Health-related quality of life across all stages of autosomal dominant polycystic kidney disease

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ABSTRACT

Background. A limited number of studies have assessed health-related quality of life (HRQoL) in autosomal dominant polycystic kidney disease (ADPKD). Results to date have been conflicting and studies have generally focused on patients with later stages of the disease. This study aimed to assess HRQoL in ADPKD across all stages of the disease, from patients with early chronic kidney disease (CKD) to patients with end-stage renal disease.

Methods. A study involving cross-sectional patient-reported outcomes and retrospective clinical data was undertaken April–December 2014 in Denmark, Finland, Norway and Sweden. Patients were enrolled into four mutually exclusive stages of the disease: CKD stages 1–3; CKD stages 4–5; transplant recipients; and dialysis patients.

Results. Overall HRQoL was generally highest in patients with CKD stages 1–3, followed by transplant recipients, patients with CKD stages 4–5; transplant recipients; and dialysis patients.

Conclusions. Later stages of ADPKD are associated with reduced physical health. The value of early treatment interventions that can delay progression of the disease should be considered.

Keywords: ADPKD, chronic kidney disease, patient-reported outcomes, polycystic kidney disease, quality of life

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is a dominantly inherited systemic disease characterized by progressive growth of renal cysts. Recent studies of European populations estimate the prevalence rate in Europe at less than 4 in 10 000 [1, 2].

Kidney volume growth due to progressive cyst formation and expansion precedes functional renal deterioration [as measured by glomerular filtration rate (GFR)] by several decades [3]. Clinical symptoms of renal disease can occur at any age but typically begin in the third or fourth decade of life. The severity of manifestations related to the disease are heterogeneous and well documented to include hypertension, pain, extrarenal cyst formation, intracranial aneurysms, mitral valve prolapse and renal failure [4]. Around 50% of patients require renal replacement therapy due to kidney failure, which typically develops in the fourth to sixth decade of life [3]. It is generally assumed that ADPKD accounts for around 10% of patients who are dependent on renal replacement therapy [5].

No patient-reported outcome measures are available that fully capture the burden of symptoms reported by patients with ADPKD. A recent literature review of patient perspectives of living with ADPKD identified greater patient engagement in pain management, counselling to reduce the burden of ‘genetic guilt’ and specific family planning decision support tools as prioritized health care interventions [6]. The review highlighted that the unpredictable onset of volatile pain had a negative impact on daily living and prevented patients from pursuing long-term life goals.
A handful of studies have assessed general health-related quality of life (HRQoL) in ADPKD. However, results to date have been conflicting and studies have generally focused on patients with later stages of the disease. A study of pre-dialysis patients that used the validated Short Form-36 (SF-36) instrument found no differences in HRQoL compared with the general US population [7]. In addition, a subgroup analysis of patients with established renal insufficiency (20 < GFR < 65 mL/min/1.73 m²) found no differences compared with a renal disease population with similar levels of renal function. Another study using the SF-36 found significantly lower scores for ADPKD patients (49% of whom were on dialysis) compared with the general Japanese population [8]. The study also observed a difference between dialysis and non-dialysis patients in terms of physical health, but not mental health. An analysis of data from the HALT-PKD trial showed that pain was common in patients with early disease (GFR > 60 mL/min/1.73 m²) [9]. Pain was however not related to height-adjusted total kidney volume except at levels greater than 1000 mL/m². All SF-36 health domain scales, stratified by estimated GFR (eGFR), were comparable to the age-matched general US population. Finally, a recent cross-sectional study of ADPKD patients not on dialysis in the UK revealed a high prevalence of reduced quality of life and increased psychosocial risk with lower eGFR and increased kidney size [10].

We present the first study of HRQoL in ADPKD that includes all stages of the disease, from patients with early chronic kidney disease (CKD) to patients on dialysis and transplant recipients.

