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Editorial Comment

EDITORIAL COMMENT

Autosomal dominant polycystic kidney disease: possibly the least silent cause of chronic kidney disease

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ABSTRACT

Pain is the highest prioritized patient-reported outcome in people with autosomal dominant polycystic kidney disease (ADPKD) but it remains infrequently and inconsistently measured across countries, studies and trials. The study by El-Damanawi *et al.* integrated a network of ADPKD expert clinicians, pain specialists, researchers and patient representatives from the national UK PKD charity, with the aim of addressing the lack of validated ADPKD-specific pain assessment tools (APATs). The APAT designed by the authors included several pain measurement tools and was tested in ADPKD patients, although further validation through assessment in larger cohorts is needed. Establishing a standardized instrument for pain measurement will ensure that pain is measured and reported in a consistent way to inform decision-making and identify effective interventions aimed at managing pain and minimizing the impact pain has on patients with ADPKD. In this context, the APAT established by the authors is to be warmly welcomed.

Keywords: ADPKD, assessment, pain, patient-reported outcome, trials

Chronic kidney disease (CKD) is commonly referred to as a 'silent epidemic'. When CKD patients complain that their 'kidneys' hurt, we try to explain that the kidneys, even if they are not working, do not hurt and that the source of patients' pain is likely to be their back. Autosomal dominant polycystic kidney disease (ADPKD), however, represents an exception and is possibly the least silent cause of CKD. Increased kidney size, cystic bleeding, cystic infections and the higher prevalence of lithiasis, among other lesser-known factors, rightly cause patients to complain of kidney-related pain.

ADPKD is the most prevalent genetic kidney disease and the reason for kidney replacement therapy (KRT) in a significant percentage of patients, ranging between 7% and 15%, depending on the prevalence of the other causes of CKD in each country [1]. In the majority of studies and clinical trials, the interest in this disease lies in its progression and the ultimate need for KRT. In addition, extrarenal manifestations such as polycystic liver disease and intracranial aneurysms are often studied. Beyond KRT, which obviously has the greatest impact, quality of life is probably most affected by pain and liver involvement in the form of massive polycystic liver disease.

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While massive polycystic liver disease is fortunately relatively rare, abdominal pain and discomfort are very prevalent. Acute and chronic pain is a common complaint in patients with ADPKD and afflicts >60% of patients [2–4]. Acute pain may be related to cyst haemorrhage, cyst rupture, nephrolithiasis and urinary tract infection. These are all disease-related situations, but they may also be unrelated to the disease and require a differential diagnosis. Pain is considered chronic when it lasts >4 weeks. The exact cause of chronic pain in ADPKD patients cannot always be elucidated [5]. The most feasible explanation is that increased organ volume causes distension of the renal and hepatic capsules and/or compresses the adjacent tissues [6, 7]. Also, back pain may be produced by the adaptive stance adopted due to increased abdominal volume [2]. ADPKD patients report chronic pain located in the low back (71%), abdomen (61%), head (49%), chest (30%) and legs (27%), often with radicular features [2]. Glomerular filtration rate (GFR) decreases when the kidneys are large, so it is to be expected that in the presence of a lower estimated GFR (eGFR), the kidneys will be larger and cause more pain. In a subanalysis of the HLAT-PKD (HALT Progression of Polycystic Kidney Disease) study, in patients with an eGFR >60 mL/min/1.73 m^2 there was no relationship between pain and height-adjusted total kidney volume (htTKV) unless the patients had very large kidneys (htTKV >1000 mL/m). In the group of patients with an eGFR of 20–60 mL/min/1.73 m^2, htTKV was not measured, therefore the relationship with pain was not evaluated. However, patients with an eGFR of 20–44 mL/min/1.73 m^2 more often reported that pain had affected their daily life and had lower scores on the 36-item Short Form Health Survey compared with the 45–60 mL/min/1.73 m^2 eGFR group [8]. The few studies that have assessed quality of life specifically in patients with ADPKD have found that pain, abdominal distension and sleep disturbances impair overall quality of life [9, 10]. Similarly, Tong *et al.* [11] identified an immediate impact of pain on lifestyle, but also highlighted longer-term repercussions, including social isolation, loss of employment potential and family burden. Recently Winterbottom [12] disclosed preliminary results of the collaborative European CYSTIC 1 study. In a cohort of 465 patients with a mean age of 44 years, flank pain showed significant negative associations with the highest number of Kidney Disease Quality of Life Short Form subscale scores assessed [12].

Pain management varies greatly among countries in terms of both initiation and choice of treatment. Even taking into account that populations are not exactly comparable among studies, very significant differences are evident in the management of symptoms. The abstract by Sanon [13] highlights that 70% of North American patients with ADPKD consume analgesics, whereas a British study reported that only 29% do so [14]. Similarly, only 7.7% of UK ADPKD patients receive opioid treatment, while in North American studies, the percentage reaches up to 50% [13]. Furthermore, ~3–4% of the adult US population are prescribed long-term opioid therapy [15], while this approach is much less common in European countries. In this context it should be noted that most clinical guidelines and consensus documents recommend not using opiates for pain attributable to ADPKD [16]. More generally, harm due to opioid medications increased dramatically during the 2000s and early part of the 2010s in the USA. Fatal overdoses from natural and semisynthetic opioids increased from 1.0 per 100 000 adults in 1999 to 4.4 per 100 000 in 2016 [17]. In order to address the problem, the Centers for Disease Control and Prevention released the Guideline for Prescribing Opioids for Chronic Pain in March 2016 [18]. This guideline was intended to improve therapy for chronic pain [19]. Hopefully this guideline will also impact on pain management in ADPKD patients.

