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Review Article

Review on "Polycystic kidney disease pathophysiology and prognosis"

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ABSTRACT

A class of genetic diseases known as polycystic kidney disease (PKD) includes renal cyst formation and expansion, gradual renal function loss, and a variety of extrarenal symptoms. Autosomal-dominant PKD, the most prevalent kind, is brought on by mutations in either of the two PKD1 or PKD2 genes. Recent advances in genomic and proteomic science have led to the identification of novel genes involved in a wide range of recessive, less common PKD disorders. Polycystic kidney disease caused by autosomal dominant mutation-based, molecular, diagnosis. (ADPKD)Is complicated by genetic and allelic heterogeneity, large multi exongenes, duplication of PKD1, and a high level of unclassified variants (UCV). Present mutation detection levels are 60 to 70%, and PKD1 and PKD2 UCV have not been systematically classified.

INTRODUCTION

End-stage renal failure is most commonly brought on by polycystic kidney disease, which is also a frequent reason for dialysis or renal transplantation. Recent research has provided fresh insights into the mechanisms behind these diseases' etiology and prognosis as well as suggested new possibilities for treatment. One in 800 live babies experience autosomal dominant polycystic kidney disease, the most prevalent type of the condition (1). The condition known as polycystic kidney disease (PKD) can be brought on by environmental triggers or be inherited as a recessive or dominant characteristic. The condition is characterized by the development of large, epithelial-lined cysts from the collecting ducts and nephrons of the affected kidneys. Cysts are assumed to begin as tiny dilations in the renal tubules, which eventually grow into relatively large cavities filled with fluid. Increased cell proliferation, tubular epithelial polarity reversal, and epithelial fluid secretion all seem to play a role in cyst formation (2). A collection of monogenic diseases known as polycystic kidney disease (PKD) cause the formation of renal cysts. The

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morbidity linked to the two most prevalent variants, autosomal dominant PKD (ADPKD) and autosomal recessive PKD (ARPKD), affects the kidney, liver, and, in the case of ADPKD, the vasculature, and affects people of all ages from newborns to the elderly. Cystic dysplasia or kidney cysts are among a collection of developmental characteristics that are present in a rarer subset of pleiotropic illnesses that are primarily recessively inherited (3). A frequency of 1:20,000 is estimated for ARPKD, and the most common manifestation is severe PKD found in utero or during the perinatal period with significantly enlarged kidneys, which is linked to high newborn mortality. The majority of ADPKD patients have a parent who is afflicted, although 10% or more of cases can be linked to an apparent de novo mutation. When appropriate diagnostic criteria have been established, the finding of numerous cysts by renal ultrasound imaging can typically be used to make a presymptomatic diagnosis of ADPKD in at-risk people. In ambiguous situations and for longitudinal investigation of illness progression, more sensitive magnetic resonance (MR) or computed tomography imaging may be beneficial (4). Systemic ailment autosomal dominant polycystic kidney disease (ADPKD) has a variety of renal and extrarenal symptoms. Although these manifestations have an impact on morbidity, it is unknown how much they contribute to the disorder's mortality. Cysts, adenomas, stones, infections, and renal insufficiency are among the renal symptoms. Liver cysts are the most prevalent extrarenal structural anomaly, happening in up to 75% of persons older than 60 years (5).

Causes

A mutation in one of the two polycystin-encoding genes, PKD1 or PKD2, results in autosomal dominant polycystic kidney disease (ADPKD), the fourth most common cause of end-stage renal disease in adults. Mutations in PKHD1 (encoding fibrocystin), which are the main cause of ESRD and mortality in newborns and children, result in autosomal recessive polycystic kidney disease (ARPKD).Cyst formation in both diseases is facilitated by pathogenic interactions of mutant epithelial cells with an abnormal extracellular matrix and alternatively activated interstitial macrophages, as well as disruption of mechanisms regulating tubular diameter, excessive cell proliferation, and fluid secretion(6).According to estimates, ADPKD occurs anywhere between 1 in 500 and 1 in 1,000 live births. Mutations on chromosomes 16 (PKD1) and 4 (PKD2) are linked to two phenotypically identical types of ADPKD (PKD1 and PKD2). Slowly expanding renal cysts are caused by mutations in these genes that encode the proteins polycystin-1 and -2, which cause anomalies in cell proliferation, apoptosis, tubular basement membranes, and tubular fluid secretion (7).

