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Autosomal Dominant Polycystic Kidney Disease Therapies

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ABSTRACT

Autosomal Dominant Kidney Disease (ADPKD) is the most common gene disorder affecting the kidney. It is thought that the disease needs at least two factors for it to appear. This literature review aims to showcase the current and upcoming disease therapies to show the outlook of this disease. This literature review took sources from PubMed and other reliable sources to formulate how the disease works, which parts of the body are affected, and how the therapies work. The results revealed that ADPKD is often based on the genes PKD1 and PKD2, which encode proteins that form a probable receptor/channel complex. Loss of function from these genes can cause cyst formation. Many minor genes may cause a similar effect. The current therapy and treatment options include a change of lifestyle, dialysis, and surgery. The only current drug approved by the FDA is tolvaptan. Unfortunately, many side effects of tolvaptan limit its usefulness to a narrow range of patients. Therefore, I researched the new and upcoming therapies to analyze the outlook of this disease. In conclusion, based on the variety of promising incoming research and therapies, the outlook of ADPKD is positive, where more patients can be treated.

INTRODUCTION

Polycystic kidney disease (PKD) is the most common single gene disorder affecting the kidney and the most common human ciliopathy. PKD is the umbrella term for a whole class of diseases that form cysts on the kidney. Autosomal dominant polycystic kidney disease (ADPKD) is a form of PKD that is caused by inheriting a dominant mutation in the PKD1 or PKD2 genes (Boletta and Caplan, “Physiologic Mechanisms Underlying Polycystic Kidney Disease”).

Polycystic kidney disease is cilia-related and leads to renal cysts and is commonly found with PCLD. ADPKD is mainly shown in adults, and renal disease is commonly more severe in men than women. Some symptoms of this disease are hypertension, abdominal fullness, abdominal pain, hematuria, and urinary tract infections. About 1 in 400 and 1 in 1000 live births are affected by it (Roediger et al.). This disease affects all races and ethnicities, with prevalence per 100,000 in White (63.2), Black (73.0), Hispanic (39.9), and Asian (48.9) patients (Aung et al.). Affected patients develop end-stage kidney disease by the age of 70 years (Mahboob et al.). End-stage kidney disease (ESKD) can happen to 75% of

people with ADPKD, and affects 5% of people who initiate dialysis (treatment that filters waste and extra fluid like a kidney) (Roediger et al.).

Patients can get a risk assessment from radiographic and genetic sequencing techniques. ADPKD is mostly caused by mutations in PKD1 or PKD2. PKD1 and PKD2 encode polycystin 1 (PC1) and polycystin 2 (PC2), respectively. Mutations in PKD1 cause about 80% of cases of ADPKD, while PKD2 causes about 15%. Patients with a mutation in PKD1 have earlier ESKD, lower glomerular filtration rate, and larger kidneys than patients with PKD2. ADPKD with cyst formation is caused by a germline mutation in one allele of PKD1 or PKD2 and one other factor, like somatic inactivation of PKD1 or PKD2 or loss of heterozygosity with renal cysts that can range from a few mm to more than 50 cm in length and weigh more than 8kg There can be a few hundred to a few thousand cysts. Environmental factors can also initiate cyst growth in ADPKD. Some environmental factors can be hypertension, elevated BMI, high-sodium diet, and acute kidney injury (Roediger et al.).

Some current treatments for ADPKD are surgery, lifestyle changes, and therapies. The main therapy being used is tolvaptan. Many disease-modifying therapies are being developed and researched. Many of which show lots of potential, so the outlook for polycystic kidney disease is positive (Fang et al.).

