J. Biomed. Ther. Sci. 2019, 6(1), 15-23 Review

Journal of Biomedical & Therapeutic Sciences

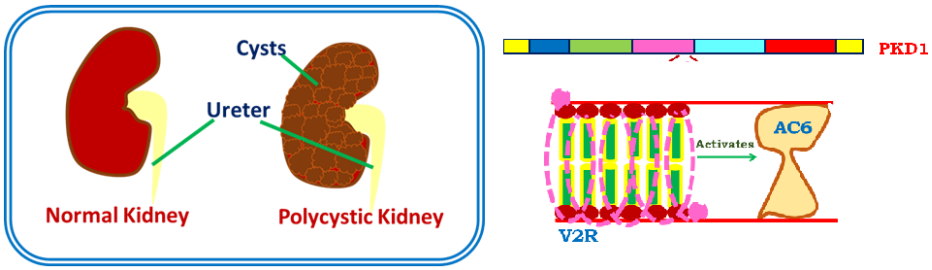
Autosomal dominant Polycystic Kidney Disease: A Review

Aparna Bansal[1,3*] Shikha Kaushik[2,3] Saami Ahmed[3] and Shrikant Kukreti[3*]

[1]Department of Chemistry, Hansraj College, University of Delhi, Delhi-110007, India. [2]Department of Chemistry, Rajdhani College, University of Delhi, Delhi-110015, India. [3]Nucleic Acids Research Lab, Department of Chemistry,University of Delhi (North Campus), Delhi 110007, India.

Submitted on: 23-May-2019, Accepted and Published on: 29-July-2019

ABSTRACT



Autosomal dominant polycystic kidney disease (ADPKD) is an inherited renal disease, characterized by gradual growth of multiple renal cysts, hypertension and end stage renal disease (ESRD). ADPKD shows progression with age where complications due to hypertension are more significant. Genetic testing and imaging have been found essential for the diagnosis, follow-up and detection of complications in patients. Genetic analysis revealed that mutation in two genes named as *PKD1* and *PKD2* is responsible for ADPKD. Several drugs like Tolvaptan, Triptolide, Somatostatin analogs etc. presently under clinical trials, have been found to show promising results. To date, there is no approved therapy for the permanent cure of ADPKD. Still, advancement in the technology and the understanding of the biological aspects of this disease has generated a spark to investigate new potential therapies to minimize the morbidity and mortality of the disease. The genetic testing and imaging, genetic analysis progeny of disease, possible drug candidates and recent advances in ADPKD management have been reviewed here.

Keywords: Kidney Stone, ADPKD, renal disease (ESRD), Genetic mapping, PC1, PC2

INTRODUCTION

Cystic renal diseases are heterogenous in origin where renal cyst arises from the nephrons and collecting tubules. Disfunctioning of the cilium signaling in tubular epithelial cells cause the cyst formation in inherited cystic renal diseases. Different types of inherited cystic renal diseases are reported like - a) autosomal dominant polycystic kidney disease (ADPKD), b) autosomal recessive polycystic kidney disease (ARPKD). Other related diseases are autosomal dominant tubule interstitial kidney disease(ADTKD), Glomerulocystic kidney disease (GCKD), Medullary sponge kidney (MSK), autosomal dominant polycystic liver disease(ADPLD) a distinct genetic disorder with multiple hepatic cyst but no or few renal cysts etc.[1] Herein, the main focus is to explain autosomal dominant polycystic kidney disease (ADPKD), its genetics, diagnosis and therapeutic action etc. as summarized in figure 1.

Polycystic kidney develops fluid filled cyst in the kidney which impairs its proper functioning and leads to kidney failure. It often expedites cystogenesis in liver, pancreas and other parts as well. Anemia, bleeding of cysts, high blood pressure, cataracts or blindness, liver failure, kidney stones and cardiovascular disease are some of the complications associated with increasing size of the renal cyst.[2,3] The cardiovascular

*Corresponding Author: Dr. Aparna Bansal, Prof. Shrikant Kukreti
Email: aparna_bansal@yahoo.co.in, shrikant.kukreti6@gmail.com

Cite as: *J. Biomed. Ther. Sci., 2019, 6(1), 15-23.*
urn:nbn:sciencein.jbts.2019v6.101

 ISSN: 2394-2274 http://pubs.thesciencein.org/jbts

impediment associated with ADPKD patients commonly include valvular abnormalities and aortic aneurysm. In a recent report, concurrent isolation of non compaction of the ventricular myocardium (NVM) and left ventricular aneurysm in a patient with ADPKD has been documented.[4] The activation of the rennin angiotensin-aldosterone system (RAAS) causes pathogenesis of hypertension in ADPKD. The contribution of RAAS system in the ADPKD progression by stimulating signaling pathways in renal cyst cells is well reviewed by Hian et al.[5]

Mutation in two genes named as *PKD1* and *PKD2* have been identified as the main cause of ADPKD where *PKD1* accounts for most of the cases (85%) and is present on the short arm of chromosome 16 whereas *PKD2* has minor role (15% cases) and is located on long arm of chromosome 4. *PKD1* gene mutation results in earlier onset of symptoms and ESRD at early age when compared with *PKD2* gene. These *PKD1* and *PKD2* genes are responsible for encoding the protein i.e. polycystin 1 (PC1) and polycystin 2 (PC2) respectively. PC1 is found mainly in primary cilia and plasma membrane while PC2 is embedded mainly in the endoplasmic reticulum and primary cilia.[6-9] Both the proteins PC1 and PC2 are membrane bound glycoproteins and constitute a subfamily of transient receptor potential (TRP) channels (TRPP1 and TRPP2 respectively) and regulate the intracellular calcium homeostatis.[10] The proliferation of single tubular epithelial cells can leads to the development of numerous fluid loaded cyst in the kidney. The prolonged existence of proliferation and fluid seepage causes cyst to grow in size which eventually replaces the renal parenchyma tissue and weakens its healthy functioning. The protein polycystin is also present in the tissue of pancreas, myocardial smooth muscle cells, endothelial cells and bile duct as well.[11] The primary cilium, apical junctions and plasma lateral membrane of renal tubular cells were reported as a tissue where PC1express itself by forming a complex with PC2 along with intracellular binding moieties.[12,13] Further, the urinary exosome are found to carry dissect form of polycystin proteins that seems to interact with the primary cilium.[14] This is how the localization of PC1 takes place at distinct cellular site. Though the role of polycystin in cytogenesis is partially known but significant progress has been achieved in understanding the physiological disorder associated with ADPKD.

