Management of Pain in Autosomal Dominant Polycystic Kidney Disease and Anatomy of Renal Innervation

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Purpose: Chronic pain is a prominent feature of autosomal dominant polycystic kidney disease that is difficult to treat and manage, often resulting in a decrease in quality of life. Understanding the underlying anatomy of renal innervation and the various etiologies of pain that occur in autosomal dominant polycystic kidney disease can help guide proper treatments to manage pain. Reviewing previously studied treatments for pain in autosomal dominant polycystic kidney disease can help characterize treatment in a stepwise fashion.

Materials and Methods: We performed a literature search of the etiology and management of pain in autosomal dominant polycystic kidney disease and the anatomy of renal innervation using PubMed® and Embase® from January 1985 to April 2014 with limitations to human studies and English language.

Results: Pain occurs in the majority of patients with autosomal dominant polycystic kidney disease due to renal, hepatic and mechanical origins. Patients may experience different types of pain which can make it difficult to clinically confirm its etiology. An anatomical and histological evaluation of the complex renal innervation helps in understanding the mechanisms that can lead to renal pain. Understanding the complex nature of renal innervation is essential for surgeons to perform renal denervation. The management of pain in autosomal dominant polycystic kidney disease should be approached in a stepwise fashion. Acute causes of renal pain must first be ruled out due to the high incidence in autosomal dominant polycystic kidney disease. For chronic pain, nonopioid analgesics and conservative interventions can be used first, before opioid analgesics are considered. If pain continues there are surgical interventions such as renal cyst decortication, renal denervation and nephrectomy that can target pain produced by renal or hepatic cysts.

Conclusions: Chronic pain in patients with autosomal dominant polycystic kidney disease is often refractory to conservative, medical and other noninvasive treatments. There are effective surgical procedures that can be performed when more conservative treatments fail. Laparoscopic cyst decortication has been well studied and results in the relief of chronic renal pain in the majority of patients. In addition, renal denervation has been used successfully and could be performed concurrently with cyst decortication. Nephrectomy should be reserved for patients with intractable pain and renal failure when other modalities have failed.

Key Words: anatomy; innervation; kidney; pain management; polycystic kidney, autosomal dominant
**RESULTS**

**Chronic Renal Pain**
Renal cysts can lead to pain in the back, abdomen and flank region. Patients with ADPKD often experience multiple types of pain, which can be described as dull, an uncomfortable fullness, stabbing and cramping.\(^3\) Chronic pain due to cyst formation may also present as persistent discomfort localized to a small area that is aggravated by standing or walking.\(^6\) Many patients also experience sudden onset of pain while performing physical activities.\(^4\) Renal mechanosensory nerves, which respond to changes in pressure, and renal chemosensory nerves, which respond to ischemia or alterations of the renal interstitial fluid, have been identified in the kidney.\(^7\) Cystic compression of the renal capsule and parenchyma can lead to transmission of pain through afferent sensory nerve fibers around the renal vasculature, in the corticomedullary connective tissue and in the renal pelvic region.\(^8\) Pain is not related to kidney size early in the disease process (estimated glomerular filtration rate greater than 60 ml/minute/1.73 m\(^2\)) unless the kidneys are extremely large, with a height adjusted kidney volume greater than 1,000 ml/m.\(^5\) Pain presentation based on cyst size can be variable, as some patients with smaller cysts can experience severe pain while others with larger cysts remain pain-free.\(^6\) Renal pain in ADPKD can present in various ways, making it difficult to clinically confirm its etiology. Clinical findings often need to be correlated to diagnostic images to confirm the source of the pain.

**Mechanical Back Pain**
Cystic enlargement of kidneys can lead to lumbar lordosis and an asymmetrical cystic enlargement of the kidneys can cause postural changes of the spine. These mechanisms can lead to stress and degeneration of the spine, resulting in mechanical back pain. Cystic enlargement of the liver can cause mechanical back pain through this same mechanism. An observation was made that patients with ADPKD have lumbar dorsal muscle hypertrophy, serving as further evidence of the mechanical changes that can occur in patients with ADPKD.\(^6\)

**Abdominal Fullness and Early Satiety**
The feeling of abdominal fullness can occur due to cystic expansion of the kidney or liver and is present in 20% of patients with ADPKD.\(^5\) Compression on the stomach and duodenum can result in decreased appetite and abdominal fullness, leading to a risk of malnutrition.\(^5,6\)

**Chronic Liver Pain**
Hepatic cysts in ADPKD can be identified with magnetic resonance imaging in up to 94% of...
patients 35 to 46 years old. Cyst volume and incidence increase with age as the disease progresses. Although most patients with hepatic cysts are asymptomatic, some experience abdominal fullness and severe pain. Compression on the diaphragm can also lead to shortness of breath. Compared to pain from renal cysts, liver cysts can cause pain that is more severe, and resistant to conservative, medical and surgical intervention.

