through its two primary receptor subtypes, ETa and ETb.[46] It is interesting to note that the development of the disease depends on the equilibrium between ETa and ETb, as shown using antagonists of ET-1 receptors.

ETb blockage enhanced cyst formation but concurrent ETa blockade neutralized this effect.[47]

2.2.2 Inflammation

The advancement of CKDs has been associated with subclinical inflammation. There is little indication of the progression of ADPKD. An inflammatory condition is not PKD. However, growing research suggests that inflammation begins to develop at the earliest possible stage of the disease. Several studies have suggested that PKD in humans as well as rodent versions of the condition has an inflammatory component.[48] These results were further supported by Zhou and coworkers, who discovered that the severely cystic cpk mouse kidneys had a much-increased expression of the monocyte and macrophage markers.[49] They discovered a significantly elevated and active CD14, a hallmark of alternatively-activated macrophages. Toll-like receptors (TLRs) interact with the pattern recognition receptor CD14 to activate the innate immune system.[50][51][52] The data show that inflammation begins early in ADPKD even when renal function is retained, despite the sample size being very small. Polycystin-2's capacity to localize to the plasma membrane and primary cilia was discovered to be inhibited by TNF-α.[53] TNF-α inhibitors like Etanercept, a biologic drug with FDA approval, are used to treat autoimmune disorders. By acting as a TNF-decoy receptor, etanercept has been shown to stop the growth of renal cysts in Pkd2+/ mice.[54] It has also been shown to slow the progression of PKD in animal models by lowering inflammatory pathway activity.[55] Even though resveratrol has significant in vivo and in vitro evidence that it can be utilized effectively to treat a variety of diseases. clinical trials have been significantly hampered by its low bioavailability.[56]

2.2.3 Oxidative Stress

The etiology of both acquired and genetic polycystic kidney disease has been linked to oxidative stress. An imbalance between the production of too many oxidants, such as free radicals, and their breakdown by antioxidants as a kind of internal defense results in oxidative stress. One can assume that OS may be implicated in the pathophysiology of ADPKD given that cardiovascular disease is the primary cause of death in individuals with ADPKD and that oxidative stress has a substantial role in the onset and progression of cardiovascular events.[57] In various rodent models, evidence has linked poor oxidant protection to the pathogenesis of PKD 4). The development of PKD in bcl-2 gene knockout mice may be connected to the loss of bcl-2's antioxidant capabilities (5). In the Han: SPRD-Cy rat model, treatments that weaken renal antioxidant defense or change renal redox metabolism can aggravate PKD. The C57BL/6J-cpk mouse's cystic kidneys have been found to have low expression levels of several antioxidant enzyme genes.[58] Data on oxidative stress in ADPKD patients are limited. In a mouse and rat model of ADPDKD, researchers examined the mRNA expression of the oxidative stress indicators. They found that the expression of antioxidant enzymes was downregulated and the expression of heme oxygenase-1 was elevated, both of which were related to how severe the illness was. They also demonstrated decreased protein levels, increased glutathione peroxidase and superoxide dismutase antioxidant enzyme activity, accumulation of lipid peroxidation byproducts in the plasma and kidneys of these animals.[59] In a study of 27

individuals with early ADPKD, levels of the oxidative stress marker 13-hydroxy octadecadienoic acid in the plasma and urine were higher than in controls of the same age.[60] A study found that those with ADPKD had significantly lower SOD and higher plasma 8-epi-PGF2. Although the levels of these oxidative stress markers were altered in early ADPKD patients, they did not appear to shift as kidney or blood pressure levels declined. According to Raptis et al., oxidized LDL and 15-F2t-isoprostane levels are both positively correlated with an increase in asymmetric dimethylarginine (ADMA) levels. Overall, it can be concluded that OS and endothelial dysfunction may both contribute to the onset and progression of kidney injury in ADPKD patients.[61] This theory is supported by several investigations using ADPKD rat models (Han: SPRD: PKD strain). The mesenteric resistance arteries of rats and later humans with ADPKD were found to have defects in eNOS function and decreased endothelium-dependent relaxation.[62]

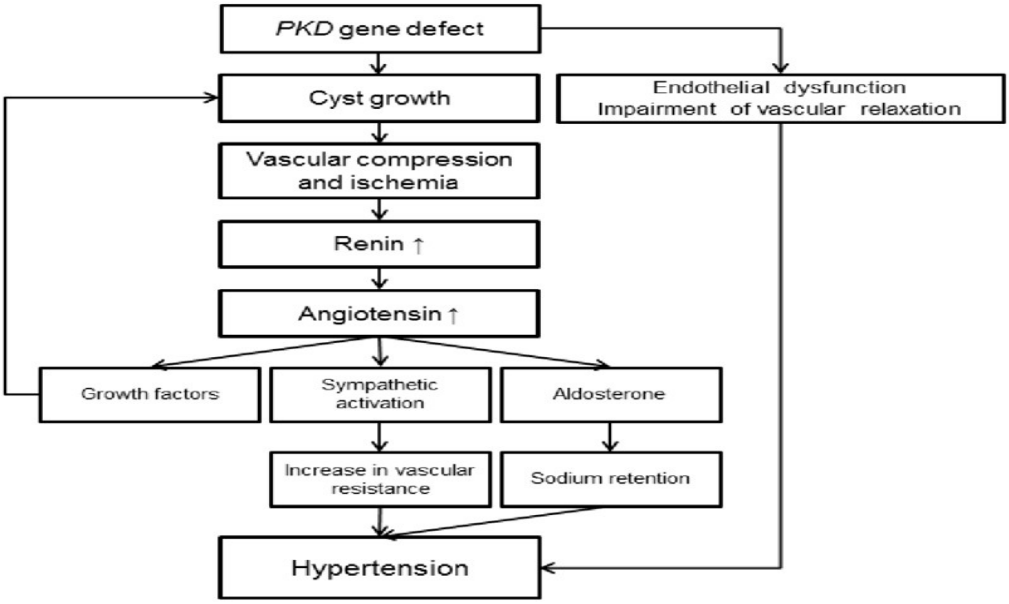

Figure 1: Pathophysiology of PKD.