GENETICS

As mentioned earlier, ADPKD is a hereditary disease caused by mutation in one of the two genes *PKD1* and *PKD2*. Comprehensive screening for *PKD1* and *PKD2* gene mutations in large patient cohorts has been reported by several recent studies. **To date, more than 1272 *PKD1* and 202 *PKD2* different pathologic mutations have been reported.**[15]Despite comprehensive screening, 6–11% of patients with PKD do not have an identifiable *PKD1* or *PKD2* mutation.[16-21] Some of these patients with no mutation detected may carry mutations in one of the six genes that cause autosomal dominant polycystic liver disease (ADPLD) (i.e. *ALG8*, *SEC61B*, *SEC63*, *PRKCSH*, *LRP5* and especially *GANAB*), which can be associated with a mild kidney phenotype (i.e. a few to multiple but not innumerable kidney cysts).[22-25] Patients with ADPLD may be diagnostically confused as having ADPKD, but they are not at risk for progressive kidney failure.[23]

It has been determined that not only the mutation, but the type of mutation plays an important role in causing the severity of this renal dysfunction disease. Clinical evidences suggest that truncating mutation is responsible for more severe symptoms than non- truncating mutation.[16,26]

It has been documented that Human *PKD1* contains long stretches of polypyrimidine sequence in intron-21 and -22that are composed of the imperfect repeats $(CCTCCCC)_n$, which cause aberrant splicing and the production of mRNA with in frame stop codons soon after the 3'-end of exon- 20. Thus, this premature translational termination of mRNA produce low molecular mass product named as Trunc_PC1 protein, which extends from the extreme N terminus of PC1 but terminates before the end of the G protein-coupled receptor autoproteolysis inducing GAIN domain. This domain is responsible for linking the N- and C- termini of the cleaved form of PC1. Hence, as a result, formation of these small protein products (Trunc_PC1) may reduce PC1 signaling below a critical "cystogenic" threshold.[27,28] This poor signaling pathways may cause some phenotypic changes like deregulation of calcium homeostatis, cAMP accumulation and activation of protein kinase A (PKA), mammalian target of rapamycin (mTOR)kinases and other intracellular signaling mechanisms. Thus, an overview of deregulation of ion channels due to aberrant splicing in introns-21 and -22 have been depicted in figure 2**.**

EPIDEMIOLOGY

Today, we have entered into medicine era, where drugs to control or cure most of the rare genomic disease has been developed. Accurate prevalence figures especially of rare disease (RD) is more important for purpose of health care and societal planning. A large number of reports have been published to discuss about the prevalence of ADPKD. Iglesia et al. have extensively discussed the data between Jan 1, 1935 to Dec 31, 1980. They reported that adult polycystic kidney was diagnosed in 40 residents of Olmsted County, Minnesota, resulted in an age and sex adjusted annual incidence rate of 1.38/100,000 persons per year which further enhanced to 2.75 by taking the cases of autopsy into consideration. Therapeutic advancement with time caused improvement in kidney and survival rate in the period of 1956-1980 as compared to diagnosis during 1935-1955.[29] In another epidemiological study of kidney survival in ADPKD with 513 ADPKD subjects for two separate periods i.e 1985-1992 vs. 1992-2001, a significant delay in renal progression in both male and female patients with significantly lower mean arterial pressure (MAP), by use of more angiotensin converting enzyme inhibitors (ACEIs) was found in the period of 1992-2001 as compared to 1985-1992.[30]

