Management of Pain in ADPKD and Anatomy of Renal Innervation

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Abstract

Purpose: Chronic pain is a prominent feature of autosomal dominant polycystic kidney disease (ADPKD) that is difficult to treat and manage, often resulting in a decrease in quality of life. Understanding the underlying anatomy of renal innervation and different etiologies of pain that occur in ADPKD can help to guide proper treatments to manage pain. Reviewing the previously studied treatments for pain in ADPKD can help to characterize treatment in a stepwise fashion.
Materials and Methods: We performed a literature search of the etiology and management of pain in ADPKD 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 ADPKD 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 with an understanding of the mechanisms that can lead to renal pain. Understanding the complex nature of renal innervation is essential for surgeons to perform a renal denervation procedure. The management of pain in ADPKD should be approached in a stepwise fashion. Acute causes of renal pain must first be ruled out due to the high incidence in ADPKD. For chronic pain, non-opioid analgesics and conservative interventions can be first used before opioid analgesics are considered. If pain continues, there are surgical interventions that can target pain produced by renal or hepatic cysts. Surgical options include renal cyst decortication, renal denervation, and nephrectomy.
Conclusion: Chronic pain in patients with ADPKD is often refractory to conservative, medical, and other non-invasive treatments. There are effective surgical procedures that can be implemented when more conservative treatments fail. Laparoscopic cyst decortication has been well studied and results in relief of chronic renal pain in the majority of patients. In addition, renal denervation has successfully been utilized 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.

Introduction

ADPKD is a relatively common disease that has a worldwide prevalence of 1:400 to 1:1000[1]. Pain is a prominent feature of all types of polycystic kidney disease **a**ffecting over 60% of patients, and is most commonly located in in the flank, followed by the back and abdomen.[1, 2] Pain is often present early in the disease process and is the most common symptom that leads to a diagnosis of the disease.[3] In patients with ADPKD, the hardships of living with chronic pain can prevent them from performing both physical and social activities, detrimentally affecting their quality of life.[4] The difficulty of pain management is demonstrated by many patients, with up to 39% of patients being somewhat or completely dissatisfied with pain treatment because they are physically unable to do what they would like.[5] A better understanding of the etiology of pain that occurs in ADPKD in addition to the underlying anatomy can help to guide treatment.

Materials and Methods

We performed a literature search of the etiology and management of pain in ADPKD using Pubmed® and Embase® from January 1985 to April 2014 with limitations to human studies and English language. Search terms included pain management, chronic pain, treatment, therapy, polycystic kidney, autosomal dominant, cyst, hepatic, liver, kidney, and renal. References of the studies found were reviewed. Further searches were performed using MEDLINE® and Embase® for each relevant treatment of ADPKD identified with additional search terms added including analgesics, Alexander Technique, tolvaptan, opioids, aspiration, celiac plexus, splanchnic nerves, splanchnicectomy, block, ablation, spinal cord stimulation, sclerotherapy, decortication, laparoscopic, marsupialization, denervation, percutaneous, sympathectomy, nephrectomy, transplant, and transcatheter arterial embolization. A comprehensive review of the literature identified 140 studies involving the presentation of pain and symptomatic treatment in ADPKD. Thirty of those studies were selected for this review based on appropriate study design, duration of follow up, number of patients, and method of measuring pain control. The literature selected consisted of systematic reviews, randomized controlled trials, cross-sectional studies, retrospective case series, and case reports.

A literature search was also performed to better delineate the anatomy and histology of renal innervation using Pubmed® and Embase® with limitations to English language. Search terms included anatomy, histology, renal, kidney, nerve, innervation, splanchnic, celiac, sympathetic, autonomic, sensory, and afferent. References of the studies found were reviewed and textbooks were consulted for additional information. Fifty-four articles of anatomy and histology were reviewed, and 17 were included based on the number of samples in the study, method of histopathological sectioning, and presence of afferent neural tissue.

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 a persistent discomfort localized to a small area that is aggravated by standing or walking.[6] Many patients also experience a 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 (eGFR>60mL/min/1.73m^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 other patients with larger cysts remain pain free.[6] Renal associated 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 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 lumbodorsal muscle hypertrophy, giving further evidence of 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 in ADPKD

Hepatic cysts in ADPKD can be identified in up to 94% of patients ages 35-46 years through magnetic resonance imaging. The cyst volume and incidence increases with age as the disease progresses.[9] Although most patients with hepatic cysts are asymptomatic, some patients develop 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.[6]

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.[10, 11] This pattern has been confirmed using retrograde tracers in various animal models, although there is variation in paravertebral and dorsal root ganglia of origin.[7]

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.[7, 10-12]

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.[10] These connections could not be verified in other dissections.[11]

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.[10] 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.[10, 13] 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.[10, 13]