2.2.4 Alteration in mitochondrial dynamics

The principal site of energy synthesis in cells is found in the mitochondria.[63] Lower OXPHOS was discovered by researchers to be an enriched pathway in both studies.[64] reduced OXPHOS did not garner much attention, possibly because this shift was not the focus of these two experiments. A recent study found that in comparison to controls, Pkd1/ MEFs maintained the mitochondrial membrane potential (m). This suggested that OXPHOS's mitochondrial contribution to overall ATP generation was modest.[65] Additional experimental support for the lowered OXPHOS was provided by two studies. Menezes et al.'s initial investigation found lower levels of mitochondrial FAO and OXPHOS.[66] When Padovano et al.[67] compared control heterozygous Pkd1fl/ cells to Pkd1/ mouse renal proximal tubule cell lines, they discovered for the first time that OCR was generally reduced regardless of the substrate fed to the cells.

Pathways leading to the development of renal cysts were found using a cDNA microarray to analyze the expression of genes in human PKD1 cysts.[68] According to the research, the top 50 gene sets that were down-regulated the most in PKD1 renal cysts included oxidative phosphorylation.[69] PPAR gene expression was decreased by miR-17 expression in human.

ADPKD cysts and ADPKD model organisms. In accordance with these experimental results, ADPKD animals. The cyst-lining cells of the ADPKD animal expressed less PGC-1 than the non-cystic tubules of the control animal.[70]

Mouse models of PKD that progressed slowly (Pkd1RC/RC) or quickly (Pkd1RC/-) were both improved by overexpressing mitochondrial-targeted catalase.[71] The mitochondrial antioxidant mitoquinone inhibited the proliferation of human ADPKD cyst-derived cells and lowered intracellular superoxide. Probucol, an antioxidant that lowers plasma cholesterol but is no longer used due to significant unfavorable side effects, prevented the development of PKD in pcy mice. Treatment with SS31 (Elamipretide), a tetrapeptide mitochondrial antioxidant, lowered cyst formation and reduced fibrosis in the kidneys of Pkd1RC/RC animals.[72] As a result, the miR-17 family is a potential drug target for ADPKD, and the inhibition of mitochondrial metabolism by miR-17 may represent a novel mechanism for the progression of ADPKD.[73]

2.2.5 Clinical Presentation and Diagnosis

PKD1 or PKD2 mutant carriers almost universally eventually develop kidney cysts that can be seen using

ultrasonographic imaging tests.[74] Clinical symptoms including hypertension or impaired renal function can appear in affected people at various ages. Patients with PKD1 mutations exhibit symptoms earlier than those with PKD2 mutations, as was already mentioned.

Patients with PKD1 often have bigger kidneys and more cysts than those with PKD2 at any given age.[75] According to one study, patients with PKD1 and PKD2 had median ages of 54 and 74 years, respectively, when they first presented with end-stage kidney disease (ESKD).[76]

However, both variants have been linked to early-onset illness.

Hypertension, hematuria, proteinuria, or impaired kidney function can all be symptoms of ADPKD in patients. The most frequent complaint made by patients is flank pain, which might be brought on by a urinary tract infection, obstructive calculi, or renal bleeding[77] Most patients with normal kidney function who are in their fourth decade of life or older have hypertension; this frequency rises to about 100% in patients with ESKD.[78] Patients may also exhibit signs of cysts in other organs, such as the liver, pancreas, spleen, or epididymis. Large kidney and liver cysts may compress the inferior vena cava (IVC), which may result in hypotension, thrombosis, and obstruction of the liver's venous outflow in the event of a significant obstruction.[79] In one investigation, compared to controls who were age and sex-matched, one-third of patients with ADPKD exhibited IVC compression that was less than 50%.[80]

The first step in the diagnosis of ADPKD is to ask the patient for a thorough family history. Imaging is largely used to confirm the ADPKD diagnosis. Genetic testing is typically only used in exceptional circumstances or to exclude ADPKD in a young potential kidney donor. However, patients should get advice regarding the risks and advantages of having a proven diagnosis of ADPKD before undergoing any imaging or genetic testing, particularly if they are asymptomatic.[82] In asymptomatic patients with normal kidney function who have a family history of ADPKD, ultrasonography is often adequate to make a diagnosis or rule out the existence of illness. If the ultrasound results are unclear or if problems (such as renal masses or complicated cysts) are accidentally discovered in these patients, MRI may be required.[83] When genetic testing is available to confirm the diagnosis, some professionals choose this over MRI follow-up imaging. If the ultrasound confirms the diagnosis of ADPKD, a baseline CT or MRI to measure height-adjusted total kidney volume (htTKV) may be required to evaluate the risk for disease development and the need for disease-modifying medication (such as tolvaptan).[84]

There are no established imaging-based criteria for the diagnosis of ADPKD in patients without a family history. If a person has 10 or more kidney cysts (each measuring less than 5 mm), especially if the kidneys are enlarged or liver cysts are present, and no other cystic condition is evident, the diagnosis is ADPKD. If possible, genetic testing should be done on individuals whose imaging results are unclear or when a precise diagnosis is required (for example, in the case of transplant candidacy or prenatal planning).[85]

3. Current Treatment Approaches for PKD

3.1 Conventional Treatment

Even though there is currently no cure for PKD, there are treatment options that can slow the progression of the condition and reduce the possibility of cyst formation. Another component of it is managing individual symptomatology. There are several treatment options, including medication, surgery, and others.[86] The main medication recommended for preventing kidney cyst formation in ADPKD patients is tolvaptan. Additionally, it slows the loss of kidney function. Tolvaptan may interact with other drugs and have significant effects on the liver. When using this drug, regular follow-up with a nephrologist (kidney expert) can aid in monitoring any problems and adverse effects.[87] Keeping blood pressure under control can also decrease the disease's course. Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) are frequently used to achieve this goal. Antibiotics may be used for bladder or kidney infections brought on by PKD. The pain can be reduced with over-the-counter or prescription medication. Underweight or undeveloped infants with ARPKD may require growth treatment. Growth hormones or nutritional therapy are two examples of this.[88] An operation to drain out the cyst fluid may be carried out by a medical practitioner if the PKD-related pain is unmanageable with medicines. This involves employing a needle to drain the fluid and injecting a sclerosing chemical to reduce the cysts.[89] This destroys unwanted tissue under controlled conditions. PKD frequently leads to renal failure. The blood may need to undergo dialysis treatment to eliminate waste and extra fluid. Hemodialysis and peritoneal dialysis are the two dialysis methods that are available. In a hospital or dialysis facility, hemodialysis is commonly performed three to five times per week or four to seven times per week for at-home dialysis.[90-92]

3.2 Lifestyle Management and Supportive Care

3.2.1 Management of blood pressure — If there are no contraindications, an ACE inhibitor is usually prescribed to young, healthy individuals between the ages of 18 and 50.[93]

3.2.2 Dietary sodium restriction — Research advised all trial participants to limit their daily sodium consumption to less than 2400 mg.[94] The degree of salt decrease in the urine was a moderate and variable indicator of participant adherence to dietary sodium restriction. Increased risk of renal growth and declining eGFR were linked to higher salt excretion.[95][96] However, in these cohorts, it

was hypothesized that vasopressin release, rather than kidney development, was responsible for the connection between sodium and Egfr.[97] Reducing sodium consumption will help people with ADPKD better control their blood pressure in addition to having positive effects on eGFR.