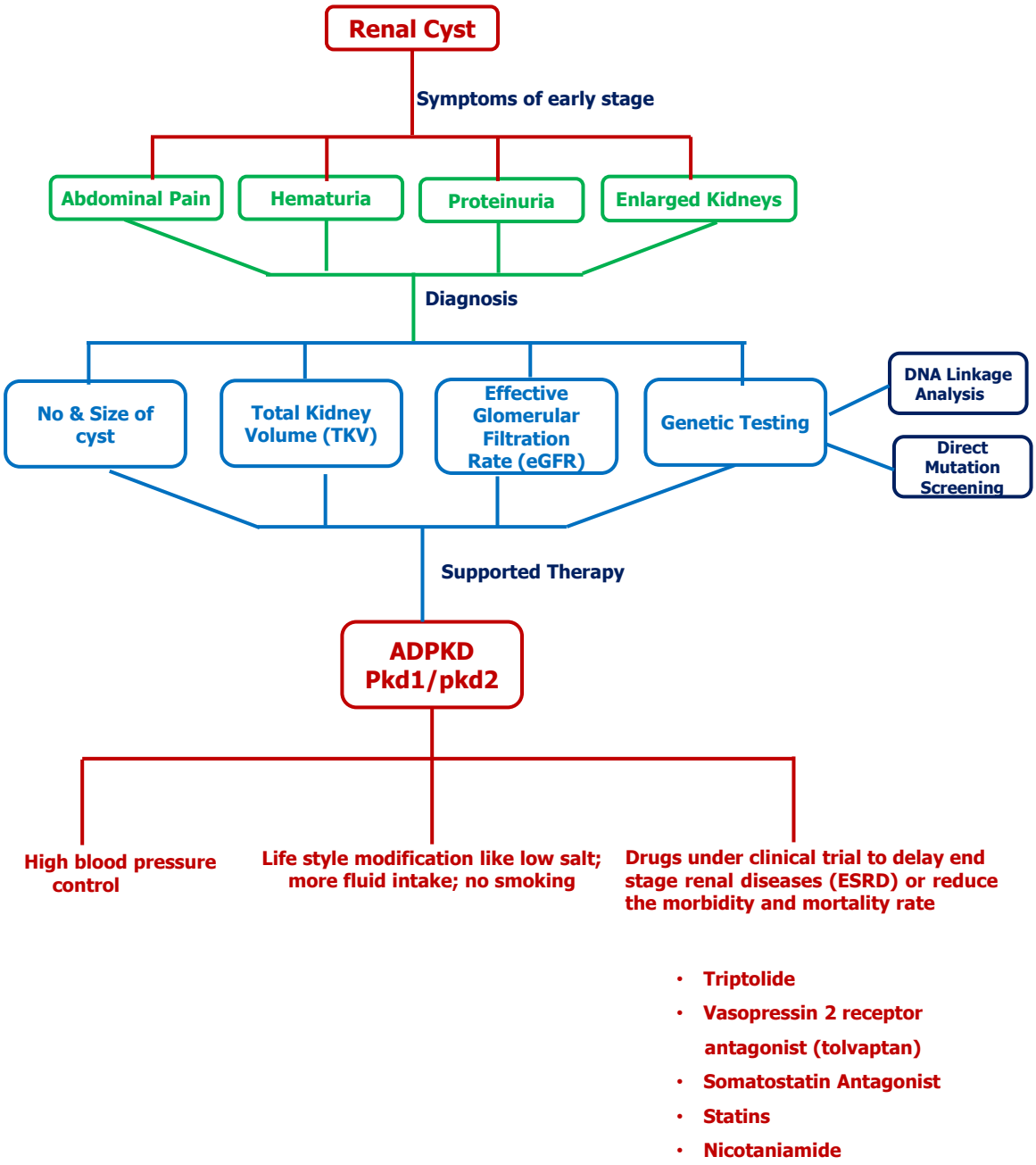


Figure 1. Schematic diagram of ADPKD analysis

Further, in depth clinical epidemiological study for south western Germany was published in 2013, in which 891 ADPKD subjects, 658 index cases, 233 relatives, aged 10-89 were registered. The overall prevalence of ADPKD was estimated as 32.7/100,000 reaching a max of 53.7/100,000 in 6th decade of life.[31] On similar lines, occurrence of ADPKD was investigated in European Union by estimating point prevalence and screening prevalence. It was found that ADPKD point prevalence is <5/10,000, the threshold for rare disease in EU.[32,33] Another cohort based study to estimate the association between antihypertensive therapy and mortality in patients with ADPKD in UK was carried out and it was demonstrated that from 1991-2008, the mortality rate decreased as the number of antihypertensive drug prescribed in a year increased.[34] Similar studies have also been conducted with ADPKD patients in England and Whales.[35] In a recent report, the prevalence and risk of acute myocardial infarction(AMI) in patients with ADPKD in Taiwan population was analysed. Based on population cohort study it was concluded that the Taiwanese ADPKD group had significantly higher prevalence of AMI as compared with non-ADPKD group. Further, on comparing with population of United States, data revealed the low prevalence of AMI in Taiwanese ADPKD group than Americans.[36] Similarly, in another report, the risk of aortic aneurysm dissection (AAD)

was found significantly high in ADPKD patients.[37] Likewise, nephrologists from China found many PKD mutations in Chinese ADPKD patients earlier through polymerase chain reaction and liquid chromatography which has now been replaced by next generation sequencing.[38]

ROLE OF cAMP IN THE FORMATION OF CYST

Cyst growth involves at least three primary pathogenic mechanisms: epithelial cell proliferation that increases the surface area of renal tubules from which the cysts derive, accumulation of fluid within the cavity derived from glomerular filtrate and trans epithelial secretion, and remodeling of the extracellular matrix surrounding cysts.[39,40]

Two key features associated with cyst formation in ADPKD are cell proliferation and fluid secretion, both of which are stimulated by cAMP. The effect of cAMP on cell proliferation varies among different cell types.[34] For example, in smooth muscle cells, fibroblasts, and mesangial cells, elevation of intracellular cAMP blocks growth factor-stimulated cell growth by inhibiting the mitogen-activated protein (MAP) kinase cascade.[41–43] On the other hand, in cell types such as thyroid cells, hepatocytes, and PC12 cells, cAMP activates cell proliferation.[41,44]

Cyclic AMP levels are normally regulated by the balanced activity of G-protein coupled receptor (GPCR) associated adenylyl cyclases (ACs) and phosphodiesterases (PDEs). Altered calcium signal inhibits the activity of PDEs (*PDE1* and *PDE3*) and activate AC6 and hence produce a net increase in cAMP concentration. The compartmentalized nature of cAMP signaling illustrates the importance of certain AC (AC6) and PDE (1, 3 and 4) over others in the pathogenesis of ADPKD.[45, 46] There are other pathways also where cAMP has been found to show its effect on several elements of ADPKD pathophysiology. For example- protein kinase-A (PKA) mediated cAMP signaling has been found to be responsible for hyperproliferative cellular phenotype observed in ADPKD.[47]

DIAGNOSIS

Inherited cystic renal diseases are diagnosed by observing the radiological findings like distribution and morphology of the renal cysts and involvement of other organs. For example, the cyst growth in liver has been found most common in women where estrogen is responsible for developing cyst from cholangiocytes lining of biliary duct.[48]Other symptoms may include abdominal pain, back pain, hematuria, proteinuria, decreased urinary concentration and reduced blood flow can be seen in early stage of the disease.

In ADPKD patients, the kidneys are enlarged with multiple cysts which are typically bilateral and diffuse. However, atypical distributions including unilateral, segmented and asymmetric distribution is also reported in some patients (2-9%).[49] The imaging techniques used for diagnosis of ADPKD are ultra sound (US), CT scan and MRI. US is the initial screening method with a positive family history. CT scan and MRI are more sensitive in depicting renal cysts. Pie *et. al.* have reported in their study that the comparative performance of high resolution US and MRI in patients younger than 40 years of age and at risk of ADPKD. They reported that MRI is highly sensitive and specific for diagnosis of ADPKD. High resolution US also has the potential to compete the diagnostic performance of MRI but it is both center and operator dependent.[50] Further, clinical studies also use total kidney volume (TKV) measured by MRI as an image based biomarker to follow the disease progression because larger TKV shows poor prognosis in ADPKD.[51] However, there are few constraints in using TKV as a marker of disease progression like, it does not inform on microscopic disease processes involved in piecemeal destruction of healthy renal tissue. In addition to this, TKVs measurements are costly and time consuming. Hence, these shortcomings of TKVs have been overcome with use of magnetization transfer (MT) renal quantitative imaging technique.[52,53]

Genetic testing is recommended when definitive diagnosis is required. There are two methods for genetic testing: DNA linkage analysis and direct mutation screening. Linkage analysis has some limitations as it cannot be used if family is small; at least DNA samples from 4 affected family members in 2 generations are required. Direct mutation analysis involves sequencing of the entire coding regions of both *PKD1* and *PKD2* including intron/exon boundaries.Moreover, linkage analysis cannot exclude the possibility of ADPKD even with negative test result while the direct mutation can identify the causative mutation even in an unlinked ADPKD pedigree.[5,54]

TREATMENT

There are less than 40% chances of survival in ADPKD patient with the end-stage renal disease.[55] To date, there is no approved therapy for the permanent cure of ADPKD and the current treatments include dialysis and renal transplantation which are burdensome and costly. Advancement in the research has achieved some milestones to minimize the morbidity and mortality of the disease. Small changes in lifestyle like low salt diet, sufficient fluid intake, no smoking and blood pressure control have been recommended by Kidney Disease – Improving Global Outcomes (KDIGO) for ADPKD patients.[38] Some of these measures are listed below:

BLOOD PRESSURE CONTROL

Hypertension is an important risk factor for progression to ESRD, cardiovascular morbidity and mortality. The use of anti-hypertensive therapy in ADPKD has been proven to be useful in delaying ESRD. A number of studies have found that blood pressure control in children with chronic kidney disease (CKD)resulted in better glomerular filteration rate (GFR) and reduced progression to ESRD.[56]Another study conducted in a Denmark population demonstrated that reduced cases of ESRD were associated with the use of anti-hypertensive drugs like angiotensin converting enzyme(ACE) inhibitors for RAAS blockade and drugs for angiotensin receptor blockade (ARB).[57] Hence, use of ACE inhibitor improves renal blood flow; reduces proteinuria and delays renal failure.[58]Based on the studies conducted to date, in the children with high risk of progression

