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Current and Advance Treatment Approaches of Autosomal Dominant Polycystic Kidney Disease

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Abstract
Polycystic kidney disease is a genetic or acquired disorder in which balloon-like structures called cysts which are filled with fluid are formed inside the kidneys. The most common type of PKD is autosomal dominant polycystic kidney disease (ADPKD). The major cause of ADPKD are found to be abnormalities in the genes, and these abnormalities are inherited within generations. Genetic mutations such as spontaneous mutations are observed in some cases of ADPKD. Other causes of ADPKD can be hypertension and proteinuria. ADPKD develops due to mutations in the genes PKD1 or PKD2. It is found that 85% of the ADPKD patients have mutated PKD1 and 15% of the ADPKD patients have mutated PKD2. It is the 4th common cause which results in End-Stage Renal Disease (ESRD). Different researches and studies are undergoing to find novel treatments for the diseases. There is a need to have a clear understanding of molecular and genetic pathogenesis of ADPKD to help build novel therapies. After the approval of Tolvaptan, an V2R antagonist, slow growth of cyst and less chances of kidney failure were observed in ADPKD patients. Some other therapies like mTOR pathways inhibitors, somatostatin therapies also help in halting the progression of disease. Complementary therapies such as ayurveda and homeopathy, yoga, acupuncture which can help prevent the progression and symptoms of ADPKD. More and more advancement of technologies, stem cell and nanoscience have emerged in finding solutions for renal replacement therapies and restoration of renal function.
Keywords: *Autosomal dominant polycystic kidney disease (ADPKD), complementary therapies, stem cell and nanoscience.*

Introduction

Polycystic kidney disease (PKD) is an inherited disorder in which cysts formation takes place in the epithelial layer of the renal tubule. The cysts are filled with fluid and are non-cancerous in nature. The cysts are formed in the primary cilia of the renal tubule. The cysts are usually small in size but grow in size and damage underlying tissue of kidneys which results in chronic kidney diseases (CKD) and kidney failure or End-Stage Renal Disease (ESRD) (Bergmann et al., 2018). The inherited or genetic PKD are: Autosomal

dominant PKD (ADPKD) and Autosomal recessive PKD (ARPKD). The autosomal dominant polycystic kidneys are more common than autosomal recessive PKD affecting the renal system. Autosomal Recessive Polycystic Kidney Disease (ARPKD) is a rare kind of PKD and is diagnosed in the younger group of population. The main characteristic of ARPKD is cystic dilation (choledochal cysts) of the collecting ducts of the kidneys accompanied by dysgenesis of the biliary ductal plate, which results in congenital hepatic fibrosis and it can also result in death due to respiratory failure in perinates. The acquired PKD occurs in persons having atrophic end-stage kidneys with non-cystic forms of renal diseases. The cystic diseases found in kidneys are classified as: ADPKD, nephronophthisis and medullary cystic diseases. Autosomal Dominant Polycystic kidney diseases can also lead cysts to develop on other organs such as liver, pancreas, bile and other parts of the body. ADPKD varies in severity depending upon the complications and size of the cysts. The major cause of ADPKD are found to be abnormalities in the genes, and these abnormalities are inherited within generations. Genetic mutations such as spontaneous mutations are observed in some cases of ADPKD. Other causes of ADPKD can be hypertension and proteinuria. In rare cases, ADPKD arises sporadically.

ADPKD develops due to mutations in the genes PKD1 or PKD2, each gene codes for a protein. Polycystin-1 (PC-1) is encoded by PKD1 which is located in the short arm of chromosome16 (16p13.3 region) and polycystin-2 (PC-2) is encoded by PKD2 which is located in the long arm of chromosome 4 (4q21.2 region). It is found that 85% of the ADPKD patients have mutated PKD1 and 15% of the ADPKD patients have mutated PKD2 (Noel et al., 2015). However, both the genes produce the same phenotypic effect. Patients with mutated PKD1 have more renal cysts and are rapidly advancing towards end-stage renal disease. Heterozygous mutation in both PKD1 and PKD2 causes more severe PKD and homozygous mutation of PKD1 is seen to be lethal in utero. A study done in 9 patients of ADPKD with PKD1 and PKD2 mutation using whole-exome sequencing and long-range PCR techniques intricate in renal epithelial cells, somatic mutations were identified (Nobakht N et al., 2019). This disease is marked by the 'second hit' phenomenon. In this phenomena, a mutated dominant allele of ADPKD gene causing cyst formation in the parent is inherited to the child with the wild type allele having 2nd genetic hit, which results in tubular cysts formation and disease succession. (Halvorson C et al., 2010)