3.2.3 Increased fluid intake — Unless their eGFR is less than 30 mL/min/1.73 m2 or they are at risk for hyponatremia (for instance, if they are using a thiazide diuretic), patients with ADPKD are recommended not to consume more than 3 L of fluid each day. A 24-hour urine sample is periodically taken in order to track fluid intake. When there is a clinical improvement or decline, this is frequently done during the initial evaluation and again whenever it occurs. It is also beneficial to have a precise history of fluid consumption that has been estimated or quantified. By lowering plasma vasopressin levels, increased fluid intake may prevent cyst formation and lower the incidence of nephrolithiasis in ADPKD patients.[98,99]

In a small proof-of-concept research, 13 patients with ADPKD had mean water intake of at least 3 liters per day. As a result, it is possible that increasing fluid intake to reduce plasma vasopressin levels could be an effective therapeutic strategy to prevent cyst formation in ADPKD.[100,101]

3.3 Challenges and Limitations of Current Treatments

The reported adherence rate for individuals who were given prescriptions for blood pressure medication was 75%, which is higher than the previous rates of 50% for chronic conditions.[103-106] Similarly, most individuals reported that they exercised, ate a low-salt diet, and drank a lot of water.[107] [108] [109-114] [115, 116]

Personal convictions, though, could also make adhering difficult. Additionally, Ross et al. found that people were less likely to take their medications.[117] Similar to this, study participants who disregarded recommendations detailed personal encounters that contradicted the advice. Because he believed diet and exercise were better strategies to control his blood pressure, one patient in our study, for example, refused to take his blood pressure medication as prescribed.

The confusion caused by ambiguous instructions, particularly about water intake, was another barrier to adherence that we discovered. Many participants complained that they only got recommendations from non-medical sources or received instructions from doctors that were contradictory or unclear.[118,119] [120] These results suggest that patients' perceptions of what their doctors have told them and their real understanding of their condition and suggested treatments may differ.[121]

The need for better patient-physician communication is further supported by the participants' misunderstanding regarding the recommendations. Patients should be informed if they are receiving conflicting advice because of a lack of data or differing stages of kidney disease. According to studies, giving detailed directions.[123]

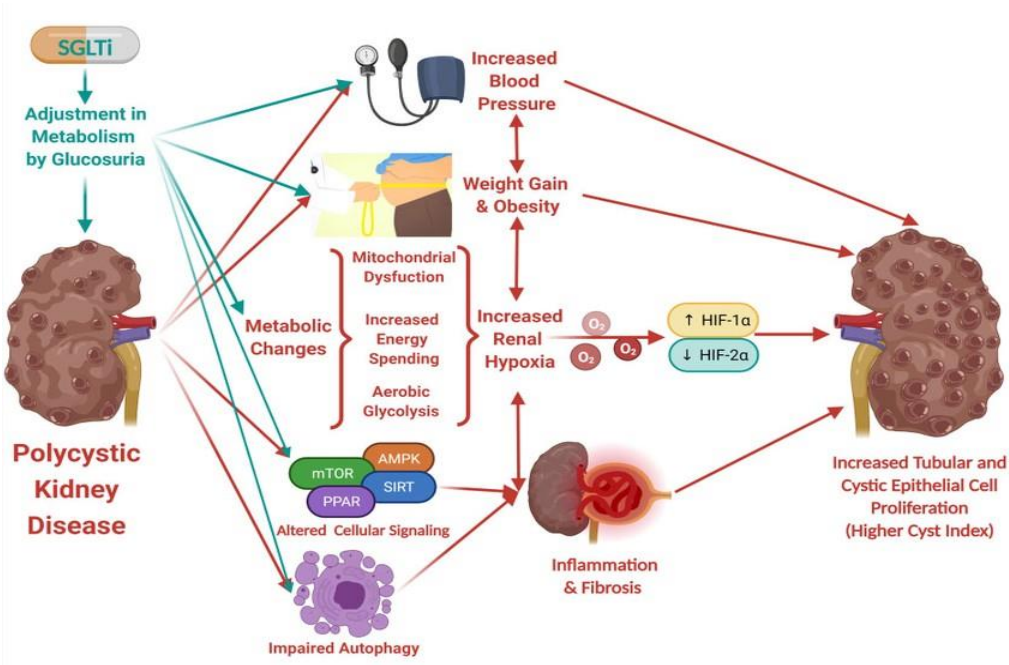

Fig. 2: The suggested mechanisms of polycystic kidney disease (PKD) leading to higher tubular and cystic epithelial cell proliferation with higher cyst index are shown with red arrows. The possible beneficial effects of

SGLTi on polycystic kidney disease (PKD) are shown with green arrows as they can interfere in multiple pathological processes of PKD by adjustments in metabolism via their glucosuric effects. SGLTi, sodium-glucose co-transporter inhibitor; HIF, hypoxia-inducible factor.

4. Emerging therapies for polycystic kidney disease

4.1 Disease-Modifying therapies

4.1.1 *cAMP inhibitors*

The effect was reversed when the V2R agonist 1-deamino-8-d-arginine vasopressin was given. Cyst growth was greatly suppressed in PCK rats (created by crossing PCK and Brattleboro rats) lacking circulating vasopressin.[124] According to one study,[125] when vasopressin was reduced by increasing water intake, PKD evolution was retarded. Vasopressin acting on V2 receptors is the main hormonal regulator of adenylyl cyclase activity in freshly dissected collecting ducts. The consequences of V2-induced alterations in cAMP and water permeability may be mitigated by the activity of AVP on V1a receptors on apical and basolateral membranes, which increases phospholipase C, phosphoinositide hydrolysis, and Ca2 release from the endoplasmic reticulum.[130][131][132] In animal models, blocking other GPCRs connected to G's proteins has been shown to be protective against the development of PKD. The 3-adrenergic receptor (3-AR) is significantly expressed in the loops of Henle and cortical collecting ducts of both murine and human polycystic kidneys.[133][134] AQCA brand-new, focused V2 receptor antagonist is called lixivaptan. A significantly decreased incidence of hepatotoxicity was also anticipated for lixivaptan compared to tolvaptan.[135] In comparison to controls, PCK rats given low doses of lixivaptan had kidney weight/body weight ratios that were 26% lower, kidney cystic scores that were 54% lower, kidney cAMP levels that were 23% lower, and plasma creatinine that were 13% lower. As a result of cholangiocytes expressing the V2 receptor, a significant decrease in the burden of liver cysts has been reported.[136]