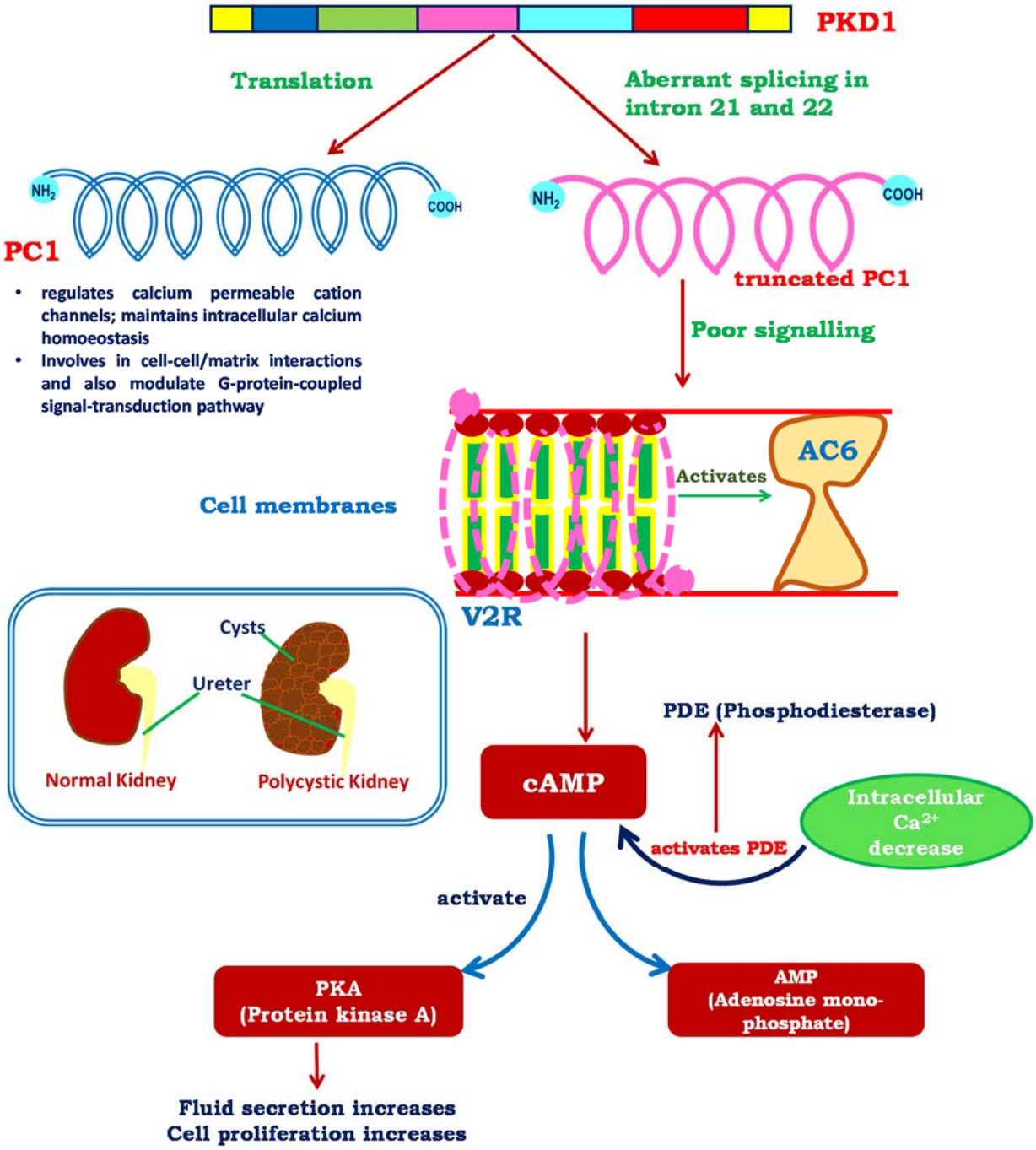


Figure 2: Overview of ion channel deregulation due to aberrant splicing in intron 21 and 22 causing ADPKD

and eGFR above 60mL/min, blood pressure should be less than 110/70mm Hg while in the patient with eGFR >60mL/min target blood pressure should be less than 120/80mm Hg.[59]

TRIPTOLIDE

Triptolide is a biologically active diterpene, obtained from the medicinal vine *Tripterygium wilfordii HookF* (''ThunderGodVine'')and used as medicine for centuries. Its therapeutic uses against cancer, inflammation, and autoimmune diseases are well known.[60] It has been reported that triptolide induces cellular calcium release through a polycystin-2-dependent pathway, arrests cell growth, and reduces cystic burden in embryonic mice. Triptolide shows promising applications in animals. Clinical trial on ADPKD human showed that triptolide arrests the enlargement of kidney size, improves kidney functions and reduces the protein level in urine. So triptolide seems to cure the symptoms of ADPKD to some extent.[60-63]

STATIN

Statin has been known for its anti-inflammatory effect in vasculature, kidney and bone.[64] Some preclinical studies on different animal models have illustrated the beneficial use of statin drugs to lower the progression of ADPKD. For example- in a study with lovastatin on a group of animals, it was found that lovastatin increases total renal blood flow (RBF) and maintains GFR.[65] In another study on heterozygous Han: SPRD rats, the effect of HMG-CoA reductase inhibition with lovastatin and angiotensin-converting enzyme (ACE) inhibition with enalapril were demonstrated.[66] Simvastatin has also been found to ameliorate renal function in ADPKD patients by increasing renal plasma flow via improvement of endothelial function.[67] Similarly, the clinical trials of GαsPCR antagonists (i.e. vasopressin V2 receptor antagonists and GiPCR agonists (i.e. somatostatin analogs) have shown promising results as they target cAMP and Ca^{2+} levels in cystic tissues.[68] Furthermore, somatostatin therapy has been found safe and also slows down renal volume expansion.[69-72]

VASOPRESSIN V2 RECEPTOR (V2R) ANTAGONISTS – TOLVAPTAN

Vasopressin is a small peptide hormone secreted by the pituitary gland and it induce the reabsorption of water in the collecting duct by binding to the G- protein coupled arginine vasopressin (AVP) V2 receptor. Circulating AVP levels and renal V2R expression are increased in rodent PKD. Several preclinical trials have shown that treatment with AVP V2 receptor antagonists successfully slow down the disease progression.[73,74]