**RENAL NERVE ANATOMY AND HISTOLOGY**

**Extrinsic Renal Nerves**
The renal plexus is a network of nerve filaments and ganglia that are derived from direct branches of the celiac plexus, celiac ganglia, aorticorenal ganglia, thoracic splanchnic nerves, the upper lumbar splanchnic nerve and superior portions of the intermesenteric plexus (fig. 1). This has been demonstrated in anatomical dissections of human cadavers. This pattern has been confirmed using retrograde tracers in various animal models, although there is variation in the paravertebral and dorsal root ganglia of origin.

The greater splanchnic nerve may connect to the renal plexus from the aorticorenal ganglia and small nerve fibers branching off the renal plexus. The lesser thoracic splanchnic nerve, derived from the 9th and 10th or 10th and 11th thoracic paravertebral ganglia, innervates the celiac and aorticorenal ganglia, which send branches to the renal plexus. The least thoracic splanchnic nerve, derived from the 12th thoracic paravertebral ganglia, synapses directly on the renal plexus. The upper lumbar splanchnic nerve, derived from the 1st lumbar paravertebral ganglia, sends fibers to the intermesenteric plexus as well as branches that synapse directly on the renal plexus. Fibers from the superior portion of the intermesenteric plexus also run directly to the renal plexus.

The greater splanchnic nerve may connect to the renal plexus through the aorticorenal or celiac ganglia, which was seen in a minority of cadavers. Small connections to the renal plexus from the inferior portion of the intermesenteric plexus and superior portion of the hypogastric plexus were also found in some cadavers. These connections could not be verified in other dissections.

**Renal Nerve Penetration into the Kidney**
As the renal nerves course toward the kidney, the majority of nerve fibers converge around the renal artery and enter the kidney with the renal artery through the hilum (fig. 2). Nerve fibers from the intermesenteric plexus may join the renal plexus distally at the inferior aspect of the main renal artery or segmental arteries near the hilum. Contributions from the inferior intermesenteric plexus or superior hypogastric plexus may pass through the gonadal artery and plexus to the superior ureter and inferior aspect of the renal pelvis. Some renal innervation may occur outside the hilum on the medial side of the kidney due to direct connections from the aorticorenal ganglia and small nerve fibers branching off the renal plexus.

**Renal Neural Anatomy around the Renal Artery**
The renal plexus has historically been described as running circumferential around the renal artery based on cadaveric dissections and renal denervation procedures. Two studies examining histological cross sections of 9 and 40 renal arteries confirm a circumferential distribution of nerves around the main renal artery. However, there are more nerve fibers on the ventral aspect of the main renal artery than the dorsal aspect (11.0±3.5 vs 6.2±3.0 per section, p < 0.001). There is a significantly higher average number of nerve fibers per section on the proximal renal artery (39.6±16.7) compared to the distal renal artery (33.6±13.1) (p=0.01). The average distance of nerve fibers to the arterial lumen is greater on proximal vs distal segments (3.40±0.54 vs 2.60±0.77 mm, p < 0.001).

The trend is for a higher nerve density on the ventral aspect of the renal artery, with nerve fibers that are more numerous and further from the lumen of the artery on more proximal segments. The afferent sensory renal nerve fibers are intermixed with sympathetic nerve fibers in bundles around the renal artery and begin 0.5 mm from the lumen of the artery. The wall of a renal artery can have a depth up to 0.25 mm, based on the upper bound 95% CI of the tunica intima and media of the renal artery in an elderly subset of patients. This suggests that nearly all of the nerve fibers, which are at least 0.5 mm from the lumen, run outside of the tunica media, and are in the tunica adventitia and surrounding tissue. Examination of histological cross sections confirms the nerves to be in the adventitia and periadventitial fat where nervous tissue can be surgically stripped from the renal artery.

