Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(4s), 10-15 | ISSN:2251-6727

Long-Term Renal Outcomes in Patients with Autosomal Dominant Polycystic Kidney Disease

[1]Dr. Nitin N. Jadhav, [2]Dr. Chinthakuntla Saketh Reddy, [3]Dr. Abhieet Patil, [4]Dr. Makarand Mane

[1]Department of Medicine, Krishna Institute of Medical Sciences,Krishna Vishwa Vidyapeeth, Karad, Maharashtra,

[2]Department of Medicine,Krishna Institute of Medical Sciences, Krishna Vishwa Vidyapeeth, Karad, Maharashtra (Correspondece)

[3]Department of Medicine,Krishna Institute of Medical Sciences, Krishna Vishwa Vidyapeeth, Karad, Maharashtra

[4]Department of Medicine, Krishna Institute of Medical Sciences,Krishna Vishwa Vidyapeeth, Karad, Maharashtra,

KEYWORDS

Autosomal Dominant Polycystic Kidney Disease, long-term outcomes, renal function, end-stage renal disease, clinical study

ABSTRACT:

Introduction: A common hereditary renal illness called autosomal dominant polycystic kidney disease (ADPKD) is characterised by the development of kidney cysts. Our study focused on the deterioration in renal function and the emergence of end-stage renal disease (ESRD) in order to examine the long-term renal outcomes in ADPKD patients. The great clinical importance of ADPKD, the genetic foundation of the disease, and the requirement to monitor disease progression over an extended period of time are the driving forces for this investigation.

Methods: Over a 10-year period, we observed 48 ADPKD patients with genetic confirmation in a cohort research. Clinical information was gathered at baseline and on a regular basis, including demographics, medical history, and laboratory values. Renal imaging was carried out to track cyst growth and renal volume, and estimated glomerular filtration rate (eGFR) was used to evaluate renal function. The annual rate of eGFR fall was the main finding, and the emergence of ESRD was the secondary finding.

Results: With a mean annual fall of 1.54 mL/min across the ten-year follow-up, the mean eGFR considerably decreased. ESRD occurred in a sizable majority of patients (70.6%). The clinical burden of ADPKD and the requirement for efficient therapeutic strategies are highlighted by these results, which are in line with earlier research.

Conclusion: The findings highlight the persistent nature of ADPKD and emphasise the therapeutic necessity of ongoing surveillance and successful therapies to slow the loss of renal function. In order to enhance patient outcomes and lessen the burden of ESRD, more research is required to evaluate these therapies and explore personalised therapy techniques for ADPKD patients.

INTRODUCTION

Due to its high incidence and potential for life-threatening complications, autosomal dominant polycystic kidney disease (ADPKD) is a genetic illness of the kidneys that poses a substantial clinical challenge. This introduction seeks to offer a thorough overview of ADPKD, highlighting its clinical implications, genetic background, and the justification for carrying out a study to look into long-term renal outcomes.

Aspects of epidemiology and clinical relevance:

The most common hereditary kidney illness, ADPKD, affects people from all ethnic origins and is thought to occur in between 1 in 400 and 1 in 1,000 live births [1]. The development of fluid-filled cysts inside the renal parenchyma, which progressively expand, replacing healthy kidney tissue, and causing a wide range of consequences, is the disease's hallmark. Despite the fact that ADPKD is essentially a renal condition, it has been linked to extrarenal symptoms such as hepatic cysts, cardiovascular problems, and intracranial aneurysms [2, 3].

The varied clinical course of ADPKD is one of its distinguishing characteristics. Even within the same family, the start and rate of disease progression might differ significantly among affected people, complicating

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JCHR (2023) 13(4s), 10-15 | ISSN:2251-6727

clinical care and the prognosis. The most severe result of ADPKD is ESRD, which requires renal replacement treatment and imposes significant health and financial difficulties [4]. Therefore, it is crucial to comprehend the long-term renal outcomes in ADPKD in order to enhance patient care, direct clinical decision-making, and assess the effectiveness of novel treatment strategies.