Tolvaptan is a highly potent and selective AVP V2 receptor antagonist and slow down the cyst development and renal insufficiency of ADPKD in adults with CKD stages 1-3 at initiation of treatment with evidence of rapidly progressing disease. To date, no widely accepted clinical guidelines are available for the treatment of ADPKD. Tolvaptan treatment need two issues to be clarified: first, the CKD stage and the age that qualify patients for treatment and second, how to define evidence of rapidly progressing disease. Hence, in a recent report, guidance for making the decision as to which ADPKD patient to treat with tolvaptan has been published.[75] Based on the studies with their clinical trials the Europian Medicines Agency (EMA) approved the use of tolvaptan for ADPKD whereas the Food and Drug Administration in USA has requested for further efficacy and safety data, side effects of this drug. Thus, patients to be treated with tolvaptan should be selected carefully and should be restricted to those with rapid disease progression.[33,76]

SOMATOSTATIN ANALOGS

Somatostatin (SST) is a peptidehormoneinvolved in the endocrine regulation of cellular metabolism. Somatostatin acts on five G- protein coupled receptor (SSTR1-5), present on cholangiocytes and kidney tubular epithelial cells, inhibiting cAMP generation. Since somatostatin has very short half-life (3 minutes), more stable peptides like octreotide, lanreotide and pasireotide have been developed for clinical use.[77,78] These analogs differ in stability and receptor selectivity. Octreotide and lanreotide have half life of 2hrs in circulations and bind with high affinity to SSTRs 2 and 3 and pasireotide bind with high affinity with all SSTRs except SSTR4 and has serum half-life of 12 hrs. Clinical studies have revealed that these somatostatin analogs are effective for ADPKD patients with cystic liver disease as they reduce proliferation and intracellular cAMP concentration in cholangiocytes.[47]

NICOTINAMIDE

Nicotinamide is a known inhibitor of SIRT1. It alters SIRT1-mediated signaling pathways. SIRT1 is the most extensively studied member of a mammalian family protein, the sirtuins and has been found responsible for the pathogenesis of ADPKD. By promoting a base-exchange reaction at the expense of deacetylation, nicotinamide serves as a noncompetitive inhibitor of SIRT1. The potential use of nicotinamide is to delay cyst formation in ADPKD patients. Thus, the use of a pan-sirtuin inhibitor (nicotinamide) or a SIRT1-specific inhibitor (EX-527) has been found to delay cyst growth in *PKD1* knockout mouse embryonic kidneys.[79]

INHIBITION OF MTOR

mTOR is known as mammalian target of rapamycin. It is an atypical protein kinase and a central controller of cell growth and proliferation. Rapamycin, an inhibitor of mTOR, is highly effective in reducing renal cystogenesis. Treatment of human ADPKD transplant-recipient patients with rapamycin results in a significant reduction in native polycystic kidney size. It reduced cyst growth, preserved renal function, inhibited epithelial cell proliferation etc.[80-82]

CONCLUSION

This article is a humble attempt to explain various important features that account for the genetic factors, diagnosis and therapy for the progression of disease. Substantial advances have been made in explicating the mechanism of genetics responsible for the disorder.Thus, mutation in *PKD1 and PKD2* genes located at chromosome16 and chromosome 4 respectively is the main cause for ADPKD. US, CT scan, MRI etc are the techniques used for the diagnosis of ADPKD. To date, no remedy has been approved for the permanent treatment of ADPKD but considerable success has been achieved in developing certain drugs which can minimize morbidity and mortality of ADPKD.

Hence, in this context the coming era may witness the substantial developments for improving the life expectancy of the patient suffering from ADPKD.

COMPETING INTERESTS

The authors declare that they have no competing interests in this section.

AUTHOR'S CONTRIBUTIONS

Aparna Bansal & Shrikant Kukreti- Conceived, data collection & design of analysis and writing.

Shikha Kaushik- Data collection and preparation of figures.
Saami Ahmed- Data collection.

ACKNOWLEDGEMENT

Authors acknowledge Dr. Sanjay Goel, Principal consultant, Department of Cardiac Anesthesia, Max Superspeciality Hospital, Vaishali, UP, India, for his kind suggestions and final reading of the MS. **Funding:** University Grants Commission, New Delhi

