

## Risk Factors for Pain in Autosomal Dominant Polycystic Kidney Disease: A New Research Trajectory

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**A**utosomal dominant polycystic kidney disease (ADPKD) is a progressive, inherited disease characterized by the continuing growth of fluid-filled cysts in kidneys, leading to a wide range of complications

### Related article, p. 536

including nephrolithiasis, hematuria, infections, and progressive loss of kidney function.<sup>1</sup> Continuing loss of kidney function frequently leads to end-stage kidney disease (ESKD), and ADPKD is the fourth-leading cause of kidney failure in the United States, behind diabetes, hypertension, and glomerulonephritis.<sup>2</sup> Furthermore, ESKD occurs at younger ages in ADPKD patients than in those with other ESKD etiologies. Approximately 68% of ADPKD patients in the United States are diagnosed with ESKD between the ages of 40 and 64, as compared to 41% of patients without ADPKD.<sup>2,3</sup> The biological complications of ADPKD include a wide range of symptoms and conditions beyond kidney function, including pain, infection, hypertension, and intracranial aneurysm.<sup>4,5</sup> A diagnosis of ADPKD can mean living with a lifetime of uncertainty about disease progression, continuing need for medical monitoring, challenging management of multiple comorbid conditions, and, for some patients, daily occurrence of pain.<sup>6,7</sup> Although estimates of the percentage of ADPKD patients who experience pain vary, a substantial proportion of patients are affected. In a recent nationwide claims-based analysis of 4,536 ADPKD patients, 35% of patients had ICD-10 documentation of abdominal, flank, or low back pain,<sup>8</sup> and in a cross-sectional sample of Kaiser-Permanente Southern California members with ADPKD, 37% had clinically documented abdominal pain.<sup>9</sup> Thus, over one-third of ADPKD patients in large health care systems have clinically documented pain concerns.

In this issue of *Kidney Medicine*, Nowak et al<sup>10</sup> report on modifiable risk factors for pain in ADPKD in a post hoc analysis of pooled data from 2 ADPKD randomized trials that included regular, longitudinal assessments of pain (HALT-PKD A or B).<sup>11</sup> The aim of the study is to examine overweight, obesity, and annual change in weight as a predictor of pain in ADPKD patients. The rationale behind the hypothesis is that, among the general population, greater body mass index and central obesity are associated with greater pain intensity and chronic pain.<sup>12,13</sup> In addition, obesity is associated with increased pain sensitivity,<sup>14,15</sup> and weight loss has been shown to reduce some types of chronic pain.<sup>16,17</sup> As noted by Nowak et al, “a

metabolic hypothesis of pain in obesity has gained increasing support as an important mechanism contributing to pain.”<sup>18</sup> This observation led Nowak et al to examine the potential implications of this association for understanding pain in ADPKD patients in particular.

Nowak et al provide the first evidence that pain in ADPKD is associated with a modifiable comorbid condition, obesity. Patients who participated in the HALT-PKD trial were generally younger, with an average age of 42; most were employed full time, and average estimated glomerular filtration rate was within normal ranges. Yet, despite these favorable characteristics, baseline data from the trial reported that 50% of participants reported back pain, similar to estimates from prior literature.<sup>6,19</sup>

With the identification of a modifiable risk factor for ADPKD pain, Nowak et al suggest a potential new strategy for reducing disease burden and pain in some ADPKD patients. Several implications of this finding come to mind. Given the burden of pain in ADPKD, there is clearly a need to explore the potential of weight management strategies to reduce pain in ADPKD patients. Even though the results of this study have yet to be replicated, recommending weight loss strategies for obese patients has little risk, and a high potential for benefit, given the strong evidence for benefit across many disease states.<sup>20</sup> It is encouraging to see that further research on whether weight loss promotes slowed kidney growth is ongoing in a pilot trial of behavioral weight loss interventions (NCT03342742), as these follow-up data will add key context to the Nowak et al findings. This trial and other follow-up studies can help determine whether obesity directly affects ADPKD kidney pain, whether obesity is associated with general low back pain in ADPKD patients, and whether obesity exacerbates both kidney pain and general body pain among ADPKD patients.

If ADPKD pain control is improved with weight loss strategies, a wide range of subsequent research questions will emerge. How do common comorbid conditions, such as hypertension and diabetes, modify the effect of interventions for pain? Will weight loss strategies also benefit overweight ADPKD patients, or are the results limited to those with obesity? Do pain medications differentially affect the population of ADPKD patients with obesity, and are certain medications more effective than others (arthritic/inflammatory vs neuropathic mechanisms)? Are other metabolic factors that have been associated with chronic pain relevant for ADPKD patients? The potential for “spin-off” hypotheses is both stimulating and endless,

as the overlap between metabolic risk factors for pain and ADPKD progression has yet to be explored.

The need for pain-related interventions in ADPKD patients is considerable. The high prevalence of pain observed in the administrative clinical records of ADPKD patients (35%-37%) may actually be a conservative estimate of the true proportion of patients who regularly experience pain. Tong et al<sup>7</sup> performed a comprehensive literature review of all studies that explored the perspectives of adult ADPKD patients with respect to topics such as complications, pain management, genetic testing, pregnancy risks, and lifestyle modifications. From 1,017 citations identified, 6 themes were identified, with the most common theme being unvalidated pain and inadequacy of pain management. Similarly, in a cross-sectional study comparing patient and physician assessments of the impact of ADPKD symptoms, patients reported a statistically greater burden from kidney pain than physicians assumed, indicating a need for more patient/physician discussion of symptoms of pain, and greater recognition of the impact of pain on daily life.<sup>21</sup> In addition, uncontrolled pain can lead to increased immobility, which may further exacerbate sensitivity to pain. The implications of uncontrolled pain also extend further to pain medication dependence, work-related and family problems, and even depression. All of these harmful sequelae could potentially be mitigated by expanding clinical approaches for ADPKD pain management.

While it is apparent that new strategies to lessen the burden of pain in ADPKD have a high potential to benefit patients and their families, there is also the possibility that a better understanding of the biologic mechanisms underlying the association between obesity and pain could further enhance our understanding of disease progression. Although obesity may be related to increased pain solely via mechanistic forces that promote degenerative changes, the association among inflammatory markers, pain, obesity, and ADPKD progression suggests a need for further exploration. We are hopeful that this area of study will begin a new trajectory of research on metabolic risk factors for pain that may eventually complement the study of the natural history of ADPKD, including identification and characterization of those with more aggressive symptoms and more rapid disease progression.

In closing, it is worth emphasizing that this study is the first to identify a modifiable risk factor for pain in ADPKD and open the door for further study. The risk factor approach, which has become the cornerstone of chronic disease prevention and management, has yet to be fully explored with respect to ADPKD pain, and obesity may be the first of many such risk factors to be identified. We are hopeful that this area of study will begin a new trajectory of research that may eventually lead to effective, innovative strategies to complement current approaches for the management of pain in ADPKD, as well as expand our understanding of risk factors for pain and ADPKD progression.

## ARTICLE INFORMATION

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