METHODS

This literature review aimed to summarize the current state of research regarding current and upcoming ADPKD treatments. To accomplish this aim, I conducted an initial review of current academic articles on the database PubMed to gain an overview of the onset, symptomology, and prognosis of ADPKD. Next, I explored literature related to current treatments to understand the mechanisms underlying the treatments and their effectiveness. Finally, I reviewed related literature that discussed upcoming or potential treatments. The search terms I used on PubMed were “Autosomal Dominant Polycystic Kidney Disease”, “ADPKD Therapies”, “ADPKD molecular mechanisms”, and specific papers on therapies like “Tolvaptan.” For sources outside of PubMed, I made sure that the sites were reputable scientific sources (ex., ScienceDirect). The sources I used were within the inclusion criteria of the time frame of the present until ten years ago and were either broader literature reviews on ADPKD or sources from experiments.

RESULTS

After reading and writing notes/summaries of thirty-one articles, I analyzed the fundamental molecular mechanisms that drive the disease, current and upcoming therapies, and the molecular mechanisms behind those therapies.

Molecular Mechanisms

Treatments, therapeutics, and lifestyle factors for Polycystic Kidney Disease are often based on the underlying mechanism of the PKD1 and PKD2 genes in the cell. PKD1 and PKD2 encode proteins that form a probable receptor/channel complex. Loss of function of these genes below a threshold may trigger cyst formation and dysregulation of metabolic processes that interact with the complex (Qiu et al.). The mutations in PKD1 cause ADPKD to be more lethal than PKD2. The PKD1 and PKD2 genes have a lot of truncating mutations that result in a loss of function, including frameshift, nonsense, splice, and large rearrangements in the genes. These mutations cause a loss of function in the gene. Mutations in PKD1 are pretty evenly split between the 5' and 3' ends, and mutations are also evenly split in the different quartiles of position. PKD2 is more scattered, and PKD1 truncating mutations are the most deadly type (Cornec-Le Gall et al.).

ADPKD is inherited as a dominant trait due to mutations in multiple genes, the most frequent being PKD1 and PKD2. Minor genes (including GANAB, DNAJB11, IFT140, and several glycosylation-machinery genes like ALG8 and ALG9) cause atypical forms of ADPKD or overlapping syndromes. Genetic testing allows clinicians to distinguish true ADPKD from phenocopies (Cornec-Le Gall and Ong). ADPKD can also be caused by gene mutations that cause Polycystic Liver Disease (PCLD), like SEC63 and PRKCSH, which transfer PC1 and PC2 (Roediger et al.). PC1 and PC2, PKD1- and PKD2-encoded proteins, are in the primary cilium and regulate ion transport. They are thought to act as a sensor and function above the signaling hub (Qiu et al.).

It is thought that cyst formation is caused when the primary cilium disrupts the normal orientation of tubular epithelial cells, which affects calcium flux and cAMP signaling. This leads to a release of fluids and a sac forming on tubules and a formation of a cyst (Roediger et al.). The protein products of these genes (polycystin-1, polycystin-2, and Fibrocystin, respectively) are in the primary cilium or are for maturing and trafficking of proteins to the primary cilium. The primary cilium's function is to sense extracellular signals and translate them into intracellular biochemical information. There has been lots of research on structures, localizations, and molecular properties of the polycystin proteins that are encoded by ADPKD-causing genes. The precise functions of the proteins and the molecular basis of renal tubule cyst formation haven't been fully understood, but cyst formation happens when the proteins lose function or in their absence (Boletta and Caplan, "Physiologic Mechanisms Underlying Polycystic Kidney Disease").