Genetic Basis: PKD1 and PKD2 gene mutations account for the majority of instances of ADPKD, which is primarily a monogenic illness [5]. These genes produce the integral membrane proteins polycystin-1 and polycystin-2, which are expressed in renal tubules. A calcium channel formed by the interaction of polycystin-1 and polycystin-2 is involved in a number of cellular processes, such as cell adhesion, differentiation, and fluid flow sensing in the renal tubules [6, 7]. Approximately 85% of instances of ADPKD are caused by PKD1 mutations, while 15% are caused by PKD2 mutations [8].

The observed phenotypic diversity is a result of the genetic heterogeneity of ADPKD, with PKD1 mutations typically being linked to a more severe disease progression and an earlier start of symptoms than PKD2 mutations. Even though the genetics of ADPKD have been well explained, research is still ongoing to better understand how genotype and phenotype relate to one another. Understanding the underlying genetics of ADPKD has made predictive genetic testing for those who are at risk possible, enabling early detection and preventive therapy.

In light of these factors, our prospective study seeks to advance our understanding of ADPKD by meticulously charting the trajectory of ESRD development and renal function deterioration over an extended period of time in a well-characterized cohort of ADPKD patients. We hope that this study will be helpful in understanding how ADPKD develops over time, informing clinical practise, and possibly identifying new therapeutic strategies for this difficult condition.

METHODOLOGY

Design of the Study and Participants:

To examine the long-term renal outcomes in patients with autosomal dominant polycystic kidney disease (ADPKD), we undertook current cohort research. A tertiary care facility hosted the study. The institutional review board granted its ethical approval, and each participant signed a written informed consent form.

Based on molecular genetic testing that revealed mutations in the PKD1 or PKD2 genes, the study comprised 48 patients with genetically proven ADPKD. A tertiary care facility's outpatient nephrology clinic was used to find participants, and they were tracked for an average of 10 years. Age >18 years and the existence of genetically proven ADPKD were inclusion criteria. Other severe renal or systemic disorders that could independently influence renal function were among the exclusion criteria.

Clinical and demographic data were gathered at baseline and then on a frequent basis during the study period. Age, gender, race, family history of ADPKD, and concomitant diseases such diabetes mellitus and hypertension were all included in the baseline data. The Modification of Diet in Renal Disease (MDRD) equation was used to produce the estimated glomerular filtration rate (eGFR), which was used to evaluate renal function.

To assess cystic load and renal volume, imaging procedures comprising renal ultrasonography and magnetic resonance imaging (MRI) were carried out. An initial radiological evaluation was performed, and it was then done again at regular intervals. The ellipsoid formula was used to compute renal volume after accounting for height. The quantity and size of cysts were also noted.

Measures of Results:

The change in eGFR over the course of the trial was the main outcome indicator. To measure the development of renal impairment, we estimated the annual rate of eGFR fall. The development of end-stage renal disease (ESRD), which is defined as the requirement for renal replacement therapy, including hemodialysis or kidney transplantation, was the secondary outcome.

Patient features: Continuous variables were expressed as means with standard deviations or medians with interquartile ranges, as applicable, and descriptive statistics were employed to summarise patient features. Proportions served as a concise summary of categorical variables.

To evaluate the evolution of eGFR over time, we applied linear regression models. The slope of the linear regression line for each participant was used to compute the annual rate of eGFR reduction. The progression of

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JCHR (2023) 13(4s), 10-15 | ISSN:2251-6727

ESRD was evaluated using survival analysis methods such log-rank tests and Kaplan-Meier survival curves.
To investigate potential relationships between baseline variables and renal outcomes, subgroup analyses were carried out. Regression models with many variables were used to account for potential confounding variables.
Participants were followed up with on a regular basis in the outpatient clinic, and data collection was overseen by qualified study staff. Regular audits and cross-validation with electronic medical records were used to assure the accuracy and completeness of the data.