**MATERIALS AND METHODS**

**Study design**

We conducted a multi-site study involving cross-sectional patient-reported outcomes (PROs) and retrospective clinical data. Nine nephrology clinics participated in total; four in Denmark, one in Finland, two in Norway and two in Sweden. Between April and December 2014, we enrolled non-randomized samples of subjects from each clinic. Resource constraints and the rarity of the disease limited the recruitment target to 200 patients evenly distributed across the stages of the disease. Patients were recruited by phone or during a routine visit. Participation did not result in a change in the standard of care.

Ethics approvals for the study were granted by the Helsinki University Hospital Ethical Review Board, the Regional Committee of Medical and Health Research Ethics in Oslo (REC South East) and the Regional Ethical Review Board in Stockholm. While the study was reported to the Danish Health and Medicines Authority, formal ethics approval was not required due to the non-interventional design. The study protocol and consent procedures were also reviewed and approved by the clinics.

**Sample and inclusion criteria**

To be able to capture the full patient pathway, subjects were enrolled into four mutually exclusive stages of the disease using a hierarchical approach:

(i) maintenance dialysis: patients currently on dialysis with or without transplanted kidney

(ii) transplant recipients: patients with a functioning transplanted kidney, currently not on dialysis

(iii) CKD stages 4–5: patients not currently on dialysis/no previous transplant (eGFR < 30 mL/min/1.73 m²)

(iv) CKD stages 1–3: patients not currently on dialysis/no previous transplant (eGFR ≥ 30 mL/min/1.73 m²)

The most recent eGFR value, as calculated by each respective laboratory, was used to establish CKD stage at the enrolment date. Eligible subjects were required to:

- be 18 years of age or older
- have been managed for ADPKD at the clinic during the past 12 months
- have been diagnosed with ADPKD at least 12 months ago
- have an eGFR laboratory result available in the past 12 months (not applicable if patient was on dialysis)
- not have been involved in an investigational clinical trial that resulted in a change in the standard of care received in the past 12 months
- if on maintenance dialysis, have initiated dialysis at least 6 months ago
- if having a working kidney transplant, have had the date of transplant at least 6 months ago
- provide written informed consent of participation

**Study questionnaires**

Prior to recruitment of patients all staff at participating clinics received training in study procedures to ensure standardization of patient enrolment and data collection. Data were extracted from medical charts using a case report form (CRF) and complemented with self-administered questionnaires to collect PROs.

Patients’ HRQoL was primarily assessed using the EuroQol EQ-5D-3L due to its applicability across a wide range of health conditions and common use in health economic evaluations. Additional information was obtained via the SF-12v2 instrument due to its ability to distinguish between mental and physical health, while keeping response burden to a minimum. The EQ-5D-3L comprises five questions and a visual analogue scale [11]. The five questions correspond to five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), each of which can take one of three responses (no problems, some problems and extreme problems). In addition to a simple descriptive profile it provides a preference-based summary score of overall HRQoL (index score), with 1 representing perfect health, 0 representing death and <0 representing a health state perceived as worse than death. The EQ-5D also contains a visual analogue scale (VAS) with the end points labelled best imaginable health state at the top (100) and worst imaginable health state at the bottom (0).

The SF-12v2 Health Survey is a shorter alternative to the SF-36v2 Health Survey to measure functional health and well-being from the patient’s point of view. The instrument provides a reliable and valid measure of physical and mental health [12]. Two overall scores, the Physical and Mental Composite Score (PCS and MCS, respectively), in addition to eight health domains, are derived using norm-based scoring algorithms that provide means of 50 and standard deviations (SDs) of 10 in the
general population. The SF-12 provides estimates of means and variances for both summary measures and for all scales that are comparable to the SF-36 [13].

Finally, the Work Productivity and Activity Impairment General Health (WPAI-GH) questionnaire was used in this study to estimate the impact of health problems on regular daily activities [14].

Statistical analyses

Summary statistics were calculated, including means and SDs for continuous variables and frequency distributions for categorical variables. EQ-5D index scores were estimated using the Kruskal–Wallis and χ² test unless otherwise specified. Data management and analysis were performed using Stata 12.1 (StataCorp LP, College Station, TX, USA).