4.1.2 *mTOR Inhibitors: Sirolimus and Everolimus*

The mTOR cascade in polycystic kidney disease (PKD) increases renal tubule epithelial cell growth, growth, and metabolic processes, which in turn encourages cyst formation. Two distinct complexes, mTORC1 and mTORC2, are connected to mTOR. While mTORC1 consists of mTOR and the regulatory associated protein of mTOR (Raptor), mTORC2 consists of mTOR and a rapamycin-independent companion of mTOR (Rictor). PIP2 is changed by PI3K into PIP3 in the mTORC1 pathway, which localizes Akt to the membrane. The interaction between TSC1 (hamartin) and TSC2 (tuberin) becomes inactive by Akt-dependent phosphorylation.[137] TSC2 inactivation results in the activation of mTOR via the GTPase Rheb. Through separate pathways, mTOR phosphorylates 4E-BP1 and p70 S6 kinase (p70S6K) to encourage cell growth. In the cells lining bile ducts and renal cysts from ARPKD cases, mTOR was highly expressed. The bile duct epithelium and larger renal cysts had mild S6K immunostaining while the strongest staining was in the smaller tubules. Controls showed mTOR and S6K expression in distal tubule segments.

Only non-cystic tubules in ARPKD were immunostained with 4E-BP1.[138] All specimens tested negative for tuberin/TSC2 immunostaining. In another study, Akt, mTOR, and S6K levels were analyzed in human kidney samples from children with ARPKD and healthy controls. The levels of phosphorylated Akt, active mTOR, and its downstream effector S6K were all significantly higher in kidney specimens but not in control tissues.[138] These results demonstrate that mTOR signaling is enhanced in human kidneys with PKD, supporting human research of mTOR inhibitors. Inhibiting mTOR kinase directly causes mTORC1 and mTORC2 to stop working, which is how new mTOR kinase inhibitors function. Everolimus, a mTOR inhibitor, delayed the growth of the total kidney volume in ADPKD patients but showed no effect on the rate of renal impairment (Funded by Novartis; ClinicalTrials.gov number, NCT00414440).[138] A recent study established Sirolimus' impact on mTORC1 inhibition. The effects of sirolimus and the mTOR kinase inhibitor torin2 on cyst size and renal function were compared using the Pkd1RC/RC mouse model. Torin2 and sirolimus were equally effective in lowering cyst loads and improving renal function because they had comparable effects on mTORC1 and mTORC2 signaling and proliferation in the Pkd1RC/RC kidney.[139]

4.2 *Inhibitors of the CFTR (Cystic Fibrosis Transmembrane Conductance Regulator)*

The Na+/K+-ATPase inhibitor ouabain[140] also inhibits cAMP-dependent fluid and anion secretion (Table 3). Tonum et al. 2022[141] investigated the pharmacological effects of Pinostrobin on CFTR-mediated Cl secretion and renal cyst growth using both in vitro and in vivo models. Animals with PKD receiving oral Pinostrobin (40 mg/kg/day) displayed a decrease in the cystic area when compared to rats treated with a vehicle. Therefore, Pinostrobin treatment decreased the expression of the CFTR protein in the kidneys of PKD rats. The CFTR protein interacts with lumacaftor (VX-809 corrector of CFTR) in the membrane in vitro and in mouse models, which prevents cyst development. Fluid secretion becomes fluid reabsorption in the cyst phenotype. The oral CFTR corrector GLPG2737 has just undergone a multicentric randomized, double-blind, placebo-controlled study to evaluate its efficacy, safety, tolerability, and pharmacokinetics in ADPKD patients.[142]

4.2.1 *JAK/STAT inhibitors*

It is well known that the Janus-Activated Kinase (JAK)-Signal Transducer and Activator of Transcription (STAT) signaling pathway mediates the cellular response to

different growth factors and cytokines. According to the results of various investigations, ADPKD has unusually high renal JAK and STAT expression.[143] According to Bhunia et al.[144] STAT1 phosphorylation and the production of p21waf were improperly carried out in the mouse embryo lacking PKD1. The role of JAK 2 in the Pkd1nl/nl mice model of ADPKD was investigated by Patera et al.[145] When compared to healthy kidneys, they discovered that JAK2 was overexpressed in the cystic cells of ADPKD patients.

Two JAK2 inhibitors, curcumin and tofacitinib, demonstrated decreased cyst development, indicating a potential role for the JAK pathway in ADPKD (Torres et al. 2012). In ADPKD, polycystin-1 controls JAK-STAT activity via two distinct mechanisms. There is unmistakableproof that polycystin-1 is involved in ADPKD, in addition to the lower production of the protein caused by the PKD1 mutation.[146] Pyrimethamine, an anti-parasitic drug, was recognized by Takakura et al.[147] as a STAT3 function inhibitor. According to a study, pyrimethamine therapy inhibits human ADPKD cell proliferation and prevents the development of renal cysts in both adult and neonatal PKD mice models. Furthermore, S3I-201, a particular STAT3 inhibitor, inhibits cyst development and expansion in a newborn PKD mouse model.

4.2.2 *Nuclear factor 2 (Nrf2) Related to Erythroid-2 activator*

Oxidative stress has emerged as a significant contributor to the onset of ADPKD. Controlling the protective response to oxidative stress requires the transcription factor nuclear factor erythroid-2 related factor 2 (Nrf2).[148] Normal conditions result in Nrf2 being coupled to one of three ubiquitin ligase complexes, most significantly Keap1-CUL3-RBX1, and as a result is susceptible to ubiquitin-proteasomal destruction. As a result of oxidative stress, the Keap1 protein undergoes conformational changes that free Nrf2 from the Keap1-CUL3-RBX1 complex and enable it to go to the nucleus. To lower oxidative stress and have other cytoprotective effects, the antioxidant response element is bound by Nrf2 in this instance.[149] This causes the transcription of several target genes. In an orthologous ADPKD mouse model, Nrf2 loss increased ROS production and facilitated cystogenesis while pharmaceutical Nrf2 stimulation reduced cystogenesis and ROS generation.[151] In patients with CKD and type 2 diabetes, this trial investigated if bardoxolone might lessen ESRD and cardiovascular events. The Falcon research, a phase 3 RCT, will involve about 300 patients and look into the effectiveness, safety, and side effects of bardoxolone methyl in ADPKD patients.[152] The therapeutic impact of obacunone on ADPKD was studied by Qiu et al. in 2022.[153] Obacunone therapy dramatically slowed the development of renal cysts in PKD mice, according to in vivo investigations. Obacunone reduced excessive cell growth by downregulating the mTOR and MAPK signaling pathways after inhibiting lipid peroxidation by upregulating GPX4., according to Western blot and morphological analyses, demonstrating its role as an NRF2 activator in ADPKD.

