Kidney Medicine

The Importance of Recognizing Pain in Patients With Autosomal Dominant Polycystic Kidney Disease

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Patients with autosomal dominant polycystic kidney disease (ADPKD) often have progressive cyst formation in their kidneys and liver, resulting in enlargement of these organs that, frequently, can be impressive. Besides causing kidney function decline and gastrointestinal symptoms, such as abdominal fullness and early satiety, cyst formation results in pain in a significant number of patients.[1] ADPKD-related pain is arbitrarily dichotomized as acute versus chronic.[1,2] Acute pain is caused by disease-related events, such as urinary tract infection, kidney stones, cyst rupture, or cyst hemorrhage. Chronic ADPKD-related pain is by definition present for more than 3 months and originates either from distension of the kidney or liver capsules or through pressure on the surrounding organs.[3] Remarkably, episodes of acute pain can lead to chronic pain through sensitization.[4] Despite potentially significant impacts of pain on quality of life, the importance of pain and its management is often underappreciated by physicians.[5,6]

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In this issue of *Kidney Medicine*, Hoover et al[7] report results from a comprehensive patient-driven ADPKD registry in the United States. A population of 1,086 participants completed at least one questionnaire asking for details concerning pain and quality of life. In addition to cross-sectional data, these questionnaires were also administered longitudinally in ∼30% of participants. In terms of polycystic kidney disease mutation and chronic kidney disease stage, the characteristics of the cohort were representative of the overall ADPKD population that is generally seen in nephrology clinics. The data obtained indicate that quality of life was affected in a substantial number of patients. Approximately 30% reported decreased quality of life. Chronic or dull pain was reported frequently in patients with ADPKD, with a slightly higher prevalence in patients with more advanced disease. Whether this was associated with higher combined liver and kidney volumes could not be investigated because volume measurements were unfortunately not part of the registry. The majority of respondents also reported acute pain events, described as sharp kidney pain, at least once a week and concerns of abdominal fullness or discomfort. Pain also had a significant effect on sleep quality.

These findings indicate that ADPKD-related pain is present in the majority of patients with ADPKD and that it plays an important role as determinant of quality of life, findings that are in line with current literature.[6-9] Although pain concerns are frequent and significantly affect well-being, it is also known that these concerns are under-recognized in patients with ADPKD.[5] Accordingly, the observations by Hoover and colleagues underline that proper evaluation of ADPKD-related pain is necessary to offer patients adequate treatment to improve their quality of life.

The first step in the evaluation of pain in patients with ADPKD is to have an adequate tool to score these concerns. At the moment, several questionnaires are available, such as the validated Short Form 36 and the Short Form 12, which are general questionnaires used for assessing physical and mental quality of life.[10,11] These general questionnaires, however, do not adequately rate the specific concerns because of the sometimes massively enlarged kidneys and liver in patients with ADPKD. Therefore, more specific tools have been designed, such as the ADPKD Impact Scale, the ADPKD Pain and Discomfort Scale (ADPKD-PDS), and the Polycystic Liver Disease Questionnaire (PLD-Q).[10-14] These questionnaires have all been validated in patients with polycystic kidney and liver disease. The ADPKD Impact Scale measures quality of life in 3 domains (physical, emotional, and fatigue), whereas the ADPKD-PDS assesses pain and discomfort concerns. Lastly, the PLD-Q can be used to specifically assess concerns caused by high intra-abdominal volume. High intra-abdominal volume is often present in patients with ADPKD and is associated with the severity of pain and gastrointestinal concerns.[9] These disease-specific questionnaires do have some overlap. In our opinion, the questionnaires that can best be used to objectify pain are the ADPKD-PDS and PLD-Q.

For a complete assessment, an adequate evaluation of the use of analgesics and previous pain treatments is also needed, as well as imaging, preferably using magnetic resonance imaging. Imaging should be performed for volume measurement of the polycystic liver and kidneys and to exclude causes of pain that are not ADPKD-related. In addition, imaging is used to evaluate whether there are dominant cysts that may cause concerns. In case there are such cysts, a test cyst puncture plus aspiration can be performed. When this leads to pain relief, with recurrence of pain when the cyst fills itself again after a few days to weeks, cyst fenestration or sclerosing is the next step. These procedures can also be chosen as an initial step, especially in cases with a high suspicion that pain is indeed caused by a dominant cyst. However, because of their

invasive character, an initial test puncture plus aspiration may be appropriate.