RESULTS

Table 1: Baseline Characteristics of Study Participants:

This table provides a snapshot of the demographic and clinical characteristics of the study participants at the beginning of the study. It includes information about age, gender, family history of ADPKD, hypertension, diabetes mellitus, presence of PKD1 mutations, and baseline eGFR.

- **Age (years):** The mean age of the participants was 42.5 years, with a standard deviation of 7.2. This indicates that the study population is relatively young and falls within a specific age range.
- **Gender (Male/Female):** The gender distribution is represented as 28 males and 20 females, showing a nearly equal split between the two genders within the study.
- **Family History of ADPKD (Yes/No):** Among the participants, 34 individuals had a family history of ADPKD, while 14 did not. This information is crucial as ADPKD is a genetic condition, and family history can influence disease severity.
- **Hypertension (Yes/No):** The majority of participants, 41 individuals, had hypertension, while only 9 did not. Hypertension is a common comorbidity in ADPKD and is relevant to the study's outcomes.
- **Diabetes Mellitus (Yes/No):** Eight participants had diabetes mellitus, while 40 did not. The presence of diabetes can be an important factor in understanding the overall health of the ADPKD population.
- **PKD1 Mutation (Yes/No):** 25 participants had PKD1 mutations, while 23 did not. The presence of PKD1 mutations is of interest as they are associated with a more severe form of ADPKD.
- **Baseline eGFR (mL/min):** The baseline eGFR (estimated glomerular filtration rate) was 63.2 mL/min, with a standard deviation of 12.4. This provides information about the initial renal function of the study population.

Table 2: Changes in eGFR Over Time:

This table tracks the mean eGFR values over ten years, showing how renal function changes during the study period.

- **Baseline:** At the study's start, the mean eGFR was 63.2 mL/min, with a standard deviation of 12.4. This is the reference point for assessing subsequent changes.
- **Year 1 to Year 10:** Over the ten-year period, eGFR values progressively declined, with a consistent decrease each year. The declining eGFR values highlight the natural course of ADPKD, where renal function tends to deteriorate over time.

Table 3: Development of End-Stage Renal Disease (ESRD):

This table presents the cumulative incidence of ESRD over the ten-year follow-up period, providing an understanding of the risk of ESRD in ADPKD patients.

- **Year 1 to Year 10:** The cumulative incidence of ESRD steadily increases over the years. By Year 10, 70.6% of the study participants had developed ESRD. This highlights the substantial risk of progression to ESRD in ADPKD patients, underlining the clinical significance of the disease.

Table 1: Baseline Characteristics of Study Participants

Characteristic	Mean (SD) or N (%)
Age (years)	42.5 (7.2)
Gender (Male/Female)	28/20
Family History of ADPKD (Yes/No)	34/14
Hypertension (Yes/No)	41/09
Diabetes Mellitus (Yes/No)	8/40

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JCHR (2023) 13(4s), 10-15 | ISSN:2251-6727

PKD1 Mutation (Yes/No)	25/23
Baseline eGFR (mL/min)	63.2 (12.4)

Table 2: Changes in eGFR Over Time

Year	Mean eGFR (mL/min)	Standard Deviation
Baseline	63.2	12.4
Year 1	59.7	11.9
Year 2	58.2	11.7
Year 3	56.8	11.5
Year 4	55.3	11.2
Year 5	54.0	11.0
Year 6	52.7	10.8
Year 7	51.4	10.6
Year 8	50.2	10.4
Year 9	49.0	10.2
Year 10	47.8	10.0

Table 3: Development of End-Stage Renal Disease (ESRD)

Year	Cumulative Incidence of ESRD (%)
Year 1	2.5
Year 2	5.3
Year 3	9.7
Year 4	15.2
Year 5	22.0
Year 6	30.0
Year 7	38.9
Year 8	48.8
Year 9	59.3
Year 10	70.6

DISCUSSION

The findings of the current study, which looked at long-term renal outcomes in people with Autosomal Dominant Polycystic Kidney Disease (ADPKD), shed important light on the physiology of this intricate genetic condition.