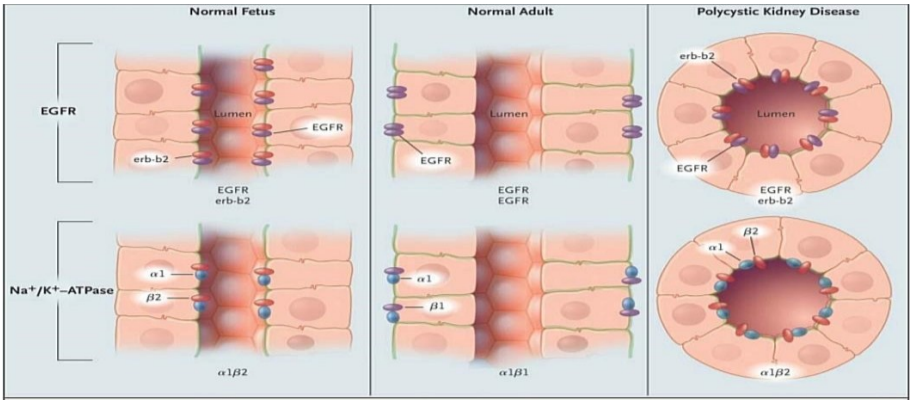

Figure 1: Normal fetus between adult fetus

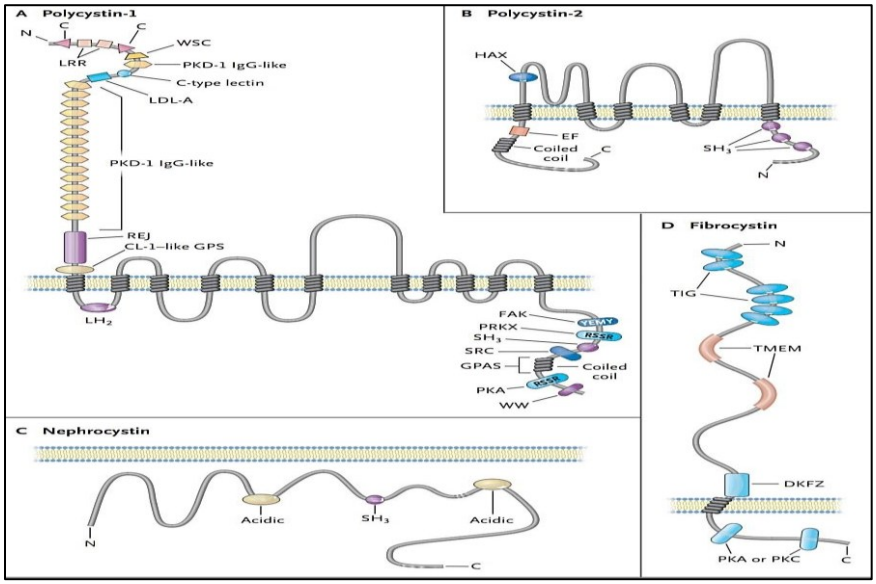

Figure 2: Path physiology of PKD

It affects 500,000 people in the United States and 4 million to 6 million people worldwide, and 7 to 10 percent of patients require haemodialysis as a result. There are two types: type I, which accounts for 85–90% of cases and is brought on by PKD1 gene mutations3, and type II, which accounts for 10%–15% of cases and is brought on by PKD2 gene mutations4. On the renal tubular epithelia, polycystin-1 and polycystin-2, the protein products of these two genes, are found. In contrast to polycystin-2, which is assumed to function as a calcium-permeable channel, polycystin-1 is a membrane receptor that can bind to and interact with several proteins, carbohydrates, and lipids as well as trigger intracellular reactions through phosphorylation pathways (8).

Polycystic kidney disease

Types of disease	Cause
Autosomal dominant polycystic kidney disease	Mutation in PKD1 and PKD2 decrease in functional polycystin- 1, 2
Autosomal recessive polycystic kidney disease	Mutation in PKHD1 loss of functional fibrocystin
Juvenile nephronophthisis	Mutation in NPH loss of functional nephrocystin.

