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Age of end-stage kidney disease development in autosomal dominant polycystic kidney disease

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ABSTRACT

Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most frequent monogenic disease of the kidney, leading to end-stage kidney disease (ESKD) in a large proportion of patients. This work aimed to assess the age of ESKD development in ADPKD patients in consecutive decades. It was assumed that parallelly to improved advancement and accessibility to diagnostics and therapy, the clinical efficiency enhances, what evinces in increased age in which ESKD occurs.

Material and methods: Retrospective analysis of data of ADPKD patients treated in the study centre. No patient was treated with tolvaptan before ESKD since tolvaptan was not available in Poland at that time.

Results: 139 patients were included and divided into 3 groups: group I (ESKD before the year 2006), group II (ESKD between 2006 and 2015) and group III (ESKD in 2016 or later). The mean age of ESKD development was 43.47, 52.65, and 55.23 in groups I, II, and III, respectively. There were statistically significant differences in the age of ESKD between groups I and III ($p = 0.0086$), but not between groups I and II, nor II and III.

Conclusions: The age of ESKD development in the course of ADPKD was higher in the last decade compared to the turn of the last century. This effect was not associated with tolvaptan, while patients analysed in the present study were not treated with it. That suggests that even without tolvaptan, efforts towards modification of lifestyle, diet, and treatment of concomitant diseases may delay ESKD development in ADPKD.

Keywords: age, autosomal dominant polycystic kidney disease, end-stage kidney disease

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Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most frequent monogenic disease of the kidney, affecting approximately 1 in every 1000 people. ADPKD is caused by a mutation in PKD1 in type 1, or PKD2 gene in type 2 of the disease, leading to disturbed structure and function of their protein products, polycystin-1 (PC-1), or polycystin-2 (PC-2), respectively. Type 1 of the disease is more prevalent (approximately 85% of cases) compared to type 2. ADPKD leads to end-stage kidney disease (ESKD) in a large proportion of patients. As a result, ADPKD is the fourth most common reason for the initiation of renal replacement therapy (RRT) [1, 2]. ESKD in a course of ADPKD occurs in adulthood, and the median age of its development depends on the mutation type; ESKD occurs in the sixth decade of life in ADPKD type 1 and the eighth decade of life in type 2 of the disease [3].

Currently, the only approved therapy to slow the progression of chronic kidney disease (CKD) secondary to ADPKD is tolvaptan [4]. However, its safety profile limits its usefulness, and many patients refuse to be treated with tolvaptan due to the risk of side effects such as nycturia and polyuria, the need for very high fluid intake, and the risk of liver damage [5]. Therefore, the question arises whether tolvaptan-free management leads to any clinical benefits.

This work aimed to assess the age of ESKD development in ADPKD patients across consecutive decades. It was assumed that parallelly to improved advancement and accessibility to diagnostics and therapy, the clinical efficiency enhances, what evinces in increased age at which ESKD occurs.

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Table 1. Characteristics of groups

Characteristic	Group I (ESKD before 2006)	Group II (ESKD 2006-2015)	Group III (ESKD in 2016 or later)	p
N	15	68	56	
Men/women, n(%)	8 (53%)/7 (47%)	37 (54%)/31 (46%)	28 (50%)/28 (50%)	p = 0.8851
Mean age at ESKD, years (SD)	43.47 (7.92)	52.65 (9.71)	55.23 (12.72)	**p = 0.0014**

ESKD — end-stage kidney disease; SD — standard deviation

Table 2. Comparison of age at ESKD between men and women

Group	Men	Women	p
All patients, median age in years (IQR, range, n)	50 (14, 24–77, 73)	55.5 (12, 32–94, 66)	p = 0.023
Group I, median age in years (IQR, range, n)	41 (7, 24–46, 8)	46 (13, 38–57, 7)	p = 0.064
Group II, median age in years (IQR, range, n)	51 (10, 29–75, 37)	56 (11, 32–76, 31)	p = 0.116
Group III, median age in years (IQR, range, n)	53.5 (19.5, 28–77, 28)	56.5 (16.5, 35–94, 28)	p = 0.279

ESKD — end-stage kidney disease; IQR — interquartile range; n — number of cases in the group

Material and methods

It was a retrospective analysis of data of ADPKD patients treated in the outpatient department of the former Department of the Immunology, Transplantology, and Internal Diseases of the Medical University of Warsaw, Poland. Adults diagnosed with ADPKD, who developed ESKD, were included in the present analysis. No patient was treated with tolvaptan before ESKD since tolvaptan was not available in Poland at that time. The following data were harvested from case records: race, sex, year of birth, and year of initiation of RRT. The time of ESKD development was considered identical to the time of initiation of RRT. Afterwards, the age of ESKD development was calculated for each patient. Then, patients were divided into 3 groups: group I (ESKD before the year 2006), group II (ESKD between 2006 and 2015) and group III (ESKD in 2016 or later).