The symptoms of ADPKD do not occur at early stages of birth but are usually seen between the age of 30-50 years. The symptoms include: hypertension, acute abdominal pain, hematuria, nocturia, nephrolithiasis, urinary tract infections and increased level of serum creatinine. One of the extrarenal indications of ADPKD is hepatic cysts, they are rare and usually develop after the development of renal cysts (Vikrant S et al., 2017). One of the most fatal extrarenal manifestations of ADPKD is intracranial aneurysms, it causes intracranial hemorrhage and deaths in 8 to 11% of ADPKD patients. It affects about 15 million people and usually occurs in people of age group between 30-65 years. It is the 4th common cause which results in End-Stage Renal Disease (ESRD). About 50% of ADPKD patients result in ESRD. The prevalence of ADPKD is more than sickle cell disease and cystic fibrosis. (Helal I., 2015) Although different drugs are being tested to find more advanced treatment in the ADPKD. A clear understanding of molecular and genetic pathogenesis of both ADPKD is required to help build novel therapies. New therapies will help in eliminating cell proliferation, apoptosis and renal function. With the advancement in technologies, more and more advanced therapies will result in exclusion of this dreadful disease. After the approval of Tolvaptan, an V2R antagonist, slow growth of cyst and less chances of kidney failure were observed in ADPKD patients. Some other therapies like

mTOR pathways inhibitors, somatostatin therapies also help in halting the progression of disease. complementary therapies such as ayurveda and homeopathy, yoga, acupuncture which can prevent the progression and symptoms of ADPKD. Stem cell research and nanomedicines can be an approach to find novel therapies for ADPKD and help in regeneration of kidney function.

Materials and Methods

In this literature of review, we have discussed the current, advanced and complementary therapies. We have studied about 28 narrative review papers which were published between the year 2010to 2021 from different journals on autosomal dominant polycystic kidney disease. Studies including different therapies such as pharmacotherapy, integrative therapies such as yoga, acupuncture and ayurveda, homeopathy and lifestyle management were included for reference. Studies which were not showing proper results in treatment and therapies on ADPKD were excluded for reference.

Pathophysiology

It is seen that formation of cysts in both the ADPKD is due to the mutation in the protein PC-1 and PC-2. Mutation in protein results in defects in cilia-mediated signalling pathways which leads to cytogenesis followed by down regulation of planar cell polarity, uncontrolled cell proliferation and fluid secretion. These signalling pathways include, cAMP-activated, Wnt signalling, and mammalian target of rapamycin pathways (mTOR). PKD is hypothesized to occur due to the abnormalities in the renal cilia, an immotile, hair-like cellular outgrowth present on the surface of the renal epithelia. Renal cilia are present on the tubular lumen of the nephrons and help in increasing surface area for reabsorption and fluid movement. According to a review study done in 2009 by patel et al on pathogenesis of PKD, it was found that accumulation of PC-1, PC-2 and fibrocystin in the renal cilia leads to PKD (Halvorson C et al., 2010).With the progressive growth of cyst, underlying tissues of the kidney are damaged which include nephrons, renal vessels etc. Damaging of renal vessels leads to renal ischemia and activates RAAS (Renin Angiotensin Aldosterone System) which results in cyst expansion, sodium retention, increased resistance of vascular systemic, bilateral kidney cysts and renal fibrosis. One of the etiological factors of ADPKD is planar cell polarity (PCP), is the polarity axis that coordinates cells in the plan of tissue. It plays a very significant role in organogenesis, polarised cell division and cellular differentiation. Defect in planar cell polarity in PKD was demonstrated by Fischer et al. They experimented on PCK rats and observed that mice have mutated PKHD1 which results in triggering renal tubular enlargement and cyst formation. A “receptor-ion channel complex” is formed on the membrane of primary cilia of renal epithelial cells by the association of PC-1 and PC-2 which triggers calcium-dependent signalling pathway. PC-1 is a transmembrane protein which acts as a membrane receptor and PC-2 is an non-selective cation channel which is permeable to Ca(2+) ions (Bastos A P et al., 2011). Mutations in ADPKD lead to upset of the calcium signalling pathway which give rise to cyst formation and vascular alterations. Expansion of tubule epithelial cells are regulated by the endocrine, paracrine and apocrine factors which play a vital role in the pathogenesis of renal cystic diseases. The fluid inside the cysts is obtained from the glomerular filtrate by transepithelial fluid secretion.