RESULTS

A total of 266 patients were contacted; of these 243 (91%) provided consent to participate in the study. The majority of patients were enrolled in Denmark (n = 118), followed by Sweden (n = 58), Norway (n = 50) and Finland (n = 17). The Modification of Diet in Renal Disease (MDRD) equation was used to estimate GFR in 86% of non-dialysis patients, followed by the Lund-Malmö equation (8%) and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (6%).

Dialysis patients comprised the oldest group, followed by transplant recipients and non-end-stage renal disease (ESRD) patients (Table 1). Mean ages ranged from 52 years in patients with CKD stages 1–3 to 64 years in dialysis patients. Employment rates were highest in the earlier stages of the disease. No differences between the disease stages were seen in sex, body mass index and systolic blood pressure.

Among those on dialysis, 10 patients (16%) had exclusively been on peritoneal dialysis during the past 12 months, while 49 patients (80%) had only received haemodialysis. Fifteen patients (25%) had initiated dialysis in the past year (6–12 months prior to study enrolment date). Among transplant recipients, six patients (10%) had received the transplant in the past year. Transplant patients were significantly younger than dialysis patients at the time of ESRD. Five dialysis patients (8%) had previously received a kidney transplant.

In general, comorbidities were most common among patients on dialysis and with CKD stages 4–5 (Table 2). Activity impairment was highest in dialysis patients (53%). The degree of impairment was lower among transplant recipients and patients with CKD stages 4–5 (30 and 29%, respectively) and lowest in patients with CKD stages 1–3 (17%) (P < 0.0001 for a difference between groups).

Table 1. Patient characteristics

| Patient characteristic | CKD 1–3 (n = 64) | CKD 4–5 (n = 55) | Dialysis (n = 61) | Transplant (n = 63) | P-value |
|------------------------|-----------------|-----------------|------------------|-------------------|--------|
| Sex (female), n (%)    | 12 (49)         | 18 (53)         | 21 (34)          | 24 (38)           | 0.177  |
| Age (years), mean ± SD | 62 ± 13         | 67 ± 12         | 64 ± 10          | 59 ± 10           | <0.0001|
| Currently employed (aged <65 years), n (%) | 80 (51) | 76 (52) | 74 (61) | 59 (90) | 0.0062 |
| eGFR (mL/min/1.73 m²), mean ± SD | 56 ± 21 | 67 ± 13 | 62 ± 31 | 44 ± 17 | <0.0001 |
| BMI (≥30 kg/m²), n (%) | 16 (11)          | 18 (12)         | 16 (25)          | 14 (22)           | 0.7667 |
| SBP (mmHg), mean ± SD | 135 ± 15        | 135 ± 15        | 132 ± 23         | 133 ± 15          | 0.4826 |
| DBP (mmHg), mean ± SD | 80 ± 9          | 80 ± 9          | 71 ± 13          | 79 ± 10           | <0.0001|
| Age at ESRD (years), mean ± SD | 50 ± 11 | 50 ± 11 | 51 ± 11 | 51 ± 11 | 0.6024 |

P-values calculated with χ² test unless otherwise specified.

Table 2. Common comorbidities

| Comorbidities, proportion (%) of patients | CKD 1–3 (n = 64) | CKD 4–5 (n = 55) | Dialysis (n = 61) | Transplant (n = 63) | P-value |
|------------------------------------------|-----------------|-----------------|------------------|-------------------|--------|
| Hypertension                             | 44              | 73              | 84               | 60                | <0.0001|
| Secondary hyperparathyroidism             | 2               | 36              | 39               | 19                | <0.0001|
| Anaemia*                                 | 6               | 20              | 80               | 11                | <0.0001|
| Non-renal cysts                          | 19              | 31              | 39               | 16                | 0.0095 |
| Renal pain*                              | 25              | 20              | 16               | 8                 | 0.0774 |
| Cardiovascular disease*                   | 5               | 9               | 39               | 10                | <0.0001|
| Intracranial aneurysm*                    | 2               | 4               | 10               | 2                 | 0.0932 |

CKD, chronic kidney disease.