**Figure 1.** Diagram of extrinsic renal innervation based on human cadaveric dissections and animal models. Lighter text and arrows represent nerve connections found in minority of human cadavers.
Sympathetic Activity and ADPKD
Increased sympathetic nerve activity has been implicated in the pathophysiology of ADPKD. There is an increase in sympathetic nerve activity in hypertensive cases with ADPKD with normal renal function and in those with impaired renal function.\textsuperscript{18} The renin-angiotensin-aldosterone system is activated to a greater extent in hypertensive cases with ADPKD than in those with essential hypertension.\textsuperscript{19} Furthermore, angiotensin II can enhance epidermal growth factor, which promotes cyst formation in the kidney.\textsuperscript{20} Early onset hypertension and increased sympathetic nervous activity could account for the high level of cardiovascular morbidity and mortality in ADPKD, with up to 41% of patients having left ventricular hypertrophy in an initial demographic study.\textsuperscript{21} More recent evidence suggests the decreasing incidence of left ventricular hypertrophy, now found in 3.9% of patients with ADPKD, could be due to improved hypertension control earlier in the disease process, in addition to the use of renin-angiotensin-aldosterone system antagonists.\textsuperscript{22} The role of renin angiotensin blockade in ADPKD will be better understood when the HALT-PKD trial is completed.\textsuperscript{23} Renal denervation in the rat model of ADPKD causes a reduction in cyst size, a decrease in blood pressure and improvement in renal function,\textsuperscript{24} suggesting a further role of sympathetic activity in the disease and potential benefit of renal denervation beyond pain control.

Initial Evaluation of Pain
Evaluation must start with a detailed history and physical examination to determine if the pain appears to be acute or chronic. Patients with ADPKD have a higher incidence of acute causes of renal pain, including nephrolithiasis, cyst hemorrhage, pyelonephritis and cyst infection, which must be ruled out.\textsuperscript{6} Physical examination may reveal palpable enlarged kidneys or liver. The presence of costovertebral angle tenderness upon percussion can result from inflammation of the kidney and should raise the suspicion for an acute cause of renal pain.

A ruptured or hemorrhagic cyst may be present when there is an abrupt onset of sharp, localized flank pain with associated gross hematuria. Conservative management can be started since the hematuria normally resolves within 2 to 7 days.\textsuperscript{6} An infectious source of pain such as pyelonephritis or cyst infection should be suspected when a patient...
has a fever and leukocytosis in addition to increasing flank pain. Urine and blood cultures must be obtained, and proper antibiotics need to be initiated. Surgical intervention or fluid drainage may be necessary if the infection does not respond to antibiotics.

The use of diagnostic imaging may be essential to isolate the source of acute and chronic causes of pain. Computerized tomography should be used rather than magnetic resonance imaging if nephrolithiasis needs to be ruled out. Positron emission tomography can be used to identify a cyst that may be infected. Once acute causes are ruled out and pain appears to be more chronic, evaluation should attempt to differentiate among mechanical, hepatic, renal or other causes of pain.

**Chronic Pain Management**

It is important to focus on helping a patient deal with chronic pain and improving functionality rather than setting intangible goals of completely relieving all pain. Initial treatment of chronic pain in ADPKD is not specific to the disease and should consist of a step-wise approach, starting with conservative treatment and nonopioid analgesics that are beneficial for renal, hepatic and mechanical causes of pain (fig. 3).

**Conservative Treatment**

Conservative treatment includes the use of ice, heat, whirlpool, psychobehavioral modification techniques and the Alexander technique. The Alexander technique helps patients understand and modify

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**Figure 3. Flowchart of evaluation and treatment of chronic pain in ADPKD**

the postures and movements that result in pain. It has been shown to be beneficial in the treatment of chronic back pain, and observations of its use by patients with ADPKD have led to recommendations of including it as a treatment option.6

**Analgesics**

The National Kidney Foundation recommends acetaminophen as the preferred nonopioid analgesic for long-term pain management in patients with underlying renal diseases. Nonsteroidal anti-inflammatory drugs can be used for acute episodes of pain. However, long-term use is discouraged due to the potential for renal toxicity and renal function should be monitored with long-term use.28 These recommendations should be applied to patients with ADPKD since 45% experience renal failure by age 60.1

Tramadol as well as other adjuvant analgesics, including clonidine, gabapentin, pregabalin, duloxetine and amitriptyline, can be added to acetaminophen to help control pain before opioids are implemented.6,26 If indicated, opioids should be initiated as a trial to determine if they are appropriate in treating pain. The initial opioid selected, dosing and titration should be based on the patient’s past analgesic use and response. Patients should be evaluated periodically for effectiveness and side effects of the medication. An opioid rotation may need to be implemented if pain is refractory to higher doses.29

Tolvaptan, a vasopressin V2 receptor antagonist, has been shown to cause a statistically significant decrease in renal pain in patients with ADPKD, likely through a decrease in cystic pressure and fluid production. However, the small decrease in pain from 7 to 5 events per 100 person-years of followup (p=0.007) in addition to the side effects of polyuria and polydipsia, limits the indication of its use for pain.30 While tolvaptan is not indicated to treat pain in ADPKD, it shows that future medical treatment that limits cyst growth could potentially improve pain control in ADPKD.