Table 2. Risk Factors for ADPKD

S. no	Risk Factors
1	PKD1 mutation
2	Hematuria
3	Hypertension
4	Male Sex
5	Obesity

Challenges in drug development in ADPKD

Different challenges are faced by investigators and researchers to bring up therapies to clinical trials and obtain regulatory approval. Some of the following challenges are discussed below:

1. Preclinical models are not able to predict clinical efficacy

There is no clear explanation about the pathogenesis of PKD. A lot of areas need to be researched. Till date it is accepted that there is an increase in proliferation of the renal tubule epithelial cells and there is abnormal secretion of fluid into the lumen. 3D cell culture of PKD cell proliferation and cyst formation is developed to test the drugs. Most Rodent PKD models are used for preclinical testing but they do not show complete resemblance with human disease. (Happe H et al., 2014) Non Orthologous models such as pcy mouse, Han:SPRD-cy rat shows some resemblance with human disease but they may not have the same disease mechanism as humans. Rodent kidney is simple and small in size as compared to human kidney, so to study the mechanical effects is a little difficult. Limitations can be overcome by the development of hypomorphic or delayed- onset disease models and by using large animal models. (Hopp K et al., 2012)

2. Evaluating biological efficacy is difficult

Early trial phases are conducted to determine the pharmacologic effect of the drug given through a particular dose and route. Biomarkers are thought to be the effective method to determine the pharmacodynamic effects of the drug on its target. Urine contains different molecules such as peptides and exosomes which could be informative for intrarenal biochemical occurence but no signalling molecules for drug targets are not found in urine. The fluid inside the cyst contains epithelial cells secreted factors but they are sealed inside the cysts which lack communication with the tubular fluid of nephrons.

3. Prolonged natural history of disease

In ADPKD, cysts usually show symptoms in the age group between 30-65 years but cysts occur before birth and grow rapidly throughout the life in the kidney. GFR is not affected till the cysts damage or cause inflammation to the filtration unit, nephrons. Decline in GFR is marked by renal fibrosis. Many clinical trials are demonstrated to show therapeutic benefits on cysts during adulthood. (Granthan JJ et al., 2014) Perhaps, it is very difficult to indicate any effects in the GFR and assess the progression of cysts towards end stage renal disease (ESRD). Kidneys show no effects of drugs on the later stages and symptoms are irreversible. Only treatment possible is dialysis or renal transplantation. (Yu ASL et al., 2015)

Diagnosis

To detect the presence of cyst or PKD, various tests are required to detect the size and number of kidney cysts and also to check the amount of healthy kidney tissue. Some of the methods include: Ultrasound, CT scan, MRI scan.

If there is suspicion of ADPKD, doctors always ask about the family history of disease of the last three generations. If in case, there is a negative family history of PKD then hypothetical diagnosis can be made only when there is presence of bilateral renal cysts or presence of cerebral aneurysm, cysts in the arachnoid, pineal gland, pancreas or spleen. Age-dependent criteria for diagnosis using ultrasound has been predicted as a useful method. It is observed that diagnosis of patients with age group between 15 to 35 years should be found with three or more unilateral or bilateral renal cysts and in patients with age group between 40 to 60 years should have at least 2 or 3 renal cysts. Above age of 60 should have at least 4 renal cysts. (Rangan G K et al., 2014) Different imaging methods: ultrasound (US), MRI, CT scan are used to detect cysts. Diagnosis of ADPKD gene is done by genetic testing, to analyse the mutation in PKD-1 and PKD-2 and it can only detect 41-63% of cases. Renal biopsies are avoided due to the ethical issues. Mutated genes,