One proposed mechanism for ADPKD is a two-factor model. It is proposed that ADPKD needs two factors to manifest: one is the inherited gene, and another factor, like inactivation of the PKD1 or PKD2 protein or a loss of heterozygosity. (Polycystic Kidney/liver Disease, Roediger). Based on studies from the 1970s, renal cysts in ADPKD originated from a single cell, and it is proposed that a "second hit" in the inherited allele of PKD1 or PKD2 leads to a loss-of-heterozygosity and initiates cystogenesis. However, these observations were made with major technical problems. Based on another study where they cloned PKD1 genes, one hypothesis is that haploinsufficiency could play a part in the disease

manifestation, but not sufficient to cause cyst formation. The same study supports the idea that a reduction, not a complete loss of polycystin, can cause the formation of cysts. The study also shows evidence towards needing 3 “hits” or factors to cause the disease if two of the factors are two extremely mild mutations of homozygosity. Initial studies after the cloning of the PKD1 and PKD2 genes led to the proposal that AKPKD might be a gain-of-function disease, but there isn’t sufficient evidence of such. It is estimated that about 5% of ADPKD cases aren’t caused by PKD1 or PKD2. These atypical cases are due to mutations in genes that include many components of glycosylation machineries important for maturation of membrane proteins in the secretory pathway. Many of these genes, like GANAB, affect the proper trafficking of polycystins, highlighting that polycystins correlate with ADPKD.

A comprehensive understanding of ADPKD pathogenesis requires familiarity with several interconnected classes of biological molecules that collectively govern renal cyst formation and growth. G protein-coupled receptors (GPCRs), including the vasopressin V2 receptor and the GLP-1 receptor, occupy central roles in this disease context because they initiate intracellular signaling cascades that regulate cAMP production, cell proliferation, and fluid handling within the kidney tubule (Zheng et al.). The downstream protein kinases activated by these receptors, most notably PKA and AMPK, function as opposing molecular regulators: PKA propagates pro-cystic signaling while AMPK, as a cellular energy sensor, suppresses growth-promoting pathways such as mTOR, placing their balance at the core of cyst expansion (Garcia and Shaw).

Membrane transporters and channels, including SGLT2 and aquaporin-2, govern glucose and water flux across tubular epithelial cells, and their dysregulation contributes directly to the fluid accumulation characteristic of enlarging cysts (Mateoc et al.). Metabolic enzymes such as ATP citrate-lyase further implicate altered lipid biosynthesis and energy metabolism as drivers of cyst progression, consistent with the broader metabolic reprogramming observed in ADPKD. At the post-transcriptional level, microRNAs including the miR-17, miR-200, and miR-21 families regulate the expression of genes involved in cell proliferation, tubular integrity, and tissue regeneration, and their dysregulation has been shown to contribute meaningfully to cyst pathogenesis (Hajarnis et al.).

The vasopressin 2 receptor (V2R) is a class A G protein-coupled receptor (GPCR). When bound to a G protein, the activated V2R stimulates the Gs alpha subunit and activates adenylyl cyclase. The activation leads to an increase in intracellular cyclic AMP (cAMP) levels. The increased cAMP activates protein kinase A (PKA). PKA phosphorylates aquaporin-2 (AQP2), which translocates it from intracellular vesicles to the apical membrane of the collecting duct cells. AQP2 in the apical membrane causes increased water reabsorption from the urine back into the blood, which regulates plasma osmolality. Vasopressin also influences intracellular calcium mobilization, MAPK pathway regulation, gene expression and stability, and B-arrestin signaling (Zhang et al.; Vasopressin V2 Receptor, Tolvaptan, and ERK1/2 Phosphorylation in the Renal Collecting Duct | American Journal of Physiology-Renal Physiology | American Physiological Society).

SGLT2 (Sodium-Glucose Cotransporter 2) is a specialized protein that acts as a pump in the kidneys. Its primary job is to prevent the body from losing energy by reabsorbing about 90% of the glucose filtered by the kidneys in urine and back into the bloodstream. SGLT2 proteins are embedded in the lining of the proximal convoluted tubule, which is the first segment of this tubule system. It gets its energy from the movement of sodium. The SGLT2 protein allows sodium to flow into the cell and makes it so that for each sodium ion that goes into the cell, one glucose molecule comes along with it, taking sugar out of the urine. After the glucose is inside the kidney cell, it travels across the inside of the cell to the basolateral membrane, touching the bloodstream, and passively slides out of the cell and into the blood from facilitated diffusion (Mateoc et al.).