4.2.3 *MAPK pathway modulator*

Cell proliferation induced by growth factors and tyrosine kinase receptors is thought to be regulated by the classical MAPK signaling pathway.[154] [155,156] According to one theory, calcium shortage triggers this phenotypic flip by suppressing PI3K/Akt signaling, which then raises B-Raf levels via altering the rate of synthesis and/or turnover.[157][158] The MAPK/ERK inhibitor PD184352, when administered to pcy mice with nephronophthisis, an adolescent variant of recessive PKD, was found to successfully reduce cyst formation, and kidney enlargement, and preserve renal function.[159] Targeting Raf/MEK/ERK has produced inconsistent results, perhaps as a result of redundancies with other pathways.[160] Sorafenib, a Raf kinase inhibitor, reduced cell proliferation, the development of ADPKD cysts in vitro, and cAMP-dependent activation of B-Raf/MEK/ERK signalling.[161-164] [165-168]

4.2.4 *EGFR inhibitors*

Torres and his coworkers discovered that inhibiting EGFR tyrosine kinase activity can delay the onset of PKD in the Han: SPRD rat, a widely used animal model of autosomal-dominant slowly progressive PKD (ADPKD).[169] Rats of the wild-type and cy/type were given EKI-785, EKB-569, or only a vehicle. Intraperitoneally injected EKI-785 or EKB-569 decreased kidney weights, serum blood urea nitrogen (BUN) concentrations, cyst volumes, and fibrosis scores in cy/rats. Shi et al. described USP11's biological function and clinical importance in renal fibrosis in 2023.[170]

Epidermal growth factor receptor (EGFR) nuclear gene transcription was revealed to include USP11. Together with extra-nuclear EGFR, USP11 co-immunoprecipitated, co-stained, deubiquitinated, and shielded it from proteasome-dependent degradation. Degradation of the EGFR was accelerated and the stimulation of TGF-1 and downstream signaling was reduced when USP11 was reduced genetically or pharmaceutically. Since USP11 decreased partial epithelial-mesenchymal transition, G2/M arrest, and aberrant secretome of profibrogenic and proinflammatory factors in uric acid-stimulated tubular epithelial cells, it is a promising target for treating kidney fibrosis.

4.3 Genetic Therapies

4.3.1 CRISPR/Cas9 and Gene Editing for PKD

Many of the genes underlying kidney disease have been identified, but functional studies are still required to confirm prospective genes identified through genetic research and to explain how disease-causing mutations affect cells and tissues. Furthermore, many genes linked to renal illness remain unknown.[171][172]

There is a possibility that CRISPR will unintentionally alter DNA sequences that resemble the gRNA but are not identical to it. In order to lessen the possibility of these "off-target" effects, computational methods that maximize sequence specificity can be used to choose gRNAs. One strategy to lessen the risk of accumulating mutations in the genome is to minimize the length and concentration of Cas9 exposure. A further level of specificity can be added by "Nickase" mutants of Cas9, which efficiently cleave DNA only when two gRNAs are present (on opposing sides of the target).[173,174]

In order to model certain aspects of tubular physiology and pathology, this method has led to the use of CRISPR in kidney epithelial cell lines. For example, deletion of the multidrug resistance protein 1 in Madin-Darby canine kidney cells was shown to reduce transporter substrate efflux.[175,176] Complex disease models can be developed using human pluripotent stem cells (hPSC), a cell type that contains both embryonic stem cells produced from embryos and induced pluripotent stem cells reprogrammed from somatic cells.[177] hPSC has been useful in in vitro studies on the pathways of kidney disease. Human pluripotent stem cells (hPSC) were first generated from PKD patients, influencing both autosomal dominant and autosomal recessive forms of the disease. In hPSC with heterozygous mutations in PKD1, which codes for polycystin 1, it was revealed that less polycystin 2 localized to primary cilia. This deficit was discovered in undifferentiated hPSC, differentiated somatic epithelial cells, and hepatic hepatoblasts.[178] In a recent study on mice implanted with human immune cells, CRISPR was utilized to stop HIV replication by deleting the integrated virus from DNA; the method also worked on mice who were acutely infected.[179] Additionally, Huntington's disease, Duchenne muscular dystrophy, and retinal degenerative illnesses have all been treated in vivo in mice and rats using CRISPR. Regarding the latter, local delivery, and electroporation in the fetal retina, which prevented retinal degeneration in mice, provided proof of concept for the use of CRISPR for gene therapy.[180,181]

AAV is a little virus that has demonstrated the greatest potential in pre-clinical research, and it has been selected as the delivery method for gene therapy.[182] Recent studies use single gRNAs for CRISPR-mediated gene therapy using AAV vectors to deliver the Cas9 protein locally and systemically in animal models. Targeting dystrophin mutations—which in animals result in Duchenne muscular dystrophy—and gene repair were the goals of this approach.[183–185] Effective distribution to certain cells or tissues within the body is a problem for gene editing in solid organs.[189] According to pre-clinical research in mice, AAV can effectively localize CRISPR to solid organs and reduce phenotyping.[190]

4.3.2 RNA Interference (RNAi) Therapies

Recent studies have shown that ncRNAs, especially miRNAs, regulate the formation of cysts through several pathways and may be exploited as potential therapies or biomarkers.[191] Individual miR-17-92 cluster members in the renal cells of mice and patients with ADPKD exhibit differently regulated miRNAs (DE-miRNAs).[192–195] As a result, tubular and glomerular cysts were produced, and the miR-200 cluster was downregulated. This enzyme joins Drosha to form a necessary ternary complex to produce miRNA.[196] Anti-miRNA new medications may likely promote cyst formation. Kidney cysts have both an increased level of the microRNAs 17 and 21.[197] However, at the later phases of cystogenesis, microRNA-192 and -194 were down-regulated along with hypermethylation, indicating that they might influence cyst development. MicroRNA-192 and -194 have been shown to have therapeutic benefits in both in vitro and in vivo experiments. Injections of miRNA precursors prevent the development of cysts in Pkd1 mutant mice[198] MiR-192 and -194 appear to be a promising and risk-free treatment for ADPKD. Three interventional studies actively seek ADPKD patients at the outset. Metformin, a widely used and affordable medication, will be used in two studies. Additionally, the drug that can lessen tolvaptan-related frequent urination will be researched[199-200] Animal, ex vivo, and cellular ADPKD models all produced the same results.[201] Furthermore, blocking Pkd1/2 cis-inhibition with RGLS4326 reduced the development of cysts in mice and stabilized those that already existed.[202][203]