The majority of instances are due to PKD1 and PKD2 mutations. Despite the entire overlap in clinical symptoms between both gene types, PKD1 is linked to a more severe disease than PKD2, larger kidneys, and an earlier beginning of end-stage renal disease. Furthermore, the well-documented marked within-family renal disease variability in ADPKD points to a potent moderating effect from as-yet-unknown genetic and environmental factors. The high inter- and intra-familial heterogeneity in renal disease, in turn, presents a difficulty for genetic counselling and diagnosis (9). ADPKD is frequently identified when hypertension is found, renal discomfort or haematuria suddenly appears, or nephromegaly is unintentionally found through physical or radiographic exams.8,9 Although renal insufficiency can develop at any age, the vast majority of patients don't become aware of their condition until well into their fourth decade, when their estimated GFR has dropped to an obviously abnormal level (10).

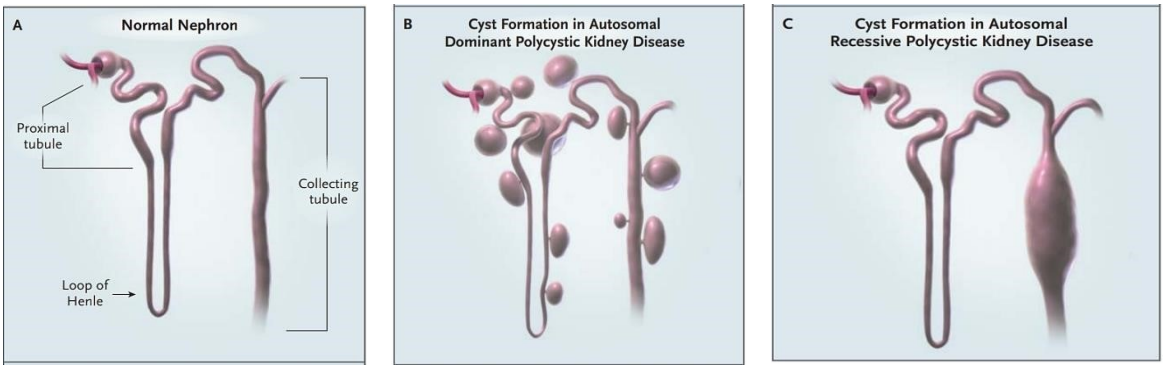

Figure 3: Normal Nephron vs Affected nephron.

Cyst development and expansion in polycystic kidney disease, an autosomal dominant condition. The cysts grew from nephrons and collecting ducts, along with hyperplasia of the epithelial cells lining the cyst walls, according to previous morphologic investigations on kidneys from adult patients with autosomal dominant polycystic kidney disease (ADPKD). In the current work, we thoroughly examined 387 cysts in polycystic kidneys taken from 10 adult patients using scanning electron microscopy. Cells typical of the proximal tubule (1.8%), glomerular visceral (2.1%), or collecting duct (7.2%) epithelium lined several cysts. A single layer of phenotypically undefinable (84.0%) or noticeably hyperplastic (4.9%) epithelium lined the remaining cysts (11).A prevalence of 1/400 to 1/1000, autosomal dominant polycystic kidney disease (ADPKD) is the most often inherited renal illness and one of the most prevalent Mendelian human disorders.1,2 This roughly translates to 12.5 million affected people around the world. ADPKD affects 5 to 10% of all patients who require renal replacement therapy. As the name suggests, ADPKD is inherited in an autosomal dominant, fully penetrant manner, meaning that nearly everyone who inherits a mutant PKD allele in their germ line will experience the development of sonographically visible renal cysts by age 30 or a little later (12).

Treatment of PKD

There is presently no known cure for PKD. Therefore, supportive measures like analgesics for pain, antibiotics for cyst infection, blood pressure control, and avoiding oestrogen and caffeine make up the majority of the management of patients with PKD. A long-acting counterpart of the somatostatin hormone is octreotide. Octreotide decreases the synthesis of cAMP by attaching to somatostatin receptors. Octreotide has been demonstrated to lower cAMP levels and prevent cyst development in the livers of PCK rats, although renal function did not significantly improve. Octreotide decreased kidney volume but did not increase GFR, according to a small randomised, crossover, placebo-controlled research that included 12 patients and was conducted over a 6-month period. At the moment, octreotide is the subject of two further clinical trials (13). Vasopressin is one of the main catalysts for cell proliferation, working through adenylyl cyclase and cAMP. Two vasopressin V2 receptor (VPV2R) antagonists, OPC31260 and OPC41061 (tolvaptan), decreased cAMP and ERK, avoided or reduced renal cysts, and preserved renal function in genetically created polycystic mice.15,16 Unsurprisingly, increasing water intake alone reduces the generation of vasopressin and the onset of polycystic kidney disease in rats.Avoid methylxanthines and caffeine because they inhibit phosphodiesterase, leaving more cAMP available