AMP-activated protein kinase (AMPK) activation has the potential to inhibit the signaling pathways that lead to cyst growth in ADPKD. AMPK is the energy sensor of cells. It keeps cellular energy levels in a safe balance. When energy levels are low, AMPK binds to AMP and changes the shape of the AMPK enzyme, activating it. When activated, it signals the cell to make more energy by phosphorylating proteins to flip two major metabolic switches. It turns on catabolism and turns off anabolism, which makes ATP and conserves existing cellular energy. ATP is made by glucose uptake, fatty acid oxidation, and autophagy. Activating AMPK can inhibit the mTOR pathway, which reduces cell proliferation (Rena et al.; Gabel et al.; Garcia and Shaw).

ATP citrate-lyase (ACLY) is an enzyme in the cholesterol biosynthesis pathway. It contributes to the levels of circulating low-density lipoprotein cholesterol (LDL-C). It converts cytosolic citrate into acetyl-CoA and oxaloacetate. Acetyl-CoA is important for synthesizing fatty acids, cholesterol, and acetylcholine. Oxaloacetate is usually converted back into malate and returns to the mitochondria. ACLY is critical for the production of lipids and for fueling protein acetylation for gene regulation (Amore et al.; ATP Citrate Lyase - an Overview | ScienceDirect Topics).

GLP-1 receptors are a vital component of the G protein-coupled receptor (GPCR) family. This receptor specifically interacts with GLP-1, which regulates blood glucose levels, lipid metabolism, and several others. When the hormone GLP-1 or an agonist binds to the receptor, it triggers signaling through the activation of G-proteins. It also increases levels of the cAMP messenger, which activates PKA and EPAC (Zheng et al.).

MicroRNAs (miRNAs) are non-protein-coding RNAs. Each miRNA can inhibit thousands of mRNAs, and each mRNA may have binding sites for numerous miRNAs, so impacting miRNAs could have an important role in cyst formation in ADPKD. The miR-17 family is overexpressed in ADPKD. These microRNAs silence genes that would normally keep cell growth in check. The miR-200 family plays a role in renal tubule development and cyst pathogenesis, and is thought to maintain the normal renal tubule structure and prevent cyst formation. MiR-21 may play a role in organ regeneration by promoting cells to regenerate or die out. When affected, miR-21 may lead to the overproliferation of cells (Hajarnis et al.).

Ultimately, ADPKD is complicated. Despite decades of research, we do not know the physiological functions of the polycystin proteins. We also do not have a deep understanding of the processes that drive the formation of cysts. However, the extensive research has revealed a considerable amount of biological insight. These insights have led to multiple potential therapeutic targets and strategies (Boletta and Caplan, "Physiologic Mechanisms Underlying Polycystic Kidney Disease").

Therapeutics and Treatment Strategies

Currently, there aren't that many treatment options for ADPKD, but there are many lifestyle changes recommended to keep the disease from progressing quickly. Because ADPKD cells are similar to cancer cells, similar diets can be recommended for both types. Some recommendations from doctors are to stay hydrated, restrict sodium and protein intake, cease smoking, exercise more, and have a healthy BMI. Cysts have a high metabolism because of constant cell division and growth. Diets can limit the growth of the cells. Although they aren't full treatments, they can help keep the disease within control (Roediger et al.). Two treatment options for this disease are surgery and Tolvaptan. Surgery is usually reserved for people in critical or near-critical condition. Some options are to remove a few large cysts or to transplant the affected kidney (Roediger et al.). Currently, 70% of patients end up needing to replace their kidney by 70 years old (Fang et al.). It is estimated that 5% of patients with kidney transplants for ADPKD had diverticulum perforation. Post-transplantation UTI is about 10% higher in ADPKD patients and has about 10% lower 1,3, and 5-year overall survival rates vs. non-ADPKD transplantation patients (Illesy et al.). One downside to surgery that removes cysts is that kidneys with removed cysts can grow cysts again. Transplants have the best chances for survival. Another treatment option for ADPKD is dialysis. 5% of people who start dialysis are people with End-stage kidney disease (Roediger et al.).