P-values calculated with χ² test unless otherwise specified.

*Fisher’s exact test.
Across the study population, a significant proportion of patients reported (some or extreme) problems with pain, as captured in the EQ-5D, ranging from 44% in transplant recipients to 59% in dialysis patients (Table 3). Dialysis patients more frequently reported problems in all five dimensions of the EQ-5D compared with non-dialysis patients. However, no significant differences between stages of the disease seemed present for pain/discomfort and anxiety/depression.

A descriptive representation of the SF-12 scales by stages of the disease revealed heterogeneity in functional health (Table 4, Figure 1). Patients with CKD stages 1–3 and transplant recipients showed less variation compared with other stages of the disease. These patients largely scored above or around average health (the population norm). Patients with CKD stages 4–5 generally reported worse physical health than transplant recipients and patients in earlier stages of CKD, whereas scores on the mental health domains showed less variation. Dialysis patients tended to have worse functional health compared with the other stages of ADPKD and showed the most heterogeneity.

Overall HRQoL, as measured by the EQ-5D and SF-12, was generally highest in patients with CKD stages 1–3 (Table 5). Patients with CKD stages 4–5 had numerically lower scores than transplant recipients on all PROs. Transplant recipients mostly reported a level of quality of life in between patients with CKD stages 1–3 and CKD stages 4–5. Group differences in physical health as captured in the SF-12 PCS largely mirrored those seen for the EQ-5D index scores and the EQ VAS, whereas scores on the mental health domains showed less variation. The mental health scores were also closer to the general population norms compared with the PCS scores. Worst HRQoL was consistently observed in dialysis patients across PROs.

DISCUSSION

This cross-sectional study of 243 patients with ADPKD explored the impact of disease progression on quality of life as captured by validated PRO measures. Overall HRQoL was generally highest in patients with CKD stages 1–3, followed by transplant recipients, patients with CKD stages 4–5 and patients on dialysis. Progressive disease predominately had an impact on physical health, whereas mental health showed less variation between stages of the disease. Dialysis patients consistently reported the worst HRQoL across measurement scales and had impaired activity levels at over 50%. The substantial burden associated with dialysis was also confirmed by high degrees of comorbidity, including patient-reported overall pain, as measured by the EQ-5D and SF-12.

Our study showed that patients with CKD stages 4–5 generally reported worse HRQoL than transplant recipients and patients in earlier stages of CKD. This was true regardless of whether the burden was measured using the EQ-5D index score or the SF-12 physical summary score. The impairment of patients with CKD stages 4–5 was also confirmed by considerably lower mean renal function, as measured by eGFR, compared with transplant recipients (17 and 44 mL/min/1.73 m², respectively). Notably, only around one in four patients with CKD stages 4–5 reported average or above average health status (compared with the general population norm) on the two SF-12 domains general health (GH: 25%) and vitality (VT: 27%). Only dialysis patients scored worse on these health domains (GH: 14%; VT: 19%), while around half of transplant recipients and patients with CKD stages 1–3 had general health and vitality scores on a par with the general population (GH: 43 and 54%, respectively; VT: 49 and 46%, respectively).

Table 3. Problems reported on the five dimensions of EQ-5D

| Problems reported on the EQ-5D, proportion (%) of patients | CKD 1–3 (n = 64) | CKD 4–5 (n = 55) | Dialysis (n = 61) | Transplant (n = 63) | P-value |
|-----------------------------------------------------------|-----------------|-----------------|-----------------|-------------------|---------|
| Mobility                                                  | 8               | 20              | 48              | 22                | <0.0001 |
| Self-care                                                 | 2               | 4               | 18              | 8                 | 0.0037  |
| Usual activities                                           | 16              | 36              | 62              | 32                | <0.0001 |
| Pain/discomfort                                           | 48              | 47              | 59              | 44                | 0.2151  |
| Anxiety/depression                                         | 30              | 31              | 41              | 22                | 0.1204  |

P-values calculated with Fisher’s exact test.