REFERENCES

1. B. Kim , B. E. King, J. J. Vrtista, M.V. Irazabal, V. E. Torres and P.C. Harris. Inherited renal cystic diseases. *AbdomRadiol*. **2016**, 41(6), 1035-1041.
2. V.E. Torres, P. Harris, Y. Pirson. Autosomal dominant polycystic kidney disease. *Lancet.***2007**, 369(9569), 1287-1301.
3. P. Krasnicki, J. Malyszko and J. S. Malyszko. Eye problems in patients on the active and inactive kidney transplantation waiting list. *Transplant Proc*.**2018**, 50(6), 1634-1636.
4. F. Fukino, J. Ishiwata, H. Shinohara, T. Oshima, T. Kozaki, M. Ikutomi, T. Amaki and F. Nakamura. Noncompaction of the ventricular myocardium and polycystic kidney disease: a case report. *Am J. Kidney Dis.***2016**, 67(6), 945-948.
5. C.K. Hian, C.L. Lee, W. Thomas. Rennin–Angiotensin-Aldosterone System antagonism and polycystic kidney disease progression. *Nephron.***2016**, 133(4), 1-5.
6. J. Hughes, C.J. Ward, B. Peral, R. Aspinwall, K. Clark, J. San Millán, V. Gamble and P.C Harris. The polycystic kidney disease 1 (PKD1) gene encodes a novel protein with multiple cell recognition domains. *Nat Genet.* **1995**, 10(2), 151-160.
7. T. Mochizuki, G. Wu, T. Hayashi and S. Xenophonto.s PKD2, a gene for polycystic kidney disease that encodes an integral membrane protein. *Science.***1996**, 272(5266), 1339-1342.
8. European Polycystic Kidney Disease Consortium. The polycystic kidney disease 1 gene encodes a 14 kb transcript and lies within a duplicated region on chromosome 16. *Cell*. **1994**, 77(6), 881-894.
9. S.V. Fedeles, A.R Gallagher, S. Somlo. Polycystin-1: a master regulator of intersecting cystic pathways. *Trends in molecular medicine*. **2014**, 20(5), 251-260
10. V.Takiar, M.J. Caplan. Polycystic kidney disease: pathogenesis and potential therapies. *BiochimicaetBiophysicaActa (BBA)*-Molecular Basis of Disease. **2011**, 1812(10), 1337-1343.
11. C. Ong, C.J. Ward, R.J. Butler, S. Biddolph, C. Bowker, R. Torra, Y. Pei and P.C. Harris. Coordinate expression of the autosomal dominant polycystic kidney disease proteins, polycystin-2 and polycystin-1, in normal and cystic tissue. Am. J. Pathol. **1999**, 154(6), 1721-1729
12. B.K.Yoder, X. Hou, L.M. Guay-Woodford. The polycystic kidney disease proteins, polycystin-1, polycystin-2, polaris, and cystin, are co-localized in renal cilia. *J. Am. Soc.Nephrol.***2002**, 13(10), 2508–2516.
13. S. M. Nauli, F.J. Alenghat, Y. Luo, E. Williams, P. Vassilev, X. Li, A. E. Elia, W. Lu, E. M. Brown, S. J. Quinn and D. E. Ingber. Polycystins 1 and 2 mediate mechanosensation in the primary cilium of kidney cells. *Nat. Genet.***2003**, 33(2), 129–137.
14. M.C. Hogan, L. Manganelli, J.R. Woollard, A.I. Masyuk, T.V. Masyuk, R. Tammachote, B.Q. Huang, A.A. Leontovich T.G. Beito, B.J. Madden and M.C. Charlesworth. Characterization of PKD protein-positive exosome-like vesicles. *J. Am. Soc. Nephrol.* **2009**, 20(2),278–288
15. K.B. Lee. Genetic diagnosis of autosomal dominant polycystic kidney disease: linkage analysis versus direct mutation analysis. *Kidney Res ClinPract.***2016**, 35(2), 67-68.
16. G.E. Cornec-Le, M.P. Audrezet, J.M. Chen et al. Type of PKD1 mutation influences renal outcome in ADPKD. *J Am SocNephrol***2013**, 24(6),1006–1013
17. C.M. Heyer, J.L Sundsbak, K.Z Abebe et al. Predicted mutation strength of nontruncating PKD1 mutations aids genotype-phenotype correlations in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol*, **2016**, 27(9), 2872–2884
18. S. Rossetti, K. Hopp, R.A. Sikkink et al. Identification of gene mutations in autosomal dominant polycystic kidney disease through targeted resequencing. *J Am SocNephrol* **2012**, 23(5), 915–933.
19. Y.H Hwang, J. Conklin, W. Chan et al. Refining genotype-phenotype correlation in autosomal dominant polycystic kidney disease. *J Am SocNephrol.***2016**, 27(6), 1861–1868
20. I.A Iliuta, V. Kalatharan, K. Wang et al. Polycystic kidney disease without an apparent family history. *J. Am. Soc. Nephrol.* **2017**, 28(9), 2768–2776
21. S. Rossetti, M.B. Consugar, A.B Chapman et al. Comprehensive molecular diagnostics in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol*. **2007**, 18(7), 2143–2160
22. G.E. Cornec-Le, R.J. Olson, W. Besse et al. Monallelic mutations to DNAJB11 cause atypical autosomal dominant polycystic kidney disease. *Am. J. Hum Genet.***2018**, 102(5), 832–844.
23. B. Porath, V.G. Gainullin, E. Cornec-Le Gall et al. Mutations in GANAB, encoding the glucosidaseIIa subunit, causeautosomal-dominant polycystic kidney and liver disease. *Am. J. Hum. Genet.***2016**, 98(6), 1193–1207.
24. W. Besse, K. Dong, J. Choi et al. Isolated polycystic liver disease genes define effectors of polycystin-1 function. *J. Clin. Invest*. **2017**, 127(9), 1772–1785.
25. W.R. Cnossen, R.H. TeMorsche, A. Hoischen et al. LRP5 variants may contribute to ADPKD. *Eur J Hum Genet* **2016**, 24(2), 237–242.
26. Y. Pei, Z. Lan, K. Wang et al. A missense mutation in PKD1 attenuates the severity of renal disease. *Kidney Int*. **2012**, 81(4), 412-417.
27. K.B. Piontek, G.G. Germino. Murine Pkd1 introns 21 and 22 lack the extreme polypyrimidine bias present in human PKD1. *Mammalian genome*. **1999**, 10(2), 194–196.
28. W.A. Lea, S.C. Parnell, D.P. Wallace, J.P. Calvet, L.V. Zelenchuk, N.S. Alvarez and C.J. Ward. Human- Specific abnormal alternative splicing of wild type PKD1 induces premature termination of Polycystin-1. *J Am SocNephrol.***2018**, 29(10), 2482–2492,
29. C.G.Iglesias, V.E. Torres, K.P. Offord, K.E. Holley, C.M. Beard, L.T. Kurland. Epidemiology of adult polycystic kidney disease, Olmsted County, Minnesota: 1935-1980. *Am J Kidney Dis*. **1983**, 2(6), 630-9.
30. R.W. Schrier, K.K. McFann, A.M. Johnson. Epidemiological study of kidney survival in autosomal dominant polycystic kidney disease. *Kidney Int*. **2003**, 63(2), 678-85.
31. H.P. Neumann, C. Jilg, J. Bacher, et.al. Else-Kroener-Fresenius-ADPKD-Registry. Epidemiology of autosomal-dominant polycystic kidney disease: an in-depth clinical study for south-western Germany**.** *Nephrol Dial Transplant.* **2013**, 28(6), 1472-87
32. C.J. Willey, J.D. Blais, A.K. Hall, H.B. Krasa,, A.J. Makin, F.S. Czerwiec, Prevalence of autosomal dominant polycystic kidney disease in the uropean Union. *Nephrol Dial Transplant.* **2017**, 32(8), 1356-1363.
33. C. Sommerer. and M. Zeier. Clinical Manifestation and management of ADPKD in western countries. *Kidney Dis.***2016**, 2(3), 120-127.
34. C. Patch, J. Charlton, P.J. Roderick, M.C. Gulliford. Use of antihypertensive medications and mortality of patients with autosomal dominant polycystic kidney disease: a population-based study. *Am J Kidney Dis.***2011**, 57(6), 856-62
35. C. Shaw, R.J. Simms, D. Pitcher, R. Sandford. Epidemiology of patients in England and Wales with autosomal dominant polycystic kidney disease and end-stage renal failure. *Nephrol Dial Transplant.***2014**, 29(10), 1910-8
36. PH. Sung, H.J. Chiang, Y.H. Yang, C.J. Chen, J.Y. Chiang, H.K. Yip. An association between autosomal-dominant polycystic kidney disease and the risk of acute myocardial infarction in Asian population - results of a nationwide study. *Oncotarget.***2017**, 8(12), 19365-19375
37. P.H. Sung, Y.H. Yang, H.J. Chiang, J.Y. Chiang, C.J. Chen, C.T. Liu, C.M. Yu, H.K. Yip. Risk of aortic aneurysm and dissection in patients