Tolvaptan is the only current FDA-approved disease-modifying agent for high-risk progression therapy for ADPKD and is clinically approved. It was found by Otsuka Pharmaceuticals in Japan to treat ADPKD and first approved by the FDA in 2018 for this use. Before it was used for ADPKD, this drug was under the brand name Samsca to treat hyponatremia ("Jynarque (Tolvaptan) FDA Approval History"). Tolvaptan is a vasopressin V2 receptor antagonist (blocks vasopressin) and suppresses abnormally increased intracellular cyclic adenosine monophosphate levels in cyst epithelial cells (Jdiaa et al.). Tolvaptan works by inhibiting cAMP production, which suppresses cyst growth and kidney dysfunction (Sekine et al.). Tolvaptan inhibits the V2 receptor by first penetrating deeply into the orthosteric binding pocket and making direct contact with at least 13 amino acid residues. This is different from the larger peptide ligands or toxins that interact with the outer surface of the V2 receptor. Then, tolvaptan directly interacts with Tryptophan and shapes the residue into its inactive rotamer conformation, and acts like a block that stops the toggle switch from flipping. By locking the toggle switch at the core of the receptor, Tolvaptan restrains the entire TM6 helix, which prevents the cavity from closing. This prevents the G protein from docking to the receptor and completely shuts down cAMP production (Fouillen et al.).

Tolvaptan has a half-life of about 3.5 hours, so it doesn't accumulate in the body, and steady concentrations can be reached on the first day (Reddy et al.). Unfortunately, tolvaptan can have a few downsides. It can cause liver injury, hypernatremia, severe dehydration, and is also costly (Aung et al.).

Tolvaptan also seems to decrease in effectiveness and isn't usually recommended for patients older than 55 years, and children typically aren't recommended to use tolvaptan (Jdiaa et al.). However, some studies show positive results for children to use tolvaptan (Mekahli et al.). Unfortunately, information about the structure of antagonist-bound V2R hampers the understanding of the V2R antagonist recognition and targeted design (Zhang et al.).

Because of upcoming research and findings about ADPKD, many other therapies are being developed and tested to help treat ADPKD. SGLT2 inhibitors are also being tested as a possible therapy for ADPKD. SGLT2i is being carefully tested to see if it could improve ADPKD. Currently, it is in Phase III of clinical testing. In some animal studies, it may stimulate vasopressin activation to control fluid volume maintenance, which is a challenge because vasopressin may increase cyst growth. SGLT2 inhibitors interact directly with the SGLT2 transport protein in the kidneys. Blocking these proteins causes the body to excrete excess sugar and salt through urine. Other animal studies have shown potential benefit from SGLT2 inhibitors in slowing disease progression. Overall, SGLT2i has mixed effects on cyst growth and kidney function. This therapy strategy can do the opposite of Tolvaptan. SGLT2 does show some signs of positive outcomes by fixing the metabolic defects of cyst cells, activating protective pathways, and lowering damaging filtration pressures, but it also activates vasopressin, which can enlarge kidney cysts (Masuda et al.).

Metformin is another one of the promising therapy that could be used by ADPKD patients in the future. It is currently in Phase III of clinical testing. Metformin can stimulate AMPK by lowering mitochondrial respiration and energy production in renal epithelial cells. AMPK can inhibit CFTR activity and mTOR signaling, which can slow the rate of cyst growth. Studies with mice showed decreased cystic progression with salsalate. A study in pigs using metformin and 2-deoxyglucose (2DG) displayed a decrease in cystogenesis. Several studies have shown favorable results that metformin slows the decline of eGFR, but it is cautioned for the use of metformin in late-stage PKD as it could further cystogenesis in Pkd1 deficiency (Takiar et al.).