**Autonomic Nerve Block and SCS**

Celiac plexus nerve block is used to control chronic visceral pain and has been suggested to be of benefit in ADPKD.6,26 Anatomy previously discussed suggests that this procedure may only block a portion of renal sensory innervation since the least thoracic and lumbar splanchnic nerves do not relay through the celiac plexus. Targeting splanchnic nerves would produce a wider blockade of renal sensory outflow compared to a blockade of the celiac plexus. Although it has not been documented in ADPKD, radio frequency ablation of the splanchnic nerves provided pain relief in a patient with loin pain hematuria syndrome.31 Celiac plexus nerve blocks with radio frequency ablation of the intercostal nerves has been used to provide short-term pain relief in a patient with ADPKD, followed by the use of SCS for longer term pain relief.32

**Cyst Aspiration and Ablation**

Cyst aspiration under ultrasound guidance is the least invasive procedure used to reduce cyst size for relief of pain. However, pain recurs in 67% of patients after 18 months as the cysts reform.31 In conjunction with cyst aspiration, sclerotherapy can be added for further reduction in cyst size. These procedures are most useful when there are only a few dominant cysts responsible for the patient’s symptoms, which is uncommon in ADPKD. A variety of sclerosing agents have been used, including ethanol, minocycline and n-butyl cyanoacrylate with iodized oil. There is evidence of successful reduction of clinical symptoms with sclerotherapy in 17 of 21 patients (81%) with ADPKD at a mean followup of 28.5 months.34 All patients had between 3 and 6 cysts, which is a low number for ADPKD.

**Cyst Decortication**

Cyst decortication can relieve pain by releasing pressure on the renal capsule and parenchyma in addition to reducing compression on the surrounding tissue. Cyst decortication is the most extensively studied procedure for chronic pain relief in ADPKD, with a review showing successful pain relief in all 15 studies and evidence of sustained pain relief in the majority of patients 5 years out.35 Pain relief continued 1 year after the procedure in 80% to 92% of patients, which decreased slightly with time at longer followup visits. A long-term followup at a mean of 10.9 years showed that 8 of 12 patients (67%) continued to have more than 50% pain improvement.36 There does not appear to be any improvement in blood pressure control or renal function.35 Caution is advised in performing laparoscopic cyst decortication in patients with renal impairment as a decreased preoperative estimated glomerular filtration rate is associated with progression to end stage renal disease after LCD.36 However, there is no known cause for this association.

LCD remains an option for pain management in patients with decreased renal function to preserve remaining function by avoiding nephrectomy as an alternative treatment for pain. For LCD to be most effective, almost all cysts that are accessible on all surfaces of the kidney must be addressed. The kidney will need to be extensively mobilized and nephropexy may be required at the end of the procedure. Laparoscopic ultrasound may be required to ensure that the collecting system is not entered and smaller cysts are identified. Patients should be
advised that they may experience a temporary increase in pain postoperatively due to irritating fluid released from hemorrhagic cysts.

Renal Denervation

Laparoscopic renal denervation has been performed in an adolescent age group in a case series of 4 and 12 patients with ADPKD (mean age 17 and 12.4 years, respectively) who had chronic flank pain refractory to narcotics of 6 to 9 out of 10 on the Bieri modified and Wong-Baker pain scales. Division of all nervous tissue near the hilum was performed, followed by circumferential dissection of the kidney to divide any nerves that did not course through the hilum. All patients were pain-free without the need for analgesics at a mean followup of 11.5 and 25.5 months, respectively.37,38

A thoracoscopic approach of renal denervation has been performed for pain refractory to narcotics and repeated cyst aspirations. Sympathosplanchnicectomy of the sympathetic chain and splanchnic nerves was performed, resulting in pain relief the day after the procedure and at a 2-year followup with no need for analgesics.39 This approach is being used in a clinical trial (NCT00571909) with initial reports of 6 of 9 patients being pain-free without analgesics at 3-month followup.26 A thorough wide dissection of the renal artery at the hilum may need to be performed during renal denervation to dissect nerves that may not have run the course of the renal artery. Alternatively it would be safer to perform circumferential renal denervation of the renal artery near its origin with care to dissect nerve fibers on the lateral aspect of the aorta that may join the renal artery at more distal segments. Division of all tissue on the medial aspect of the kidney and along the proximal ureter can denervate remaining nerve connections. Multiple renal arteries are present in 28% of patients, based on a review of the anatomy of renal arteries.40 Renal innervation follows each artery entering the kidney, implying that renal denervation would need to be performed around each artery.