with autosomal-dominant polycystic kidney disease: a nationwide population-based cohort study. *Oncotarget*. **2017**, 8(34), 57594-57604.
38. C. Xue, C.C. Zhou, M. Wu, C.L. Mei. The clinical manifestation and management of autosomal dominant polycystic kidney disease in China. *Kidney Dis.***2016**, 2(3), 111-119
39. F.A. Carone, S. Nakamura, R. Bacallao, W.J. Nelson, M. Khokha, Y.S Kanwar. Impaired tubulogenesis of cyst-derived cells from autosomal dominant polycystic kidneys. *Kidney Int***1995**, 47(3), 861–868
40. F.A. Carone, R. Bacallao, Y.S. Kanwar. Pathogenesis of polycystic kidney disease: Basement membrane and extracellular matrix. In: Polycystic Kidney Disease, edited by M.L. Watson, V.E. Torres, Oxford, UK, Oxford Medical Publications, **1996**, pp 111–124
41. J.E. Dumont, J.C. Jauniaux, P.P. Roger. The cyclic AMP-mediated stimulation of cell proliferation. *Trends Biochem Sci.* **1989**, 14(2), 67–71.
42. J. Wu, P. Dent, T. Jelinek, A. Wolfman, M.J. Weber, T.W. Sturgill. Inhibition of the EGF-activated MAP kinase signaling pathway by adenosine 3',5'-monophosphate. *Science*. **1993**, 262(5136), 1065–1069.
43. X. Li, F. Zarinetchi, R.W. Schrier, R.A. Nemenoff. Inhibition of MAP kinase by prostaglandin E2 and forskolin in rat renal mesangial cells. *Am J Physiol.* **1995**, 269 (4 Pt 1), C986–C991
44. M.R. Vossler, H.Yao, R.D. York, M.G. Pan, C.S. Rim, P.J. Stork. cAMP activates MAP kinase and Elk-1 through a B-Raf- and Rap1-dependent pathway. *Cell.***1997**, 89(1), 73–82.
45. S. Rees, W. Kittikulsuth, K. Roos, et al. Adenylyl cyclase 6 deficiency ameliorates polycystic kidney disease. *J Am SocNephrol.***2014**, 25(2), 232–237
46. H. Ye, X. Wang, et al. Genetic Approach to Evaluate the Role of PDE3 Subfamilies in Polycystic Kidney Disease. J Am SocNephrol. 2012, 23.
47. W.B. Lariviere, M.V. Irazabal and V.E. Torres. Novel therapeutic approaches to autosomal dominant polycystic kidney disease. *Transl Res.***2015**, 165(4), 488-498.
48. P.A. Gabow, A.M. Johnson, W.D. Kaehny, M.L. Manco-Johnson, I.T. Duley, Everson GT. Risk factors for the development of hepatic cysts in autosomal dominant polycystic kidney disease. *Hepatology.***1990**, 11(6), 1033–1037
49. M.V. Irazabal, L.J. Rangel, E.J. Bergstralh, S.L. Osborn, A.J. Harmon, J.L. Sundsbak, K.T. Bae, A.B. Chapman, J.J. Grantham, M. Mrug and M.C. Hogan. Imaging classification of autosomal dominant polycystic kidney disease: a simple model for selecting patients for clinical trials. *J. Am. Soc. Nephrol.* **2015**, 26(1), 160-172.
50. Y. Pei, Y.H. Hwang, J. Conklin, et al. Imaging based diagnosis of autosomal dominant polycystic kidney disease. *J. Am. Soc. Nephrol.***2015**, 26(3), 746-753.
51. J.J. Grantham, V.E. Torres, A.B. Chapman, et al. Volume progression in polycystic kidney disease. *New Engl. J. Med.* **2006**, 354, 2122-2130.
52. T.L. Kline, M.V. Irazabal, B. Ebrahimi, K. Hopp, K.N. Udoji, J.D. Warner, P. Korfiatis, P.K. Mishra, S.I. Macura, S.K. Venkatesh, L.O. Lerman, P.C. Harris, V.E. Torres, B.F. King and B.J. Ericson. Utilizing magnetization transfer imaging to investigate tissue remodeling in a murine model of autosomal dominant polycystic kidney disease. *Magn. Reson. Med.* **2016**, 75(4), 1466-1473.
53. M.V. Irazabal and V.E. Torres. Total kidney volume and autosomal dominant polycystic kidney disease: A long standing relationship. *Am. J. Nephrol.***2018**, 48(1), 65-66.
54. M.B. Lanktree, I.A. Iliuta, A. Haghighi, X. Song and Y. Pei. Evolving role of genetic testing for the clinical management of autosomal dominant polycystic kidney disease *Nephrol Dial Transplant,* **2018**, doi: 10.1093/ndt/gfy261. [Epub ahead of print].
55. United States Renal Data System. 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. Bethesda, MD, USA: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; **2013**. Available from: http://www.usrds.org/atlas.aspx. Accessed September 14, 2014
56. ESCAPE trial group, E. Wuhl, A. Trivelli, S. Picca, A. Litwin, A. Peco Antic, A. Zurowska, S. Testa et al. Strict blood pressure control and progression of renal failure in children. *N. Engl. J. Med.* **2009**, 361(17), 1639-1650.
57. J.G. Heaf and S. Wehberg. Reduced incidence of end stage renal disease among the elderly in Denmark: an observational study. *BMC Nephrol.***2012**, 13, 131.
58. C.R. Halvorson, M.S. Bremmer, S.C. Jacobs. Polycystic kidney disease: inheritance, patho-physiology, prognosis and treatment. *Int. J. NephrolRenovasc Dis.* **2010**, 3, 69-83.
59. E. Wolfgang and G. Walz. The treatment of autosomal dominant polycystic kidney disease**.** *DtschArztebl Int.***2015**, 112(51-52), 884-90
60. S.J. Leuenroth, D. Okuhara, J.D. Shotwell, et al. Triptolide is a traditional Chinese medicine-derived inhibitor of polycystic kidney disease. *Proc. Nat. Acad. Sci U S A.* **2007**, 104(11), 4389–4394.
61. S.J. Leuenroth, N. Bencivenga, P. Igarashi, S. Somlo, C.M. Crews. Triptolide reduces cystogenesis in a model of ADPKD. *J. Am. Soc. Nephrol.***2008**, 19(9), 1659–1662.
62. S.J. Leuenroth, N. Bencivenga, H. Chahboune, F. Hyder, C.M. Crews. Triptolide reduces cyst formation in a neonatal to adult transition Pkd1 model of ADPKD. *Nephrol Dial Transplant.***2010**, 25(7), 2187–2194.
63. D. Chen, Y. Ma, X. Wang, et al. Triptolide-containing formulation in patients with autosomal dominant polycystic kidney disease and proteinuria: an uncontrolled trial. *Am. J. Kidney Dis.***2014**, 63(6), 1070–1072.
64. S.I. McFarlane, R. Muniyappa, R. Francisco, J.R. Sowers. Clinical review 145: Pleiotropic effects of statins: lipid reduction and beyond. *J. Clin. Endocrinol. Metab.* **2002**, 87(4), 1451–1458.
65. K.S. Hafez, S.R. Inman, N.T. Stowe, A.C. Novick. Renal hemodynamic effects of lovastatin in a renal ablation model. *J. Urol.* **1996**, 48(6), 862–867.
66. I. Zafar, Y. Tao, S. Falk, K. McFann and R.W. Schrier, C.L. Edelstein. Effect of statin and angiotensin-converting enzyme inhibition on structural and hemodynamic alterations in autosomal dominant polycystic kidney disease model. *Am. J. Physiol Renal Physiol.***2007**, 293(3), F854–F859.
67. M.A. van Dijk, A.M. Kamper, S. van Veen, J.H. Souverijn and G.J. Blauw. Effect of simvastatin on renal function in autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant.***2001**, 16(11), 2152-2157.
68. A. Tripathi, G. Srivastava, S. Srivastava, I. Das..Liesegang patterns, growth kinetics, inhibition and dissolution of calcium phosphate: A constituent of renal stone. *Chem. Biol. Lett.,* **2016**, 2(2), 30-40.
69. V.E. Torres, P.C. Harris. Strategies targeting cAMP signaling in the treatment of polycystic kidney disease. *J. Am. Soc. Nephrol.***2014**, 25(1), 18–32.
70. A. Caroli, N. Perico, A. Perna, et al. Effect of long-acting somatostatin analogue on kidney and cyst growth in autosomal dominant polycystic kidney disease (ALADIN): a randomised, placebo-controlled, multicentre trial. *Lancet.***2013**, 382(9903), 1485–1495.
71. P. Ruggenenti, A. Remuzzi, P. Ondei, et al. Safety and efficacy of long-acting somatostatin treatment in autosomal-dominant polycystic kidney disease. *Kidney Int.***2005**, 68(1), 206–216.
72. M..C. Hogan, T.V. Masyuk, L. Page, et al. Somatostatin analog therapy for severe polycystic liver disease: results after 2 years. *Nephrol. Dial. Transplant.***2012**, 27(9), 3532–3539.
73. V.E. Torres, X. Wang, Q. Qian, et al. Effective treatment of an orthologous model of autosomal dominant polycystic kidney disease. *Nat Med.* **2004**, 10(4), 363–364
74. V.H. Gattone 2nd, X. Wang, P.C. Harris, et al. Inhibition of renal cystic disease development and progression by a vasopressin V2 receptor antagonist. *Nat Med.* **2003**, 9(10), 1323–1326
75. R.T. Gansevoort, M. Arici, T. Benzing, H. Birn, et al. Recommendations for the use of tolvaptan in autosomal dominat polycystic kidney disease: a position statement on behalf of the ERA-EDTA working groups on inherited kidney disorders and European renal best practice. *Nephrol Dial Transplant.* **2016,** 31(3), 337-348.
76. S.Al Therwani, M.E.S. Malmberg, J.B. Rosenbaek, J.N. Bech and E.B. Pedersen. Effect of tolvapton on renal handling of water and sodium,