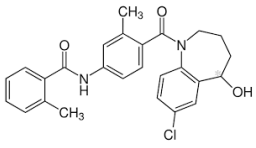
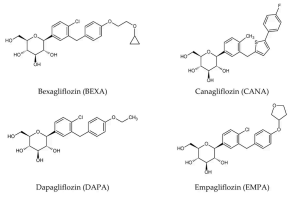
A similar treatment to metformin is Bempedoic acid. Currently, it is in Phase II clinical testing for ADPKD. Bempedoic acid is an adjunctive treatment with statins and dieting for further LDL-C reduction in individuals with familial hypercholesterolemia. It inhibits ATP citrate lyase (ACLY) to prevent fatty acid biosynthesis. Mouse models have shown that BA stimulates AMPK, which deters mTOR. In other studies, BA therapy has been shown to slow cyst proliferation and reduce the percentage of total kidney weight to body weight. BA is generally safe, but further study is needed as BA hasn't been tested on human ADPKD (Fang et al.).

Gulcagon-like peptide-1 receptor agonists (GLP-1 RAs) are promising candidates for treatment of ADPKD. In the present circumstances, it is in Phase II of clinical testing. In mouse models, it has significantly slowed kidney cyst growth. This class of medications mimics the natural GLP-1 hormone to stimulate insulin release, slow stomach emptying, and suppress appetite (Rosen and Ingelfinger). Treatment has also displayed improvements in kidney metabolism, normalization of mitochondrial

structure, reduced expression of key glycolytic enzymes, and a reduction in kidney fibrosis. Many trials with individuals with multiple conditions have also shown a decline in eGFR. There is some concern that GLP-1RAs may increase cAMP, and future study is needed (Vertex Announces FDA Clearance of Investigational New Drug Application for VX-407 for the Treatment of Autosomal Dominant Polycystic Kidney Disease (ADPKD)).

RNA-based therapy is another possible route for ADPKD. It is promising in its current Phase III clinical testing. MicroRNAs are small, noncoding RNAs involved in modulating gene expression and thus disease progression. Many sequences of genes (e.g., miRNAs) have been found for ADPKD, making this therapy theoretically possible. So far, only investigational therapies for miR17 inhibition exist. Inhibition of miR17 has been shown to reduce kidney-to-body-weight ratio (KW/BW) and decrease in-cyst epithelial cell proliferation. If a Phase 3 clinical trial of Farabursen evaluating its long-term safety and impact on TKV and eGFR is successful, miR-17 inhibition can be the first RNA-based therapy for showing ADPKD progression. Polysystin 1 correctors may modify disease activity in mutations of the PKD1 gene. VX-407 is the first Polysystin 1 corrector that aims to correct PC1 folding to reduce cystogenesis and eGFR decline. It aims to correct defective PC1 folding to restore function. Monoclonal antibodies may also be a disease-modifying strategy for ADPKD by targeting key upstream regulators of cyst-promoting pathways (Fang et al.; Vertex Pharmaceuticals | R&D Pipeline | Autosomal Dominant Polycystic Kidney Disease).

Each of the therapies mentioned before is very promising for patients with ADPKD. That being said, ADPKD therapies are still being tested and are rapidly evolving. Many treatments are close to being implemented. In a combination of pharmacologic, dietary, and genetic strategies, ADPKD trajectories can be modified. More large-scale and long-term studies are needed to validate that these therapies are beneficial to patients (Fang et al.).