GANAB and DNAJB11 have recently been identified in the small group of patients but the symptoms are different from the mutation caused by PKD1 and PKD2. mutation in GANAB causes mild cysts formation with no progression to ESRD and mutation in DNAJB11 causes cysts formation to progress to ESRD but no sign of renal enlargement. (Torra R., 2019)

Current Treatment

There are different ways through which symptoms of the ADPKD can be treated. Recently there is a new treatment found which can stop the progress of cyst. Following are the ways of prevention of progress of symptoms in ADPKD:

Supportive Therapies

1.. Hypertension:

Hypertension is one of the most common signs of presence of ADPKD at early stages. If not controlled, it can lead to end-stage renal disease (ESRD) and cardiovascular complications. Antihypertensive medications are given to ADPKD patients which block the RAAS by using Angiotensin-converting Enzyme (ACE) inhibitors, thus helps in controlling hypertension (Wuthrich RP et al., 2015). It was found that patients with ADPKD when treated with diuretics showed faster response of GFR declination than patients treated with ACE inhibitors. A prospective, randomised study was done to compare the effects of the calcium channel blocker, amlodipine and angiotensin-converting enzyme (ACE) inhibitor, enalapril as primary therapy on hypertension, renal function and albumin in the urine in hypertensive patients with ADPKD. Twenty-four patients of ADPKD with hypertension and serum creatinine clearances greater than 50mL/min/1.73m² were included in the study. Out of which twelve patients were intervened with amlodipine of 9 mg/d and twelve patients were intervened with enalapril of 17 mg/d. The follow up period was five years. It was observed that enalapril showed significant effect in decreasing the urinary albumin excretion. but still data for RAAS inhibition is not accurate because of the increased plasma renin and aldosterone in ADPKD patients. It was hypothesized that use of combination ACEI/ARB Therapy could show improvement in renal blood flow and less proteinuria. Two HALT-PKD, Halt progression of Polycystic kidney disease studies were conducted by National Institute of Diabetes and Digestive and Kidney Disease (NIDDK). It was multi-centric, concurrent, randomised controlled trials (RCT) in which study group A with 558 ADPKD patients having estimated GFR > 60mL/min/1.73 m² and study group B with 486 ADPKD patients having estimated GFR 25-60 mL/min/1.73m². It was tested on study group A that whether low BP control (95 to 110/60 to 75 mm Hg) would retard the progression of PKD compared to standard BP control (120 to 130/70 to 80 mm Hg) and when combination of ACEI/ARB (lisinopril + telmisartan) is studied in both the study group And B whether decrease in BP was observed compared to ACEI monotherapy (lisinopril + placebo) (Chapman AB et al. 2010). In both the study group A and B, no significant benefit of ACEI and ARB combination therapy was observed as compared to monotherapy.

2. Dialysis

Patients with ADPKD results in End-stage renal disease and kidney Failure and dialysis is common treatment for renal replacement therapy for patients. Both hemodialysis and peritoneal dialysis are given to PKD patients. But peritoneal dialysis leads to poor complications such as abdominal wall complications, intestinal perforation. A retrospective study on 56 participants with PKD receiving peritoneal dialysis compared with nondiabetic patients ESRD control group with a follow up period of 37 months. It is observed that increased intraabdominal pressure made use of peritoneal dialysis difficult. Hemodialysis shows 5 year survival of ADPKD patients 10%-15% more than non-ADPKD controls.

3. Transplant

ADPKD results in End-stage renal disease which requires kidney transplantation. A study of 445 renal transplant patients was conducted in 2009. Out of which 48 patients were diagnosed with ADPKD. The average life of kidney transplant ADPKD patients was found to be 51.2 ± 8.6 with no significant difference in other renal transplant patients. However, the ADPKD patients with kidney transplant have diabetes mellitus.