EQ-5D, EuroQol 5 dimension; CKD, chronic kidney disease.

Table 4. Average or above health on the SF-12 profile

| Proportion (%) of patients scoring ≥50 on the SF-12 domains | CKD 1–3 (n = 64) | CKD 4–5 (n = 55) | Dialysis (n = 61) | Transplant (n = 63) | P-value |
|------------------------------------------------------------|-----------------|-----------------|-----------------|-------------------|---------|
| Physical functioning                                       | 68              | 35              | 12              | 41                | <0.0001 |
| Role physical                                              | 62              | 36              | 14              | 40                | <0.0001 |
| Bodily pain                                                | 60              | 49              | 27              | 44                | 0.0030  |
| General health                                             | 54              | 25              | 14              | 43                | <0.0001 |
| Vitality                                                   | 46              | 27              | 19              | 49                | 0.0007  |
| Social functioning                                         | 68              | 69              | 29              | 63                | <0.0001 |
| Role emotional                                             | 71              | 64              | 36              | 62                | 0.0007  |
| Mental health                                              | 62              | 76              | 51              | 70                | 0.0272  |

SF-12, Short Form-12 Health Survey; CKD, chronic kidney disease.

P-values calculated with χ² test unless otherwise specified.

All SF-12 scales are standardized to have a mean of 50 and standard deviation of 10 in the US general population (range: 0–100).
The relatively low rates of renal pain in comparison with patient-reported pain may indicate that physicians underestimate the impact of renal pain in patients with ADPKD. The observed higher prevalence of renal pain in earlier stages of CKD, as captured in the medical charts, could possibly be explained by differences between patient groups in the recording of symptoms by physicians as well as by coping mechanisms of patients.

The prevalence of extra-renal cysts in transplant recipients was relatively low compared with patients with CKD stages 4–5 and dialysis patients. It is possible that this finding could be confounded by age or comorbidity levels. Dialysis patients were in fact older at the time of ESRD compared with transplant recipients (mean age of 59 and 51 years, respectively). Furthermore, patients burdened by extra-renal cysts may be less likely to become transplant candidates.

Previous studies of patients with ADPKD have mainly focused on later stages of the disease and results on the link between progressive disease and quality of life have been conflicting [7–10]. The findings of our study are consistent with a recent UK study, which showed a clinically relevant decline in quality of life scores across eGFR groups [as defined by the minimal clinically important difference (MCID) in the SF-36 of at least 3–5 points] [10]. Using the same MCID definition, since the SF-12 provides comparable estimates to the SF-36 [13], the PCS scores reported in our study were considerably lower compared with the general population norm for all levels of the disease except for CKD stages 1–3.
points between CKD stages 1–3 and 4–5 confirms the considerable loss in quality of life prior to ESRD.

Generic tools such as the SF-36, and by extension the SF-12, have been criticized in the past for not being able to detect clinically important changes in quality of life among patients with ADPKD [7, 10]. While significant differences were detected on the SF-12 PCS in our study, functional mental health as captured by the MCS was similar to the general population for all stages of ADPKD. These results are in line with other studies that did not detect a significant association between mental health and stages of the disease or a difference compared with the general population [7, 8, 10]. There are however ongoing initiatives to address this issue by establishing a new disease-specific instrument that captures the impact of coping with the diagnosis of a genetic disease and the associated psychological burden [10].

Some other limitations should also be noted. As with any observational study, selection bias may be an issue as predominantly patients seeking healthcare were included. Furthermore, we could not use kidney size as a proxy for disease severity since such data are not routinely recorded in clinical practice; in our population only 113 (47%) patients had an available kidney length measure. Finally, a disadvantage of the norm-based scoring of the SF-12 is that the mean health in all countries is not 50. In Sweden and Denmark the mean MCS SF-12 scores have been found to be nearly three points higher than in the USA [13], which may result in an underestimation of the burden of disease in our study.