4.3.3 *Histone deacetylase (HDACs) inhibitors*

The family of enzymes known as histone deacetylases (HDACs) works on nonhistone proteins to control a variety of intracellular processes and alter gene expression.[204] The class I HDAC inhibitor valproic acid (VPA) and the pan-HDAC inhibitor trichostatin A (TPA) were discovered to influence the pathogenic deficits of laterality and body curvature in zebrafish in this study.[205] In an orthologous mouse model (Pkd1flox/flox; Pkhd1-Cre), VPA therapy was also demonstrated to protect kidney function and reduce the development of renal cysts.

ACY-1215 and tubacin, which are both specific HDAC6 inhibitors, limit cyst growth in vivo and prevent cyst formation in vitro, respectively, in ADPKD models.[206, 207] This is thought to lessen the formation of cyst-lining epithelia. Additionally, it was found that the levels of cyclic adenosine monophosphate (cAMP) were decreased by both tubacin and ACY-1215; however, additional study is required to identify the precise mechanism underlying this discovery.[208][209] As epigenetic indicators of ADPKD, histone acetyl group alterations have also been discovered. Both histone acetyltransferases (HATs) and histone deacetylases (HDACs) have been linked to cystic load and severity in ADPKD mouse models. BET proteins, which have both a bromodomain and an extra-terminal motif, may control how active HATs are. In support of this, Zhou et al[210] demonstrated that Brd4 targeting with the thieno-

triazole-1, 4-diazapine inhibitor JQ1 prevents renal cyst formation in Pkd1 mutant mice.[212]

4.4 Novel Drug Targets and Small Molecule Inhibitors

4.4.1 *Adenosine monophosphate stimulated protein kinase (AMPK) modulators*

The enzyme AMPK is essential for maintaining the equilibrium of cellular energy. It works to restore energy balance by encouraging ATP generation and blocking ATP-consuming processes when the cellular energy levels are low, such as when there is a high energy demand or low glucose level. Because AMPK is essential for controlling cell growth, metabolism, and autophagy, researchers have been looking into how it might be related to PKD.[213] According to certain research, AMPK activation may be protective in PKD.[214] These researchers showed that cells lacking PC1 expression show a significant shift in their metabolic functions. This behavior is comparable to the Warburg effect, which many varieties of highly proliferating tumor cells exhibit.[215] The AMP-activated protein kinase (AMPK) activator metformin (MET), which has already been approved for type 2 diabetes, is currently being studied as a potential treatment for ADPKD. MET has shown variable therapeutic effectiveness in preclinical ADPKD investigations, despite having great tolerability.[217] Dagron et al. investigated PXL770, a potent and specific clinical stage direct allosteric AMPK activator, in canine and patient-derived 3D cyst models as well as an orthologous mouse model of ADPKD. PXL770 boosted AMPK activation and dose-dependently lowered cyst formation in Madin-Darby Canines, which are similar in principle. Forskolin-stimulated kidney cells and desmopressin-stimulated kidney epithelial cells from ADPKD patients. PXL770 promoted kidney AMPK pathway activation, delayed the onset of renal failure (decreasing blood urea by 47%), decreased cystic index by 26%, and increased the kidney weight to body weight ratio by 35% when compared to untreated control Pkd1 knockout mice. As a result, AMPK activation raises the possibility of treating ADPKD and promotes further research and development of PXL770 for this purpose. Aspirin's active component, salicylate, physically binds to the AMPK -subunit and causes AMPK activation that is not dependent on phosphorylation (37, 62, 63).[218]

4.4.2 *Hedgehog Inhibitors*

Renal cystogenesis is an understudied aspect of Hedgehog (Hh) signaling, which is impacted by all major cilia structural abnormalities during development. In human ciliopathies, which prominently display renal cysts as a clinical characteristic, the ciliary gene Thm1 (Ttc21b), which adversely affects Hhsignaling, is most frequently altered. Cystic kidney disease with elevated expression of Gli genes, which encode the final mediators of the Hh pathway, is brought on by Thm1 deletion in conditional knock-out (cko) mice.[219] Thm1 cystic kidney disease is less severe when Gli2, the main transcriptional activator of the Hh pathway, is lost. Additional evidence from Gli2 double conditional knock-out (dko) mice points to an elevated Hhsignaling causative role in Thm1 renal cystogenesis. jck and Pkd1 and Hh inhibitors decreased the capacity of jck and Pkd1 cultured kidneys to generate cysts, which is relevant given that Gli genes are also increased in recognized animal models of Autosomal Dominant Polycystic Kidney Disease (ADPKD).[220] As a result, increased Hh activity might contribute to renal cystogenesis in general and serve as a promising therapeutic target for ADPKD. Sant 2 (an SMO antagonist) and Gant61 (a GLI inhibitor) are Hedgehog inhibitors that reduce ADPKD cell proliferation, according to Silva et al.[221] The tetratricopeptide repeat-containing hedgehog modulator-1 (THM1), a protein whose deficiency has been found to result in renal cysts, was found to have less cAMP-mediated cytogenic potential when GLI2, a transcription activator of the Hh pathway, was genetically deleted in a mouse model of ADPKD by Tran et al.[120]

4.4.3 *Ferroptosis inhibitors*

It was initially demonstrated by Zhang et al.[222][223] (2021) that ferroptosis controls the course of ADPKD and offers a possible therapeutic target.[224] Collectively, these studies highlight ferroptosis' promise as a cutting-edge therapeutic strategy and highlight its critical function in the control of CKD progression. Zhang et al. 2021[225] looked at the Pkd1 mutation that leads to iron and lipid metabolism dysregulation in renal epithelial cells, which causes ferroptosis. Additionally, it suggests ferroptosis rather than apoptosis is the primary form of controlled cell death in ADPKD kidneys, which resolves the debate over the function of apoptosis in ADPKD. In addition, erastin induces ferroptosis, which enhances cyst growth in Pkd1RC/RC animals, while Fer-1 inhibits ferroptosis, which slows cyst growth in both mouse models of rapidly and slowly progressing ADPKD. Ferroptosis may therefore represent a cutting-edge approach to the therapy of PKD. In polycystic kidney disease (PKD), TMEM16A (anoctamin 1) promotes cyst growth, which ultimately results in kidney failure. However, it is not well-known how channels are activated.