to induce cyst development.19,20 Follow a low-sodium diet (2,300 mg/day), which may aid in maintaining smaller cysts and kidneys in addition to lowering blood pressure and preventing the development of kidney stones(14). A multinational clinical trial (TEMPO NCT00428948) is now evaluating a novel therapy for ADPKD that targets AVP/cAMP. Tolvaptan, a V2R inhibitor, is given to patients with the goal of lowering intracellular cAMP levels in cyst epithelial cells. Additionally, V2R inhibition reduces CDs' ability to absorb solute-free water, which results in partial nephrogenic diabetes insipidus and increased thirst (15). The quality of life and life expectancy have increased as a result of numerous strategies, and ADPKD is now more routinely diagnosed. These include the early diagnosis and treatment of hypertension, dietary and lifestyle changes, the management of complications related to chronic kidney disease, the treatment of renal and extrarenal complications, and renal replacement therapy. However, there are currently no widely accepted practise guidelines and methods for diagnosing, evaluating, preventing, and treating ADPKD vary greatly between and within nations (16).

the usage of EGF receptor tyrosine kinase inhibitors, rapamycin (to inhibit mTOR), and R-roscovitine (to inhibit cdk2). Rapamycin's inhibition of mTOR reduced cell proliferation and stopped cyst growth in a number of animal models, including the Han:SPRD rat, orpk-rescue, and bpk mouse models. Cyst formation in bpk mice was significantly decreased by the administration of the EGF receptor tyrosine kinase inhibitors EKB-569 and EKI-785(17). Polycystin-2 in combination with Polycystin-1 is thought to be the mediator of Ca2+ signalling dysregulation in cystic cells. Triptolide, an active diterpene used in traditional Chinese medicine, has been used as the first illustration of a therapeutic approach to encourage an increase in cytosolic Ca2+ in PKD. Through the restoration of Ca2+ signalling, triptolide treatment of Pkd1 -null homozygous embryos through maternal administration of the drug resulted in the arrest of cellular proliferation and inhibition of cyst formation (18).

Table 1 -Comparison of potential treatment for PKD

Compound	Mechanism	Molecular target	Potential side effects	Effect on liver cysts
Rapamycin	Antiproliferative	mTOR	Oral mucositis, tremor, hypertension	Unknown
Vasopressin V2R antagonist	Inhibit fluid secretion	cAMP	Hypernatremia, thirst	No
Somatostatin	Inhibit fluid secretion	cAMP	Diarrhoea, anorexia, gallstones	Yes
Triptolide	Antiproliferative	Ca2+signalling (PC2dependent)	Male infertility	Unknown
Tyrosine kinase inhibitor	Antiproliferative	EGF receptor	Diarrhoea, rashes	No

The discovery of potential novel treatments has been made possible by developments in molecular biology and genetics, which have led to a better understanding of the cellular pathophysiologic mechanisms underlying the onset and progression of PKD (20).

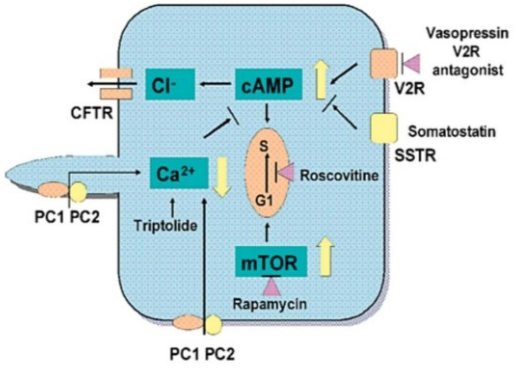

Figure 4: Hypothetical scheme, of signalling abnormalities and molecular target in ADDED.

CONCLUSION

The choice of disease-relevant targets for therapeutic testing has become possible because to recent developments in our fundamental understanding of the molecular pathophysiology of PKD.of order to preserve the differentiated condition of the epithelia lining the tubules of the kidney and biliary system, polycystin-1 and -2 may function as a sensor on the cilium. utilising substances like rapamycin, somatostatin, triptolide, tolvaptan, etc. to stop cyst development and slow down cyst growth. Primary cilia have been found to have unexpected functions in controlling tubular growth and healing following injury, as revealed by the inactivation of ciliary proteins in the postnatal kidney.