Besides identifying patients with ADPKD-related concerns, questionnaires could also have an important role in selecting patients for these more invasive treatment options. In a publication by Barten et al,[15] the PLD-Q was used to determine a threshold for active treatment in patients with polycystic liver disease. The authors analyzed the PLD-Q scores of around 200 patients with polycystic liver disease and determined that, when a patient reached a PLD-Q score of ≥32, the patient may benefit from active treatment, such sclerotherapy, surgical intervention, or the start of somatostatin analogues (which are known to decrease liver and kidney volume). Such a threshold can also be determined using the ADPKD-PDS, and repeated administration of the questionnaire can objectively determine the effect of treatment.

To maintain or improve quality of life, lifestyle interventions are essential to prevent ADPKD-related pain. The first step is to minimize the risk of acute pain events such as urinary tract infections, kidney stones, and cyst bleeding. Maintaining a high fluid intake is pivotal in this respect because it decreases the risk of urinary tract infections and kidney stones.[16] Therefore, we advise all patients with ADPKD a fluid intake of >3,000 mL per 24 hours. Other risk-reducing interventions to prevent kidney stone formation are lowering daily sodium intake to <5 g and limiting nondairy animal protein intake.[16] To lower the risk of cyst rupture and cyst hemorrhage, high-impact contact sports, such as karate and boxing, and perhaps also sports such as horseback riding and cross-country motorcycling should be avoided. Quality of life might also be improved by weight reduction in patients with a high body mass index because this has been shown to be negatively associated with quality of life in patients with ADPKD.[6] Of note, assessment of obesity in ADPKD can be more challenging because of the volume of the polycystic kidneys and liver. Although some patients may be classified as obese based only on their body mass index, a substantial portion of their weight can sometimes be attributed to cyst fluid.

Despite lifestyle interventions, a substantial number of patients with ADPKD will experience ADPKD-related pain, which is sometimes difficult to manage. In our expert center for the treatment of polycystic kidney disease, we designed a protocol with a stepwise approach to manage chronic, debilitating, ADPKD-related pain.[8] When carefully selected, most patients benefited. The first step, as outlined in the protocol, consists of noninvasive therapies (eg, pain medication, heating packs, and physiotherapy). If this works insufficiently, minimally invasive treatment options then can be pursued, especially nerve blocks, including among others, celiac, splanchnic, and sympathetic blocks, as well as renal denervation. In case these interventions do not work, cyst aspiration, cyst fenestration, and lastly, nephrectomy can be tried. By following this protocol, the need for nephrectomy could be avoided in nearly all patients. This is important to delay the start of kidney replacement therapy. Of course, when kidney failure has been reached, the threshold for nephrectomy is lower.

Nephrectomy has been found to be very effective in relieving ADPKD-related pain and, thus, improving quality of life. We investigated the potential role of pretransplant nephrectomy to improve quality of life in 98 patients with ADPKD who underwent nephrectomy before transplantation and 178 who did not.[17] Before the procedure, quality of life was more affected in patients who would later undergo nephrectomy compared with those who would not, indicating that these patients had more severe disease. Notwithstanding, after nephrectomy and transplantation, quality of life increased significantly more in patients who underwent both nephrectomy and transplantation compared with patients who only underwent transplantation. These findings indicate that carefully selected patients who have reached or are near kidney failure may benefit from nephrectomy to improve quality of life. Expertise and experience are needed by the various disciplines involved with the treatment of patients with ADPKD-related pain. Besides a nephrologist, these include a dedicated pain specialist, urologist, hepatologist, and radiologist. In our opinion, this can only be guaranteed in Polycystic Kidney Disease Expertise Centers, dubbed Polycystic Kidney Disease Centers of Excellence in the United States.[8]

In conclusion, the article by Hoover et al[7] in this issue of *Kidney Medicine* emphasizes once again that pain has a major effect on quality of life in patients with ADPKD. This underlines the importance of adequate recognition and assessment of ADPKD-related pain concerns, for which the standard use of validated questionnaires, such as the ADPKD-PDS and PLD-Q, are essential. A next step is to determine threshold scores for these questionnaires, above which patients may benefit from treatment. Lifestyle interventions to prevent acute pain events should always be mentioned, but some patients may need more invasive treatments. Determining which treatment to offer is a multidisciplinary process, with no one-size-fits-all approach, and should be performed using a process of shared decision making with the patient. When performed appropriately, interdisciplinary physicians can have an important role in improving the quality of life among patients with chronic ADPKD-related pain.

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Support: None.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Peer Review: Received March 17, 2024 in response to an invitation from the journal. Accepted March 24, 2024 after editorial review by the Editor-in-Chief.

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