It was demonstrated for the first time that renal TMEM16A is triggered by the oxidation of phospholipids in plasma membranes. As a result, the calcium-sensitive adenylate cyclase ADCY1 is activated, promoting calcium signaling and further stimulating CFTR.[226] Idebenone, an antioxidant, and ferrostatin-1 both greatly slow cyst growth, showing that under PKD, the apoptosis-independent controlled cell death process ferroptosis is activated. As a result, blocking TMEM16A and inhibiting lipid peroxidation are two promising innovative treatment options to postpone cyst development in PKD.[227] Numerous metabolic abnormalities were seen in Pkd1-deficient kidney cells and tissues, including decreased expression of GPX4, an iron exporter (ferroportin), and the system Xc-amino acid antiporter, which is essential for the import of

cystine. Researchers also found increased erastin in the kidneys of Pkd1 mutant animal models. Ferrostatin-1 also prevented Pkd1-deficient cells from proliferating and undergoing ferroptotic cell death. 4HNE promotes the synthesis of lipid peroxidation in Pkd1-deficient cells, boosts the proliferation of Pkd1 mutant cells.[228]

4.4.3.1 *PDE enzymes activator*

A variety of phosphodiesterases (PDEs) can hydrolyze cAMP. There are 11 families (PDE1-PDE11) of mammalian PDEs, each having 21 genes and more than 50 isoenzymes. PDE family members either solely hydrolyze cAMP or cGMP (PDE4, PDE7, and PDE8), both (PDE1, PDE2, PDE3, PDE10, and PDE11), or both (PDE1, PDE2, PDE3, PDE10, and PDE11).[229-230]

Families and subfamilies of PDE1 (PDE1A, PDE1B, and PDE1C) and PDE3 (PDE3A and PDE3B) may be particularly significant in PKD. In addition to phosphorylation, calcium-calmodulin binding, cGMP or cAMP binding, and protein-protein interactions, they are also controlled genetically. PDE1 is the only PDE that calcium14,15 (which is diminished in PKD cells) can activate, and cystic kidneys have lower levels of PDE1 activity.[231] The majority of the PDE activity in renal tubules is attributed to it16,17. Ye et al. conducted research on the most important PDEs and the function of cAMP hydrolysis in the pathophysiology of PKD in 2015.[232] In Pkd2/WS25 mouse kidney nuclear preparations, Pde1a, Pde1c, or Pde3a but not Pde1b or Pde3b knockouts, higher quantities of protein kinase A-phosphorylated (Ser133) cAMP-responsive binding protein (P-CREB), activating transcription factor-1, and CREB-induced CRE modulator proteins were discovered. The results show that calcium- and calmodulin-dependent PDEs (PDE1A and PDE1C) and PDE3A control the beginning of PKD, possibly via controlling compartmentalized cAMP pools that control cell proliferation and CFTR-driven fluid secretion. Compounds that activate PDE4 reduce intracellular cAMP levels, impede cAMP-mediated signaling activities, and significantly limit cyst formation. Thus, PDE4 activator substances have potential as treatments for diseases caused by increased cAMP signaling. They also offer a means of assessing how long PDE4 isoforms regulate cAMP-mediated cellular activities.[233] Additionally, metformin stimulates phosphodiesterase (PDE) activity, which phosphorylates and activates AMPK at Thr172. The greater cAMP content in ADPKD influences cell proliferation because the PDE activation adversely affects the cAMP synthesis. Additionally, adenylyl cyclase (AC) activity is directly inhibited by the activation of AMPK brought on by the inhibition of mitochondrial complex I, which lowers the synthesis of Camp.[234]

4.5 Stem Cell Therapies and Regenerative Medicine

However, recent advances in the direct differentiation of human pluripotent stem cells for the restoration of kidney tissues may present a distinctive platform for disease modeling. We have created a step-by-step process for the selective generation of nephron progenitor cells (NPCs), which produce kidney organoids.[235] Since they can develop into the cell types affected by human diseases, patient-derived human induced pluripotent stem cells (hiPSCs) are especially interesting. Human embryonic stem cells (hESCs) generated from homozygous PKD1- and PKD2-mutant individuals have been shown to replicate cyst formation in vitro.[236,237] The hiPSC-derived kidney organoids from controls and ADPKD patients did not, however, exhibit different characteristics in that investigation. The use of heterozygous PKD1-mutant kidney organoids, including those made from patient hiPSCs, in disease models is not well supported.[238] A more modern method of treating renal illness involves the transplantation of mesenchymal stromal cells (MSCs). They have the capacity to differentiate in vitro into chondroblasts, adipocytes, and osteoblasts. Numerous studies suggest that they can treat renal disorders via various mechanisms.[241] Several studies showed that the production of cysts and inflammation in ADPKD was reduced when proinflammatory cytokines were downregulated.[38–40][242] MSC's overall safety and tolerability have been evaluated, but further research is still needed to determine whether people with ADPKD can benefit from it.

5. Clinical Trials and Research Updates

5.1 Promising clinical trials

Drugs that target the cAMP pathways, the EGF receptor, AMPK, and other pathogenic pathways are all in various stages of development.[245] Successful Bardoxolone Methyl (Reata Pharmaceuticals), Tesevatinib/KD019 (Kadmon Corporation/Sanofi), and other ADPKD drug clinical trial outcomes have strengthened the portfolio, allowing for personalized therapy in the future and increasing expectations for an improved ADPKD treatment paradigm.[246] Reata Pharmaceuticals' investigational bardoxolone methyl, an orally administered once-daily Nrf2 activator, prevents inflammation and mitochondrial dysfunction while delaying cyst development.[247] Based on the impressive Phase II (NCT01559363) ADPKD clinical trial findings, it is projected to be the most successful treatment among those currently in development, Tesevatinib, an oral small-molecule tyrosine kinase inhibitor, targets the epidermal growth factor receptor, a part of the signaling pathway with the potential to inhibit cyst formation. Tesevatinib may give Sanofi the opportunity to completely change the ADPKD market scenario by acting as the first successful treatment.[248]

Table 1: Drugs under Clinical Development in PKD.