Symptomatic Therapies

The therapies developed for ADPKD mainly focus on eradication of symptoms caused by the diseases. Apart from hypertension, other symptoms like pain, control of urinary tract infection by antibiotics are prevented by therapies. Antibodies such as trimethoprim sulfamethoxazole and fluoroquinolones are given to treat urinary tract infection and cyst-penetration. Pain in the abdominal, back, and flank region are the result of enlargement of cysts and penetration associated with ADPKD (Tellman et al., 2015). NSAIDs and narcotics analgesics are used to reduce the pain. A study on 15 ADPKD patients treated with laparoscopic delamination resulted in reduced pain with an average of 63% in 73% of cases.

Novel therapies

1. **mTOR inhibitors:** It was studied in human and animal models that enlargement of renal epithelial cells in ADPKD is due to activation of the mTOR pathway. There is a need to develop novel therapies for ADPKD which include use of mTOR inhibitors that are immunosuppressants. A randomised, single-blind study in 2009 was conducted in which 8 patients with ADPKD were given 1mg/day of rapamycin by oral route for 6 months with telmisartan. Another 8 patients (control group) were only given telmisartan. Prior to the beginning of the study all patients have 2.0 mg/dL of creatinines and negative urine culture. It was seen that at the study completion that ⅝ patients have stable renal function and 2 have improved renal function and 1 has worsening creatinine in the rapamycin. Whereas patients under the control group receiving only ARB showed that 3 were having normal renal function, in 3 it became worse and in 2 it improved. There was a significant rise in TKV (total kidney volume) in the control group. It was thought that rapamycin with combination of ARB can be helpful in treating ADPKD patients.
2. **V2R antagonist treatment:** Tolvaptan, a vasopressin V2 receptor antagonist, which promotes water reabsorption by upregulation of aquaporin-2. This drug is taken orally and non-peptide arginine vasopressin (AVP). It is seen to regress the cysts growth, delay in increasing kidney volume (biomarker of PKD) and also seen to reduce pain in ADPKD patients. The widely observed adverse effects of tolvaptan is aquateric effect and rarely observed idiosyncratic hepatitis.

Through pre clinical studies in PKD rodent models, it was confirmed that V2R blockage or any kind of genetic mutation in V2R decrease cyst formation, renal function and increase survival. There was complete suppression of cytogenesis in vasopressin deficient double homozygous Brattleboro/ PCK mutant rats. The evidence of tolvaptan suppressing V2R in rodent models provides a great support in regulatory approval and initiation of clinical phases of tolvaptan in 2004.

First studies with tolvaptan were conducted on a small number of ADPKD patients with a time period of 1-3 weeks comparing the effect of tolvaptan with placebo. The primary outcome showed that the drug can be given in two doses per day for effective inhibition of V2R with urine osmolality < 300mOsm/Kg constantly for 24

hours. Daily spilt doses induce aquaresis in stage 1-4 of CKD patients associated with slight decrease in GFR without any relevant change in renal blood flow. These events are reversible with discontinuation of tolvaptan. A double-blind, Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes (TEMPO) 3:4 trial, where 1445 patients were randomly allocated to tolvaptan at the MTD(Maximum Tolerated Dose) i.e.45/15, 60/30 or 90/30 mg and placebo. The inclusion criteria include patients with renal function and rapidly progres disease, age between 18 to 55 years and urine creatinine clearance > 60mL/min and TKV > 750 mL. It was observed that an increase in TMV by 2.8% per year in tolvaptan patients and 5.5% per year in the placebo group. Tolvaptan showed a decrease in eGFR from 10.1 to 6.8mL/min/1.73m² over three years. On the basis of TEMPO 3:4 trial result, tolvaptan was approved in Japan, Canada, EU, South Korea and many other countries. In 2013, FDA asked for more additional data on advanced CKD stages in patients and disapproved tolvaptan. A double-blind Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in later stages of ADPKD (REPRISE), trial conducted by otsuka under FDA guidance to determine method to prevent early discontinuations of tolvaptan due to aquaretic adverse effects. From may 2014 to march 2016, enrollment of patients took place in 213 sites globally. A double-blind, pre-randomised, multi-centred, sequential placebo and tolvaptan run-in phases with the time period of 8 weeks. The phases were divided into screening phase, single-blind placebo run-in phase, and single-blind tolvaptan phasein which dose-adjustments were done and run-in phase. Out of 1496 only 1370 patients entered tolvaptan run-in phase, those who were having eGFR 25-65 mL/min/1.73 m² of age between 18 to 55 years and eGFR 25-44mL/min/1.73 m² in age between 56 to 65 years were able to tolerate two 60/30 mg tolvaptan doses and placebo for 1year. After discontinuation of tolvaptan serum creatinine was measured in 7-40 days. The change in eGFR from baseline was -2.34mL/min/1.73 m² in tolvaptan treated patients and -3.61mL/min/1.73 m² in the placebo group. Transaminase (aminotransferase) advancement can be controlled by discontinuation of tolvaptan. According to the evidence generated by the REPRISE trial, in 2018 FDA approves tolvaptan for use in ADPKD patients. (Atxer LS, Joly D., 2018)