Statistical analysis was performed using Statistica 13.3 (StatSoft, Tulsa, OK, USA). The normality of data distribution was assessed with the Shapiro-Wilk test. The Chi^2 test was used for comparison of patients' sex between groups. Comparison of age at ESKD onset between groups was performed using ANOVA, followed by post-hoc Tukey's Honest Significant Difference (HSD) test. Results of the above tests are presented as means and standard deviations. For the comparison of age at ESKD between men and women, the U Mann-Whitney test was used, and results were presented as medians, interquartile ranges (IQR), and ranges. Results with $p < 0.05$ were considered statistically significant.

The study was conducted according to the principles of the Declaration of Helsinki. The local Ethics Committee was informed about the study. Due to the character of the study, patients' written informed consents were redundant.

Results

One hundred and thirty-nine patients, including 73 (53%) men and 66 (47%) women, fulfilled the inclusion criteria and were included in the analysis. All patients were Caucasians. The characteristics of the groups are presented in Table 1. There were no statistically significant differences in sex distribution between groups.

Observed were statistically significant differences in the age of ESKD between groups (Table 1). Tukey's HSD test showed that there were statistically significant differences in the age of ESKD between groups I and III ($p = 0.0086$), but not between groups I and II, nor II and III.

A comparison of age at ESKD between men and women is presented in Table 2. It was higher in women compared to men, but statistical significance was achieved only for all patients included, but not for particular groups.

Discussion

Before tolvaptan became available, many patients and even physicians believed that nothing could be done to slow the progression of CKD in ADPKD. As a result, numerous patients visited nephrologists just

before initiation of RRT. The results show that these beliefs were false. According to the present results, the mean age of ESKD in a course of ADPKD increased with time, and in those who developed ESKD in 2016 or later, the mean age of ESKD is over 11 years higher compared to patients who developed ESKD before the year 2006 (Table1).

All patients included in the study were Caucasians, which may be considered a weakness of this analysis, as it does not reflect the situation in other populations. However, the Polish population contains a scant per cent of other races. On the other hand, the lack of statistically significant differences in sex distribution between groups should be considered a strength of this study, while the male sex is associated with faster CKD progression in ADPKD compared to the female sex [6]. The present results are in accordance with this opinion; age at ESKD was higher in women compared to men when all patients included in the study were analysed (Table 2).

According to current guidelines, patients with ADPKD require complex management including diet, high fluid intake, lifestyle modifications, as well as medical treatment of hypertension, and/or lipid disturbances [1, 2]. The present results represent indirect confirmation that nephrological care in the pre-ESKD period, combined with adherence to these recommendations is effective, while it may be suspected that patients living with ADPKD in the XXI century have better access to diagnostics and treatment compared to those living with the disease in the XX century.

The present results should also be considered positive news for a quite large group of patients who cannot be treated with tolvaptan due to its side effects or the impossibility of reconciling treatment with professional duties [5]; adherence to nephrological recommendations extend RRT-free life even without tolvaptan therapy.

However, the limitations of this study need to be acknowledged. First, it was a retrospective study, in which data were obtained from available case records. It is possible that some patients who developed ESKD before the year 2006 and were older at the time of ESKD, have already died. Therefore, they could fall out of this analysis due to the unavailable case records. Second, the groups were relatively small. Third, there was no data on mutations responsible for ADPKD development in included patients. As mentioned above, the type of mutation causing ADPKD influences the patient's outcome [3]. However, in the authors' opinion, there is no reason to think that the distribution of different types of mutations leading to ADPKD was differentiated between the groups. Fourth, this analysis omitted data on body mass index, concomitant diseases, e.g. hypertension, dyslipidaemia, diabetes, urologic incidents, and medical therapy before the moment of ESKD. They could be of importance, while multimorbidity and polypharmacy are common in ADPKD patients; according to a previous study [7], the median number of chronic diseases in ADPKD patients who did not require RRT was 5, and in 38% of them at least 5 medications daily were used [7]. Both concomitant disorders and medicines used could influence the course of CKD, and the time of development of ESKD in the analysed group, however, data on these factors were incomplete, and that is why it was decided not to analyse them.

To conclude, the age of ESKD development in the course of ADPKD was higher in the last decade compared to the turn of the last century. This effect was not associated with tolvaptan, while patients analysed in the present study were not treated with it. That suggests that even in the absence of tolvaptan therapy, efforts towards modification of lifestyle, and diet, as well as treatment of concomitant diseases are of importance in ADPKD patients and may improve the RRT-free survival.

Article information

Data availability: *Data are available from the corresponding author on demand.*
Ethics statement: *The study was conducted according to the principles of the Declaration of Helsinki. The local Ethics Committee was informed about the study. Due to the character of the study, patients' written informed consents were redundant.*
Author contributions: *AM, data collection and analysis, writing the manuscript, final approval; MN, idea and design of the study, patient selection, data analysis, writing the manuscript, final approval*
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