GFR and central hemodynamics in autosomal dominant polycystic kidney disease during inhibition of the nitric oxide system:a randomized, placebo-controlled, double blind, crossover study. *BMC Nephrology* **2017**, 18(1), 268, doi: 10.1186/s12882-017-0686-3.
77. F.T. Chebib and V.E. Torres. Recent advances in the management of autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol.* **2018**, 13(11):1765-177 doi: https:// doi.org/10.2215/CJN.03960318.
78. A.L. Messchendorp, N.F. Casteleijn, E. Meijer et al. Somatostatin in renal physiology and autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant.* **2019**, doi: 10.1093/ndt/gfz054.
79. X. Zhou, L.X. Fan, W.E. Sweeney, J.M. Denu, E.D. Avner, Li X. Sirtuin 1 inhibition delays cyst formation in autosomal-dominant polycystic kidney disease. *J. Clin Invest.* **2013**, 123(7), 3084–3098.
80. J.M. Shillingford, N.S. Murcia, C.H. Larson et al. The mTOR pathway is regulated by polycystin-1, and its inhibition reverses renal cystogenesis in polycystic kidney disease. *Proc. Nat. Acad. Sci. U S A.* **2006**, 103(14), 5466–5471.
81. P.R. Wahl, A.L. Serra, M.L. Hir, K.D. Molle, M.N. Hall, R.P. Wuthrich. Inhibition of mTOR with sirolimus slows disease progression in Han:SPRD rats with autosomal dominant polycystic kidney disease (ADPKD). *Nephrol Dial. Transplant.* **2006**, 21(3), 598–604.
82. J.M. Shillingford, K.B. Piontek, G.G. Germino, T. Weimbs. Rapamycin ameliorates PKD resulting from conditional inactivation of Pkd1. *J. Am. Soc. Nephrol.* **2010**, 21(3), 489–497.

AUTHORS' BIOGRAPHIES

Prof. Shrikant Kukreti

Shrikant kukreti is currently a Professor at the Department of Chemistry, University of Delhi. A Ph.D. in Biophysical chemistry, from IIT, Roorkee, India. He has been a recipient of "Marie Curie PDF" from European Commission. His research interests include biophysical & biochemical aspects of Nucleic Acid Polymorphism, Multistranded DNA structures, Molecular crowding, DNA-Protein, DNA-Drug interactions.

Dr. Aparna Bansal

Dr. Aparna Bansal is an Assistant Professor at Hansraj College, University of Delhi. She completed her graduation, post-graduation and Ph.D. in Chemistry from University of Delhi. She had CSIR-UGC JRF and SRF fellowships during her Ph.D. She was awarded SRFP-2014 by Indian National Science Academy (INSA) and has been recipient of UGC Start-Up grant.

Dr. Shikha Kaushik

Dr. Shikha Kaushik received her Bachelor's degree in Chemistry, Master's degree in Organic Chemistry and Ph.D. from University of Delhi. She has been a recipient of UGC Research Fellowship in Science for Meritorious students (RFSMS) for pursuing her research work. Currently, she is working as an Assistant Professor at Rajdhani College, University of Delhi.

Dr. Saami Ahmed

Dr. Saami Ahmed completed her graduation from University of Delhi, post-graduation (Physical Chemistry) from Jamia Millia Islamia, Delhi and Ph.D. from University of Delhi. Her research interests include physicochemical investigations of multistranded DNA structures.

.

.