Tolvaptan is the first drug which showed effective treatment against the growth of cyst and renal function in ADPKD. Other vasopressin antagonists, in association with other drugs can prevent hepatotoxicity and aquaresis in future. Furthermore, studies are being done to improve adverse effects of tolvaptan.

Somatostatin analogues

Somatostatin is a growth hormone which binds to G protein-coupled receptor (Gpcr) to inhibit endocrine secretion and neurotransmission. Somatostatin receptors are found in the renal glomerulus and function in the cAMP cycle as Tolvaptan. Therefore, somatostatin analogues are used to slow or prevent cysts growth. A randomised trial known as ALADIN trial was conducted on ADPKD patients with mean age of 36 years and placebo group with mean age 38 years and where given 2-20 mg doses of intramuscular octreotide acetate incoluated suspension or 0.9% of sodium chloride injection after 28 days for 3 years. It was observed that there is change in TKV and decline in the eGFR. (Caroli A et al., 2013)

Novel pharmacotherapies have brought a big change in the treatments and have shown promising results in maintaining the normal renal function. More clinical trials are being done to find new drugs with proper safety and efficacy.

Lifestyle management

Lifestyle management includes proper intake of dietary supplement, water retention, avoiding smoking and drinking alcohol. Smoking causes an

increase in blood pressure which results in hypertension. Alcohol is an activator of vasopressin. Drinking water up to 3000 mL/day is advisable to ADPKD patients to avoid stone formation, supersaturation of salts and loss avoid fluid deficiency.

Protein Intake

Preclinical studies have demonstrated that the development and progression of ADPKD is markedly affected by dietary intake. High protein intake accelerates the renal cytogenesis in pcy mouse. It is advisable for ADPKD patients to take protein of 0.8- 1.0 g/kg of body weight. According to the CRISP analysis, high protein intake is associated with rise in TKV and GFR decline. (Rastogi A et al., 2019)

Dietary Sodium

High intake of sodium in diet has shown a marked increase in arterial blood pressure, urine albumin, and cardiovascular transience in the public. Increased sodium intake in ADPKD patients results in stimulation of vasopressin secretion which leads to fluid retention and arterial hypertension. Studies in patients have shown decreased eGFR due to high levels of sodium.

Complementary Therapies

Complementary therapies are a different approach to treat the diseases or provide relief from its symptoms to mainstream medicine. These include herbal medicine, ayurveda, homeopathy, yoga and acupuncture etc. They can be given alongside conventional therapies or alone also.