Percutaneous transluminal renal denervation relieved pain in a patient with ADPKD and a followup procedure on the contralateral side was performed based on this success.41 The failure of percutaneous transluminal renal denervation to decrease systolic blood pressure compared to a sham operation raises some concern for the efficacy of this procedure to treat pain since the sensory nerves lie within the bundles of sympathetic fibers targeted with this procedure.42 Renal denervation would not likely be beneficial in patients who have mechanical associated pain or are experiencing early satiety. However, it could be used in conjunction with LCD or alone when renal cysts are too small or deep for LCD to be beneficial. It is our practice to perform renal denervation along with extensive laparoscopic renal cyst decortication in patients with refractory renal pain.

Nephrectomy

Nephrectomy is reserved for the treatment of chronic renal pain in patients with end stage renal disease when other modalities have failed. This procedure can be performed unilaterally or bilaterally, which necessitates the use of dialysis or renal transplantation. Bilateral laparoscopic nephrectomy has been shown to decrease visual analog pain scores from an average of 6.9 out of 10 preoperatively to 0.5 at 3-month followup in 18 patients studied,43 with evidence of long-term pain relief at 31 months in a separate study.44 A laparoscopic approach is generally preferred compared to an open procedure due to decreased blood loss, shorter recovery and decreased pain.44 Patients with extremely large kidneys with a volume greater than 3,500 cc are at an increased risk of conversion to an open procedure and, thus, open nephrectomy may initially be considered in these patients.43

Unilateral nephrectomy with renal transplantation does not increase morbidity compared to renal transplantation alone in patients with ADPKD. Renal transplantation with unilateral nephrectomy followed by laparoscopic unilateral nephrectomy has a better perioperative outcome than renal transplantation followed by bilateral laparoscopic nephrectomy.45 Unpublished data suggest that transplantation with concurrent unilateral nephrectomy in patients with ADPKD results in a greater decrease in the number of antihypertensive medications needed compared to transplantation alone.

Transcatheter Arterial Embolization

TAE of distal branches of the renal artery results in a reduction in renal volume by 47% 1 year after treatment.46 Reduction in renal volume decreases compression on surrounding organs that can alleviate feelings of abdominal fullness, discomfort and early satiety. This procedure can be used in patients with end stage renal disease in whom other treatment modalities have failed and in those who are poor surgical candidates for nephrectomy.26 Symptomatic hepatic cysts can also be reduced by embolization of the hepatic segments involved.

Hepatic Cyst Treatment

A variety of surgical approaches can be performed for pain associated with hepatic cysts, including cyst fenestration, cyst fenestration with hepatic resection, liver transplantation and TAE. Cyst fenestration alone can be used when there are a few superficial dominant cysts and the addition of hepatic resection can be used in highly symptomatic
patients if at least 1 hepatic sector can be preserved. Liver transplantation is indicated if a single hepatic sector cannot be preserved, but it may be difficult to obtain a liver for transplantation since the indication in these patients is usually for symptoms and not for liver failure. While morbidity can be up to 63% using hepatic resection with cyst fenestration, long-term success at a followup of 9 years has been demonstrated, with 75% of patients showing normalized or improved functionality measured by Eastern Cooperative Oncology Group Performance Status. \(^{47}\)

**CONCLUSIONS**
The presentation of pain in patients with ADPKD can vary due to the numerous mechanisms that can generate pain in this patient population. Knowing the etiology of pain can help a physician select an appropriate treatment. A variety of conservative, medical and noninvasive procedures can be used to treat chronic pain in ADPKD. However, pain is often difficult to control and may be refractory to conservative measures. In this event there are surgical procedures that can provide reliable relief. Laparoscopic cyst decortication has been extensively studied and proven to provide long-term pain relief in the majority of patients. Renal denervation has been highly successful in the pediatric population and could be performed in addition to laparoscopic cyst decortication. Finally, nephrectomy can be used in patients with end stage renal disease when other treatment modalities have failed.

**REFERENCES**