Patients have a very legitimate claim in proposing that these debilitating symptoms should be included in ADPKD clinical trials and studies [20, 21]. Of note, the International Standardized Outcomes in Nephrology (SONG) initiative [22], SONG-PKD, was launched in 2017 to establish a set of core outcomes for trials in patients with ADPKD based on consensus among patients, caregivers and health professionals. It should be noted that the TEMPO 3:4 clinical trial did include pain within the composite endpoint and that *post hoc* analyses have shown efficacy of tolvaptan in alleviating pain [23]. One reason why pain has been little taken into account in most studies and clinical trials is the great subjectivity of this symptom. While for one patient a specific physical situation causes 'discomfort', for another this same situation causes 'excruciating pain' [24, 25]. The way in which the professional asks about this symptom and how the patient's response is transcribed into the medical record also play an important role. There seems to be a disconnect between patients' experiences and physicians' awareness of the burden of pain in ADPKD and this highlights the need for more patient–physician discussion of symptoms and disease management [26]. For these reasons, the objective measurement of pain is an unmet need in ADPKD as well as in most diseases that cause pain. Consequently the article by El-Damanawi *et al.* [14] is of great interest.

The study by El-Damanawi *et al.* [14] integrated an interesting network of ADPKD expert clinicians, pain specialists, researchers and patient representatives from the national UK PKD Charity, with the aim of addressing the lack of validated ADPKD-specific pain assessment tools (APATs). The APAT designed by the authors was tested in ADPKD patients, covering CKD Stages 1–4 ($n = 39$), although further validation through assessment in larger cohorts is needed. Self-reported health status scores were worse among those with greater pain severity and advanced CKD, and these effects were more pronounced in males. The participants who had pain also showed anxiety and depression, but pain was additionally related to CKD Stage 4, so the anxiety and depression could have been due to the approaching need for KRT rather than the pain itself. Patients with CKD Stage 5 or with kidney transplantation were not included in the study. As bilateral nephrectomy is not routinely performed, patients may continue to suffer from abdominal or back pain following KRT, with an associated impact on quality of life. In the study by El-Damanawi *et al.* [14], the APAT used seems to have been more applicable to chronic pain, as the scales used do not assess acute pain: it would be very interesting if future studies could assess both acute and chronic pain. The majority [87.6% (113/129)] of the questionnaires were submitted through the smartphone application. This is a very important point because the adoption of this approach in studies involving quality of life questionnaires facilitates the participation of patients by allowing them to fill in the questionnaire at any time, without leaving their home and without having to go to the hospital. It also avoids patient forgetfulness when asked about symptoms during visits to the doctor, which may be ≥2 weeks apart.

The use of many different pain scales in PATs is very enriching but may be time-consuming and confusing for patients. El-Damanawi *et al.* [14] used the European Quality of Life 5-Dimensions questionnaire (EQ-5D) scale, which is a standardized instrument for health status [27] and is the preferred UK measure of health-related quality of life [28]. They also used the Modified Short-Form Brief Pain Inventory, which is a validated

clinical PAT [29] that assesses pain severity and interference with affective (mood, sleep and enjoyment) and activity (walking and work) subdimensions. This inventory enriches the global understanding of pain in ADPKD by providing greater detail than has previously been available. Another pain assessment tool used by the authors was the Modified Short-Form McGill Pain Questionnaire [30], which is designed to enable classification of pain symptomatology, with the potential to distinguish between neuropathic and non-neuropathic origins of pain. Finally, the authors used the Medication Quantification Scale (MQS) version III tool [31], which objectively quantifies the medication regimen used in chronic pain populations. The MQS score for each medication is calculated using the medication class, dosage (subtherapeutic, <50% of the therapeutic dose, >50% of the therapeutic dose and supratherapeutic dose) and the agreed detriment/risk score, which was established prior to the US opioid crisis.

The study by El-Damanawi *et al.* [14] has some limitations, including the small sample size ($n = 39$) and the fact that 69% of the patients had a kidney length >16.5 cm. Also, the patient cohort was limited by the inclusion criteria of the DRINK study and tended to include those patients less likely to be debilitated by pain compared with an unbiased ADPKD cohort. In this study, the effect of pain due to other causes related to ADPKD, such as hepatomegaly, which may be frequent and more noticeable in women, was not assessed. Interestingly, 59% of the patients studied were women and 59% of the total patient population had hepatomegaly, but the authors do not explain any relationship between these data and pain, so it would be interesting to study these aspects in the future.

When nephrologists think of ADPKD, most will anticipate some extrarenal manifestations, such as intracranial aneurysms, liver disease and abdominal or back pain, but, as shown by El-Damanawi *et al.* [14], these findings are uncommon in ADPKD patients during the early stages of CKD. However, when pain does arise as a complication of ADPKD, it has serious physical and social consequences. A tool to evaluate pain will allow the unification of diagnostic criteria and treatment strategies and, in this context, the reliable APAT established by the authors is to be warmly welcomed. Interestingly, the APAT will be tested as part of a large observational ADPKD pain study [Evaluating Chronic Pain in ADPKD using a Patient-Centred Approach to Data Collection and Synthesis: A National Prospective Observational Study (EASE-PKD)] funded by the National Institute for Health Research. Establishing a standardized instrument for pain measurement in interventional ADPKD trials will ensure that pain is measured and reported in a consistent way to inform decision-making and identify effective interventions aimed at managing pain and minimizing the impact pain has on patients with ADPKD.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Roser Torra is a Member of the CKJ Editorial Board.

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