Name	Type	Image	Impact	Stage of Clinical Development
Tolvaptan	Vasopressin 2 receptor (V2R) antagonist		Blocks vasopressin, inhibits cAMP production	Approved
Bexagliflozin, Canagliflozin, Dapagliflozin, Empagliflozin	SGLT2 inhibitors		Vasopressin activation and inhibits SGLT2 protein	Phase III

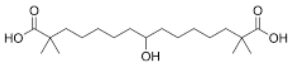
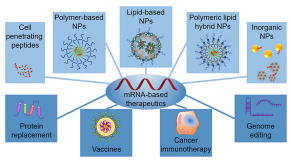
Metformin	Biguanide drug (small molecule)		Stimulate AMPK	Phase III
Bempedoic acid	ACL inhibitor (Small molecule)		Inhibits ATP citrate lyase, stimulates AMPK	Phase II
Dulaglutide, Exenatide	Glucagon-like peptide-1 receptor agonists (Hormone-like medicine)		Reducing glycolysis, deactivating pathways, restoring mitochondrial health, metabolic regulation	Phase II
VX-407	RNA-based therapy		Block harmful cyst micro-RNA	Phase III

Table 1: ADPKD therapies consisting of the name(s) of the drug, the type of drug, a visual representation, the impact, and the stage of clinical development.

Name	Mechanism	Level of Evidence and Clinical Readiness	Potential Advantages	Limitations	Future Prospects
Tolvaptan	Blocks V2-receptors in renal collecting ducts,	Level A evidence base and high clinical	Effectively slows kidney function decline,	May decrease in ability over time, limited age range, maximum 30-day	Maximizing early intervention, improving

	preventing ADH from binding and inhibiting insertion of aquaporin-2 channels in the cell membrane (aquaresis)	readiness as the only globally approved therapy for ADPKD	reducing total kidney volume growth, and delaying kidney failure	treatment restriction, dehydration, hyperkalemia, hypovolemia, and liver toxicity risk	tolerability, and expanding pediatric applications
SGLT2 inhibitors	Lower intraglomerular pressure, alter cell metabolism, and reduce inflammation	Grade C: lack of evidence and low clinical readiness	Reducing renal hypoxia, lower oxygen demand, lowering tubular workload, blood pressure control, cardiorenal protection, and changing metabolic programming to limit cyst growth	May cause increased vasopressin release, potential cyst growth, severe dehydration, genitourinary issues, acute kidney injury, may be incompatible with tolvaptan	Continuing clinical trials for effectiveness
Metformin	Activating AMPK, inhibiting mTOR, and suppressing CFTR	Low to moderate level of evidence, moderate pre-clinical readiness and low clinical readiness	Low cost, anti-inflammatory, may improve kidney structure	Potential gastrointestinal intolerance, diarrhea and bloating, nausea and abdominal discomfort, reduced appetite, vitamin B12 deficiency; inconsistent impact of slowing kidney function decline in clinical trials	Ongoing and upcoming trials to assess long-term efficacy, kidney function decline, and quality of life

Bempedoic acid	Inhibits ATP citrate-lyase (ACLY) and activates AMP-activated protein kinase (AMPK)	Low evidence level and low clinical readiness	Potentially works synergistically with tolvaptan, reduced kidney injury, targeted activation in liver and kidneys	Risk of hyperuricemia, tendon rupture, muscle and joint pain, muscle spasms, and stomach issues	Underway to test safety, tolerability, and preliminary effectiveness
Glucagon-like peptide-1 receptor agonists	Decreasing cellular glycolysis/ATP generation, deactivating cyst-promoting signaling pathways, and normalizing mitochondrial function	Grade C low to moderate evidence level, and low clinical readiness	Targeting metabolic dysfunction, reducing kidney inflammation, directly regulating cellular growth pathways, weight reduction, insulin sensitivity, blood pressure control	May cause gastrointestinal side effects, severe dehydration, unclear interaction with tolvaptan, acute kidney injury, pancreatitis and gallbladder issues, and weight reduction	Clinical trials to confirm safety and effectiveness
RNA-based therapy	microRNA inhibition, post-transcriptional gene regulation, and blocking destructive signaling pathways through custom oligonucleotides	Level IV (strong) preclinical evidence, high pre-clinical readiness, and low clinical readiness	Targeted gene regulation, fewer permanent DNA risks, reduced systemic side effects	May have poor targeted delivery to kidney cysts, rapid systemic clearance, potential renal and off-target toxicity, immune reactions, unintended gene silencing, and may wear off quickly	Going through safety phases

Table 2: Comparison of each therapy's mechanisms, level of evidence and clinical readiness, potential advantages, limitations, and future prospects.