Renal Function drop: Over the course of the ten-year observation period, our study found a significant drop in estimated glomerular filtration rate (eGFR), with an annual decline rate of 1.54 mL/min. The idea that ADPKD is characterised by an ongoing loss in kidney function over time is supported by the increasing worsening in renal function, which is consistent with earlier studies [10]. Notably, our findings concur with those of Higashihara et al., who observed a reduction in eGFR in their study [5]. The persistent indication of a significant eGFR drop in ADPKD highlights the tenaciousness of this illness and its negative effects on patient quality of life.

Development of End-Stage Renal Disease (ESRD): Our study showed that ADPKD patients had a high chance of acquiring ESRD. Renal replacement therapy was required by Year 10 because 70.6% of patients had advanced to ESRD. This high rate of ESRD is consistent with earlier research, which suggests that a sizeable portion of ADPKD patients would eventually need dialysis or a kidney transplant [11]. These results highlight the clinical burden of ADPKD and the critical requirement for treatment approaches to halt the development to ESRD.

Clinical Management Implications: The findings of our study have important clinical management implications for ADPKD. The high prevalence of ESRD

and the observed eGFR reduction point to patients with ADPKD having a significant risk of renal impairment and its related consequences. With a family history of ESRD and PKD1 mutations being linked to a more severe disease course, clinicians should be proactive in monitoring renal function in ADPKD patients.

According to our study, ADPKD patients frequently had hypertension, and controlling this condition is essential to halting the disease's progression. It is crucial to keep blood pressure under control and within prescribed goal ranges, which is frequently accomplished with renin-angiotensin-aldosterone system (RAAS) inhibitors. These drugs can lessen proteinuria and maintain renal function, which will lead to better results [12].

Our findings also emphasise the value of informing patients about lifestyle changes, such as a low-salt diet, which can help regulate blood pressure. Through genetic testing and clinical evaluation, it is possible to identify people who are at high risk of developing ESRD early on, which can inform treatment decisions and possibly enable earlier therapies.

Literature Comparative

It is useful to contrast our findings with those of earlier studies in order to put them into perspective. A slower reduction in eGFR was observed in the tolvaptan group compared to the placebo group in the TEMPO study, a significant clinical trial examining the effectiveness of tolvaptan in delaying the course of ADPKD [8]. This discovery emphasises the promise of disease-modifying treatments for ADPKD. Despite not assessing any particular therapies, our study affirms the necessity of such interventions. It is necessary to do additional research, possibly in the form of randomised controlled trials, to confirm the long-term efficacy and safety of novel medicines.

A slower rate of eGFR decline was observed in the treatment group compared to the placebo group in the REPRISE study, which evaluated the effects of tolvaptan in later-stage ADPKD [9]. Although tolvaptan is not explicitly evaluated in our investigation, the REPRISE trial's outcomes are encouraging and support the need for disease-modifying therapies in ADPKD.

mTOR inhibitors and somatostatin analogues, which target pathways implicated in cyst development and fibrosis, are two additional treatment modalities being researched [13–15]. Clinicians must be guided by comparative analyses of different therapies in order to select the best intervention for each patient.

CONCLUSION

A significant loss in renal function over time, coupled with a high prevalence of ESRD, is strongly supported by the current investigation on long-term renal outcomes in ADPKD patients. These results highlight the clinical importance of ADPKD and the critical requirement for treatment approaches to halt the disease's progression.

The findings of our investigation are consistent with earlier studies, highlighting the clinical burden of ADPKD as being characterised by a steady deterioration in renal function. Although our study did not test therapeutic approaches directly, the comparative literature suggests that new drugs like tolvaptan may be able to slow the progression of disease. In order to explore personalised treatment options for ADPKD patients and to confirm the long-term efficacy and safety of these therapies, more research is required. The ultimate objective is to optimise patient outcomes, improve quality of life, and lessen the burden of ESRD in people with ADPKD.

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