Ayurveda

Ayurveda is one of the oldest forms of treatment or healing system which includes many plant parts and organic material which originated in India around 5000 years ago. Ayurveda involves restoration of body balance by practicing lifestyle management, yoga, herbal medicine and massages. According to ayurveda, the normal functioning of kidneys are maintained by balance in between dosha; vata, pitta, and kapha and if imbalance occurs in one of them it leads to dosha srotas dushti (transport channels) which results in granthi (cyst) formation. ADPKD can be prevented through ayurveda by the management of following activities: body weight management, yoga, kultha pulse in diet, more fluid intake and avoid eating vegetables like tomatoes, spinach, sweet potatoes. Different ayurvedic herbs and drugs have shown a remarkable therapeutics effect in regeneration and long survival of kidneys. Ayurvedic drugs which are used in treatment are: 1.shatvari (Asparagus racemosus)- it is used as diuretic and helps in preventing urinary tract infection. It has shown rejuvenating properties and also found in inhibition of cysts formation. 2. Punarnava (Boerhavia diffusa)- it helps in reduction of creatinine level and improves renal and cardiac function. 3. Pashanabheda (Bergenia ciliata)- it helps in breaking kidney stones and also acts as diuretic. It helps in maintaining diabetes level by reducing the amount of blood sugar level and maintains blood pressure. 4. Bhumi amla (Phyllanthus niruri)- it is also known as ‘dukung anak’. It helps in controlling high blood pressure and sugar levels in the body. It also acts as diuretic and helps in removing kidney stones.A clinical trial of CRF(Chronic Renal Failure) was done in 100 patients at PD Patel Ayurveda Hospital, Naidad. Patients were administered with a daily dose Nirubha basti of Punarnavadi kvatha with oral medications such as Gokshuradi guggulu (combined preparation of Gokshura, Guggulu, Triphala, Trikatu and Musta) , Rasayana churna for a time period of one month. It was observed that serum creatinine level, urine albumin and blood urea level were reduced. (Patel M et al., 2011)

Herbal Medicine

Herbal medicine includes plant parts to treat a disease and maintain quality of life. They are sold in different dosage forms such as capsules, tea extracts, powders, tablets, oils. They usually are less harmful but can cause allergic reactions

(Dong Z, Sun Y, Wei G, Li S, Zhao Z. (2019). Nutraceuticals such as herbal medicine have shown remarkable effects in multiple diseases such as diabetes, cardiac, brain, cancer and renal. Many researches and studies have shown herbal medicine such as ginkgolide B, G. lucidum triterpenoids, triptolide and Sparganum stoloniferum to be effective in prevention of progression of cysts growth and ADPKD (Shao G et al., 2021). Cordyceps sinensis, chinese caterpillar fungus is a herbal medicine used to treat multiple diseases such as pulmonary, cardiovascular, renal and hyperlipidemia. Studies have demonstrated positive therapeutic effects on halting of mesangial proliferation and retarding the accumulation of extracellular matrix in the renal cortex and fibrosis of renal interstitial cells (Dong Z, Sun Y, Wei G, Li S, Zhao Z. (2019)

Homeopathy

Homeopathy is the branch of medical science which believes that the body cures itself. Homeopathy medicines cure the symptoms causing the disease. They activate the body's immune system to fight against the diseases causing pathogens. Homeopathic medicines can be plant extract or mineral ions or non harmful toxins. Homeopathy treatment is ideal for those patients which have early stage renal disease with signs of renal failure. Some of homeopathic medicines used to treat ADPKD symptoms and show effectiveness are as follows: Aconite, Apis mellifica, Apocynum, Aresenicum, Belladonna and Mercurius corrosivus. A study on Croton tiglium shows improvement in two patients of ADPKD.

Yoga

Yoga includes a set of exercises and poses or postures associated with specific breathing techniques and meditation. Yoga provides a complete balance between mental and physical health. It is the oldest practice of india. Kidney diseases are associated with hypertension, diabetes, frequent urination and pain in the abdominal region. According to a study conducted on CKD patients to show the effects of yoga in 6 months. 54 patients were divided into 2 groups; yoga group and control group. Yoga groups were assigned with yoga asanas (Tadasana Urdhva Hastasana, Uttanasana, Ardha Matsyendrasana and Pranayama (Pandey RK et al., 2017). For 5 days in a week for 40-60 min/ day. Regular monitoring of blood pressure, renal function, need of dialysis and quality of life indicators was done. It was found that there was a significant decline in the blood pressure, blood urea and serum creatinine levels in the yoga group and control group was observed to have a rise in blood pressure, destruction of renal function and poor quality of life.