DISCUSSION and CONCLUSION

Autosomal dominant polycystic kidney disease can be a life-threatening disease when not treated properly. The disease is caused by genetic mutations, including the mutation of PKD1, PKD2, and many other minor genes. The loss of function of PKD1 and PKD2 may trigger cyst formation. It is thought that ADPKD needs two factors for the disease to manifest.

Since tolvaptan, the only FDA-approved drug for ADPKD, has many side effects, like severe dehydration, liver damage, and osmotic demyelination syndrome (ODS) ("Tolvaptan (Oral Route) - Side Effects & Dosage"), new therapeutics are being developed to improve upon tolvaptan. There are also other methods of therapeutics being developed targeting vasopressin, cAMP production, SGLT2 proteins, AMPK, ATP citrate lyase (ACLY), glycolysis, and micro-RNA.

Broader clinical testing should be done because genotypes are the ones that directly impact disease severity. Truncating PKD1 mutations result in earlier kidney failure than non-truncating mutations or PKD2 mutations. Testing is also needed for younger potential donors or those with equivocal cyst findings. Genetic analysis confirms whether a donor is truly unaffected. Definitive genetic testing also allows for accurate counseling and modern family-planning options such as Preimplantation Genetic Testing (PGT). Varying disease severity within the same family can be caused by genetic nuances such as somatic mosaicism or the co-inheritance of separate genetic variants.

Some current challenges and limitations prevent a broader clinical test. The PKD1 gene is still difficult to sequence using standard exome sequencing because of its large size, high GC content, and its six homologous pseudogenes. More advanced technology, such as Targeted next-generation sequencing or whole-genome sequencing, is often needed. Many health care systems also don't fund genetic testing for ADPKD, which causes the financial burden to shift to the patient. Alternative prognostics besides genetic testing are also highly effective in predicting progression in typical cases, limiting the need for special genetic testing. Overall, adding gene testing to medical nomenclature would be critical for individualized care (Cornec-Le Gall and Ong).

This literature review does have many limitations. The primary reliance on PubMed makes it sources diversity limited. The recent and evolving evidence used may change later or turn out to be incorrect. Since there isn't a formal quality assessment of included studies, there is a risk of bias, reduced credibility, and flawed conclusions. This literature review may also have some publication restrictions and bias.

As one of the most common inherited kidney disorders, ADPKD imposes a substantial clinical and quality-of-life burden on millions of patients worldwide. This prevalence, combined with the progressive and ultimately debilitating nature of the disease, underscores the pressing need for treatment options that are not only effective but also broadly accessible and tolerable across diverse patient populations. Advances in molecular biology, imaging, and clinical trial design have meaningfully improved the understanding of disease progression, and current trends reflect modest but encouraging gains in life expectancy and delayed onset of kidney failure. Nevertheless, the only therapy currently approved to slow ADPKD progression, tolvaptan, is limited in its applicability due to hepatotoxicity concerns and tolerability issues, leaving a considerable unmet therapeutic need. The molecular complexity of ADPKD, as outlined in the preceding section, simultaneously presents this challenge and offers a path forward: the breadth of implicated pathways provides numerous rational targets for intervention, and continued investigation at both the mechanistic and clinical levels remains essential. Sustained research efforts directed at translating biological insights into safe and effective therapies will be critical to improving long-term outcomes for patients living with this disease.

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