Drug	Mechanism of action	Clinical develop ment	NCT Number	Reference
cAMP modulators				
Tolvaptan	Tolvaptan competes with vasopressin for binding to V2 receptors in the collecting ducts of the kidneys and reduces the reabsorption of water from the urine, thus slowing the growth of kidney cysts, reducing kidney volume, and Potentially preserving kidney function in ADPKD patients.	Phase 3, double-bl ind placebo- controlle d	NCT02251275	[100]
Lixivaptan	Lixivaptan reduces the fluid accumulation within the cysts and potentially slows down the progression of ADPKD by blocking the V2 receptors in the kidneys.	Phase 3, open-lab el	NCT04064346	[135]
Somatostatin analogues				
Lanreotide	Potentially inhibit the cAMP pathway by reducing the secretion of cyclic AMP, which in turn could help slow down the growth of cysts.	Phase 3, double-bl ind, placebocontrolle d	NCT01616927	[131]
Octreotide		Phase 2, double-bl ind, placebocontrolle d	NCT00426153	[128]
CFTR inhibitors				
GLPG2737	Inhibits the CFTR protein responsible for cystic fibrosis, helping to restore its function and alleviate symptoms associated with the disease.	Phase 2, double-bl ind, placebocontrolle d followed by 1-year open-lab el phase	NCT04578548	[142]
mTOR inhibitors				
Everolimus	Everolimus, a mTOR inhibitor, delays the growth of the total kidney volume in ADPKD patients but shows no effect on the rate of renal impairment	Phase 4, double-bl ind, placebocontrolle d	NCT01009957	[138]
Metformin	Metformin has been reported to modulate the mTOR pathway and might potentially impact the growth of cysts with its anti-proliferative effects.	Phase 2, double-bl ind, placebocontrolle d	NCT02656017	[199]
NfR2 Activators				
Bardoxolone	Promotes Nrf2 activation and enhances the body's ability to counteract	Phase 3, double-bl indplacebocontrolle d	NCT03918447	[151]

	oxidative stress and inflammation, potentially slowing the progression of kidney disease.			
miRNA inhibitors				
RGLS4326	Bounds to the miR-17-5p, the target miRNA, thus leading to the restoration of normal cellular processes that were disrupted by the dysregulated miRNA	Phase 1, open-label	NCT05429073	[203]
Miscellaneous				
Tesevatinib	It is a tyrosine kinase inhibitor that targets the epidermal growth factor receptor with a potential to inhibit cyst formation	Phase 2, open-label	NCT01559363	[248]
Curcumin	Curcumin is known for its anti-inflammatory and antioxidant properties. It has been studied for its potential to modulate various signaling pathways and cellular processes that could be relevant to PKD.	Phase 4, double-blind, placebo- controlled	NCT02494141	[146]

5.2 Biomarkers for ADPKD Progression

Biomarkers are measurable substances that can show whether a disease is present or is progressing. In order to help in diagnosis, disease monitoring, and potential therapeutic options for polycystic kidney disease, researchers have been looking at a variety of biomarkers. Numerous studies have been conducted on prognostic biomarkers.[249,250] None have yet been demonstrated to outperform kidney volume-based indicators.[251,252] Numerous research studies have investigated the connection between renal volume and the evolution of ADPKD. In the Tolvaptan Phase 3 Efficacy and Safety Study in ADPKD (TEMPO3:4) trial, a vasopressin 2 receptor antagonist called tolvaptan was found to lessen the rise in TKV and the deterioration in kidney function in ADPKD patients. Patients with progressing ADPKD can be detected using height-adjusted TKV and age.[253]

According to Kim et al.[254] there is a significant relationship between total kidney volume (htKTV) and serum and urinary levels of NGAL. The potential that this protein is involved in cyst development and production is increased by this discovery. Urinary NGAL levels may only increase in more advanced PKD disease, according to Meijer et al. [255] who found a correlation between urine NGAL levels and TKV. Patients with similar TKV, however, can present with drastically different morphologies, suggesting that treatment decisions are frequently arbitrary and based on unrelated factors (such as the presence of intact kidney parenchyma or a small number of cysts that significantly contribute to overall TKV).[256][257]

They did this by utilizing quantitative NMR profiling to find a variety of urinary metabolic indicators. The eGFR and the pace at which the eGFR will drop in the future are related to these markers.[258, 259][260] The degree of severity and rate of progression of ADPKD can be determined by analyzing various proteome markers. The proteins most significantly enhanced in the rapidly advancing group.[261][262] Other putative urine and plasma biomarkers of ADPKD, such as NGAL MCP-1 KIM-1, have recently been discovered. These markers, however, were found to be non-specific for ADPKD and to be present in healthy patients.[262] Gregory et al[263] investigated new image-derived biomarkers for autosomal dominant polycystic kidney disease, such as total cyst volume, renal parenchyma volume, total cyst number (TCN), and cyst-parenchyma surface area (CPSA). Total cyst number and cyst parenchyma surface area were found to be more accurate than TKV in predicting the slope of estimated glomerular filtration rate decline, kidney failure, and chronic kidney disease stages 3A, 3B, and 4. These novel, automatically derived image biomarkers will be extremely useful in future studies and therapeutic treatment for individuals with autosomal dominant polycystic kidney disease.

6. CONCLUSION AND POTENTIAL FUTURE DIRECTIONS

In summary, various pharmacological drugs that target a wide range of molecules and pathways have shown promise in preclinical research. Although the lengthy course of therapy required for ADPKD raises concerns about renal and extrarenal side effects, new strategies for medication delivery to renal cysts may be able to solve this issue.

ADPKD, one of the most common monogenic disorders in humans, is distinguished by the formation and inescapable growth of kidney cysts, which eventually leads to ESRD. The control of symptoms and complications, as well as delaying the progression of the disease, are the main goals of current therapeutic strategies. In the future, newer medicines that specifically target the mechanisms of cyst formation and growth will be developed thanks to recent genetic advancements and an improved understanding of the molecular pathways of cystogenesis. However, in preclinical research on ADPKD, higher doses of medicines like met (300 mg/kg/day) were utilized than are generally suggested (maximum 37.5 mg/kg/day for diabetic patients). Then, 25% of patients experience unfavorable side effects such as GI pain, and 5% of patients experience full medication intolerance.[219, 220] [221] [222] The tolvaptan clinical trial dropout rate was 23%, and forecasts show that only a small advantage of a 4.9-year delay in kidney failure is realized after 18 years of continued tolvaptan treatment.[223-224]

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