Our study is, to our knowledge, the first to present HRQoL in a population stratified by all stages of the disease, from early CKD to dialysis and transplantation. The study also provides the first ever Nordic EQ-5D results in ADPKD. Further strengths of this study include the high response rate and the enrolment of patients with physician-confirmed diagnosis of ADPKD.

To summarize, we demonstrated an association between disease progression and reduced physical health. As expected, dialysis patients reported the lowest quality of life, possibly due to the substantial burden of dialysis itself. Furthermore, a considerable loss in quality of life was observed prior to ESRD as patients progress to CKD stages 4–5. These findings warrant the introduction of measures in clinical practice to improve quality of life to CKD stages 1–3 and 4–5.

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CONFLICT OF INTEREST STATEMENT

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REFERENCES

1. McGovern AP, Jones S, van Vlymen J et al. Identification of people with autosomal dominant polycystic kidney disease using routine data: a cross sectional study. BMC Nephrol 2014; 15: 182
2. Neumann HP, Jäg C, Bacher J et al. Epidemiology of autosomal-dominant polycystic kidney disease: an in-depth clinical study for south-western Germany. Nephrol Dial Transplant 2013; 28: 1472–1487
3. Grantham J. Autosomal dominant polycystic kidney disease. N Engl J Med 2008; 359: 1477–1485
4. Torres VE, Harris PC, Pirson Y. Autosomal dominant polycystic kidney disease. Lancet 2007; 369: 1287–1301
5. Spithoven EM, Kramer A, Meijer E et al. Renal replacement therapy for autosomal dominant polycystic kidney disease (ADPKD) in Europe: prevalence and survival—an analysis of data from the ERA-EDTA Registry. Nephrol Dial Transplant 2014; 29 (Suppl 4): iv15–iv25
6. Tong A, Rangan GK, Ruoso M et al. A painful inheritance—patient perspectives on living with polycystic kidney disease: thematic synthesis of qualitative research. Nephrol Dial Transplant 2015; 30: 790–800
7. Rizk D, Jurkovitz C, Veledar E et al. Quality of life in autosomal dominant polycystic kidney disease patients not yet on dialysis. Clin J Am Soc Nephrol 2009; 4: 560–566
8. Sowabe T, Ubara Y, Mise K et al. Quality of life of patients with ADPKD—Toranomon PKD QOL study: cross-sectional study. BMC Nephrol 2013; 14: 179
9. Miskulin DC, Abebe KZ, Chapman AB et al. Health-related quality of life in patients with autosomal dominant polycystic kidney disease and CKD stages 1–4: a cross-sectional study. Am J Kidney Dis 2014; 63: 214–226
10. Simms R, Tong KM, Dworschak GC et al. Increased psychosocial risk, depression and reduced quality of life living with autosomal dominant polycystic kidney disease. Nephrol Dial Transplant 2016; 31: 1130–1140
11. Brooks R, Group E. EuroQol: the current state of play. Health Policy 1996; 37: 53–72
12. Ware JE, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996; 34: 220–233
13. Ware JE, Kosinski M, Turner-Bowker DM et al. User’s Manual for the SF-12v2 Health Survey Second Edition. RI, USA: QualityMetric, Incorporated, 2009.
14. Reilly MC, Zhrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics 1993; 4: 353–365
15. Dolan P. Modelling valuations for EuroQol health states. Med Care 1997; 35: 1095–1108
16. Wittrup-Jensen KU, Lauridsen J, Gudex C et al. Generation of a Danish TTO value set for EQ-5D health states. Scand J Public Health 2009; 37: 459–466
17. Burström K, Sun S, Gerdtson U-G et al. Swedish experience-based value sets for EQ-5D health states. Qual Life Res 2014; 23: 431–442

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