REFERENCES

1. Wilson PD, Falkenstein D. The pathology of human renal cystic disease. In: Dodd SM,ed.Tubulointestinal and cystic disease of the kidney. Vol. 88 of Current topics in pathology. Berlin, Germany: Springer Verlag,1995:1-50.
2. WELLING LW, GRANTHAM JJ: Cystic disease of the kidney, in Renal Pathology, edited by TISHER C, BRENNER B,
3. Philadelphia,Lippincott, 1989, pp. 1233—1277
4. Torres VE, Harris PC, Pirson Y. Autosomal dominant polycystic kidney disease. Lancet 2007;369:1287–301. [PubMed: 17434405]
5. Torres VE, Harris PC, Pirson Y. Autosomal dominant polycystic kidney disease. Lancet. 2007;369(9569):1287–1301.
6. Gabow PA: Autosomal dominant polycystic kidney diseasemore than a renal disease [Reviewl. Am J Kidney Dis 1990; 16:403-4 13.
7. Scheffers MS, van der Bent P, Prins F, Spruit L, Breuning MH, Litvinov SV, de Heer E, Peters DJM: Polycystin-1, the product of the polycystic kidney disease 1 gene, co-localizes with desmosomes in MDCK cells. Hum Mol Genet 9: 2743–2750, 2000.
8. Patel V, Chowdhury R, Igarashi P. Advances in the pathogenesis and treatment of polycystic kidney disease. Curr Opin Nephrol Hypertens 2009;18:99-106.
9. Pei Y, Paterson AD, Wang KR, et al. Bi-lineal disease and transheterozygotes in autosomal dominant polycystic kidney disease. Am J Hum Genet 2001;68:355-63.
10. Blyth H, Ockenden BG: Polycystic disease of kidneys and liver presenting in childhood. J Med Genet 8: 257–284, 1971.
11. Hildebrandt, F., Attanasio, M. & Otto, E. Nephronophthisis: disease mechanisms of a ciliopathy. J. Am. Soc. Nephrol. 20, 23– 35 (2009).
12. WELLING LW, GRANTHAM JJ: Cystic and developmental diseases of the kidney, in The Kidney, edited by BRENNER BM, RECTOR JRFC (3rd ed). Philadelphia, W.B. Sanders Company, 1986, p. 1341.
13. Torres VE, Harris PC, Pirson Y: Autosomal dominant polycystic kidney disease. Lancet 369: 1287–1301, 2007.
14. Igarashi P, Somlo S. Genetics and pathogenesis of polycystic kidney disease. J Am Soc Nephrol 2002;13:2384–2398. [PubMed: 12191984].
15. US Renal Data Services. Table A.1, Incident counts of reported

16. ESRD: all patients. USRDS 2008 Annual Data Report, Vol. 3, page
17. 7.
18. Wang X, Wu Y, Ward CJ, Harris PC, Torres VE: Vasopressin directly regulates cyst growth in the PCK rat. J Am Soc Nephrol 19: 102–108, 2008.
19. Li Y, Wright JM, Qian F, Germino GG, Guggino WB: Polycystin 2 interacts with type I inositol 1,4,5-trisphosphate receptor to modulate intracellular Ca2+signaling. J Biol Chem 280: 41298– 41306,2005.
20. Hateboer N, v Dijk MA, Bogdanova N, Coto E, Saggar-Malik AK, San Millan JL, Torra R, Breuning M, Ravine D: Comparison of phenotypes of polycystic kidney disease types 1 and 2. European PKD1-PKD2 Study Group. Lancet 1999;353:103–107.
21. Reeders, S. T., Breuning, M. H., Davies, K. E., Nicholls, R. D.,
22. Jarman, A. P., Higgs, D. R., Pearson, P. L. and Weath-erall, D. J. (1985) A highly polymorphic DNA marker linked to adult polycystic kidney disease on chromosome 16. Nature 317: 542 – 544.
23. Persu A, Duyme M, Pirson Y, Lens XM, Messiaen T, Breuning MH, Chauveau D, Levy M, Grunfeld JP, Devuyst O: Comparison between siblings and twins supports a role for modifier genes in ADPKD. Kidney Int 2004; 66:2132–2136.
24. Pisitkun T, Shen RF, Knepper MA: Identification and proteomic profiling of exosomes in human urine. Proc Natl Acad Sci U S A 101: 13368–13373, 2004.
25. Qian F, Watnick TJ, Onuchic LF, Germino GG: The molecular basis of focal cyst formation in human autosomal dominant polycystic kidney disease type I. Cell 1996;87:979–987.

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