Acupuncture

Acupuncture is the oldest chinese medical technique which stimulates regulation of the sympathetic nervous system and activates bioactive chemicals and hence, provides relief from pain. For renal-related disease patients, acupuncture has shown improvement in renal function, controls rise in blood pressure, relieves pain and insomnia (Xiong Wei., 2018). Recent studies have shown use of sham acupuncture is effective in improvement of chronic pain in the back. Imaging techniques such as MRI have shown that superficial and deep needling in acupuncture points provoke the same blood oxygen level-dependent response.

Nanoscience and stem cell therapies in ADPKD

Stem cells are well known for their ability to differentiate to any different other type of functional cells and regeneration. This ability has brought wide application of stem cells in curing disease such as immunotherapies, cardiac, renal, hepatic. Rapid increase in use of stem cells in models of acute kidney injury (AKI) and chronic kidney disease (CKD) shows the therapeutic potential of stem cells in repairing renal function. Induced pluripotent stem cells are widely used stem cells for producing new renal tissue for

transplantation and as a replacement for renal replacement therapies with no use of immunosuppression. Many in vitro models show the generation of different renal organoids from stem cells. A study done by Takasato et al proposed a protocol persuading human induced pluripotent stem cells (hiPSCs) to give rise to multicellular renal organoid inside which nephrons are connected with collecting duct adjoined by renal interstitial cells and an endothelial matrix. It was also observed that renal organoids responded to neurotoxicants to undergo apoptosis. Scaffolds have become a major tool in clinical conversation due to their property of biocompatibility, cell adhesion, proliferation, cell differentiation and they can be easily produced from rats or human kidneys. 3D culture has given supportive evidence for use of stem cells as renal replacement therapy (Liu D et al., 2020). Ciampo et al in 2019 successfully reproduce acellular kidney scaffolds in rats using the hiPSC- derived endothelial cells, which later results in formation of vessel-like renal structure (Ciampi et al., 2019). Till date no significant clinical evidence has been found to use hiPSC-derived renal organoids but they are helpful in understanding the pathophysiology and genetic mutations of kidney disease. Gene editing techniques like CRISP/Cas9 are used to correct the infective mutation caused by the inherited kidney disease in the iPSC (Liu D et al., 2020).

Nanoscience

Nanoscience includes the use of small sized particles ranging from 1-100nm called nanoparticles. Medical nanotechnology consists of nanoparticles which are used in the designing, manufacture and application of therapeutic drugs and medical devices such as imaging or diagnosis purposes. Many researchers have shown the capability of nanoparticles to be used for diagnosis and therapeutic purpose in the CKD. Nanoparticles provide more precise and accurate data about the renal morphology and physiology and pharmacology of the targeted drug. The most important entities to detect early stages and progression of disease involve specific markers. But current diagnostic methods have certain limitations and precise data about the stages and morphology of the kidney is not gained. PKD1 SNP detection method was tested in exon 29 of feline serum and urine vs large genomic sequences and duplication sites and it was found that this was effective, quick in processing large quantities of genomic data (Potts J et al., 2017).

Bioengineered kidneys: By the help of nanotechnology, artificially designed kidney filters are implanted surgically into the patient's body which minimes that the need for renal transplantation. A small chip-sized filtration membrane that functions as glomerular filtration membrane is implanted into the patients and is being developed by venderbeit Medical Centre at University of California (San Francisco Campus). This combines the use of nano and microtechnologies. The chip sized implantable kidney consists of 15 nanotechnological microchips stacked together in a plastic chamber and viable kidney cells. Preclinical and clinical data are needed to verify the safety and efficacy of the device for human use (Soriano M et al., 2018).

Conclusions

Different technologies are advancing in various fields of medical science and with that emerges the chances of having more effective medications and therapies for diseases. Although different drugs such as tolvaptan and somatostatin analogue are being tested to find more advanced treatment in the PKD, PKD still requires more research in the pathogenesis Integrative approaches of treatment can provide collective positive effects on the signs and symptoms of disease. Improvement in the screening and diagnostic methods of ADPKD has helped the nephrologist in early detection and more chances of long survival. Currently, new researchers are going to find biomarkers and devices which can detect the early stages of diseases. (Times New Roman, 10 pt, Tab 0.8 cm)

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