Renal Neural Anatomy around the Renal Artery

The renal plexus has been historically described as running circumferential around the renal artery based on cadaveric dissections and renal denervation procedures,[10, 11, 14] Two studies examining histological cross sections of 9 and 40 renal arteries confirms a circumferential distribution of nerves around the main renal artery.[15, 16] However, there are more nerve fibers on the ventral aspect of the main renal artery compared to dorsal aspect (11.0±3.5 versus 6.2±3.0 per section, $p<0.001$). There is a significantly higher number of average 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 versus distal segments (3.40±0.54mm versus 2.60±0.77, $p<0.001$).[15] 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 0.5mm from the lumen of the artery.[15, 16] The wall of a renal artery can have a depth up to 0.25mm, based on the upper bound 95% confidence interval of the tunica intima and media of the renal artery

in an elderly subset of patients.[17] This suggests that nearly all of the nerve fibers, which are at least 0.5mm 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.[15]

Sympathetic Activity and ADPKD

Elevated sympathetic nerve activity has been implicated in the pathophysiology of ADPKD. There is an increase in sympathetic nerve activity in hypertensive patients with ADPKD with both normal and impaired renal function.[18] The renin-angiotensin-aldosterone system is activated to a greater extent in hypertensive patients with ADPKD compared to patients with essential hypertension.[19] Furthermore, angiotensin II can enhance epidermal growth factor which promotes cyst formation in the kidney.[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.[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.[22] The role of renin angiotensin blockade in ADPKD will be better understood when the HALT-PKD trial is completed.[23] Renal denervation in the rat model of ADPKD causes a reduction in cyst size, decrease in blood pressure, and improvement of renal function,[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 in nature. 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.[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 the raise 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 two to seven days.[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.[1] 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 both acute and chronic causes of pain. A CT scan should be used, rather than MRI, if nephrolithiasis needs to be ruled out. Positron emission tomography can be utilized to

identify a cyst that may be infected.[25] Once acute causes are ruled out and pain appears to be more chronic, evaluation should attempt to differentiate between 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 improve functionality, rather than setting intangible goals of completely relieving all pain. Initial treatment for chronic pain in ADPKD is not specific to the disease and should consist of a step-wise approach (fig. 3), starting with conservative treatment and non-opioid analgesics that are beneficial to renal, hepatic, and mechanical causes of pain.

Conservative Treatment

Conservative treatment includes the use of ice, heat, whirlpool, psychobehavioral modification techniques, and the Alexander Technique.[6, 26] The Alexander Technique helps patients understand and modify what postures and movements result in pain. It has been shown to be beneficial in the treatment of chronic back pain,[27] and observations of its use in 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 non-opioid analgesic for long-term pain management in patients with underlying renal diseases. Non-steroidal 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% of patients experience renal failure by the age of 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 patients 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 V_2-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 amount of pain relief compared to placebo (5 versus 7 events per 100 person-years of follow-up, $p=0.007$) 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 which limits cyst growth could potentially improve pain control in ADPKD.

Autonomic Nerve Block and Spinal Cord Stimulation

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 suggest 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, radiofrequency ablation of the splanchnic nerves was able to provide pain relief in a patient with loin pain hematuria syndrome.[31] Celiac plexus nerve blocks with radiofrequency ablation of the intercostal nerves has been used to provide short term pain relief in a patient with ADPKD, followed by the use of spinal cord stimulation for longer term pain relief.[32]

Cyst Aspiration and Ablation

Cyst aspiration under ultrasound guidance is the least invasive procedure used to reduce the size of cysts for relief of pain, however pain recurs in 67% of patients after 18 months as the cysts reform.[33] 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. There are a variety of sclerosing agents that 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 out of 21 patients (81%) with ADPKD at a mean follow up of 28.5 months. All patients had between 3 to 6 cysts, which is a low number of cysts for patients with ADPKD.[34]

Cyst Decortication

Cyst decortication can relieve pain through 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 fifteen studies and evidence of sustained pain relief in the majority of patients five years out. Pain relief continues one year after the procedure in 80-92% of patients, which slightly decreases over time at longer follow up visits.[35] A long-term follow up with a mean of 10.9 years found that 8 out of 12 patients (67%) continued to have greater 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 (LCD) in patients with renal impairment, as decreased preoperative estimated glomerular filtration rate is associated with a progression to end stage renal disease after LCD.[36] However, there is no known causality of this association, and LCD remains a treatment option for pain 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 counseled that they may experience a temporary increase in pain post-operatively 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 ages 17 and 12.4 years) who had chronic flank pain refractory to narcotics of 6-9/10 on 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 follow up 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 follow up with no need for analgesics.[39] This approach is being using in a clinical trial (NCT00571909) with initial reports of six out of nine patients being pain free without analgesics at three month follow up.[26] A thorough wide dissection of the renal artery at the hilum may need to be performed during a renal denervation procedure in order 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 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,[10] implying that renal denervation would need to be performed around each artery.

Percutaneous transluminal renal denervation was able to relieve pain in a patient with ADPKD, and a follow up procedure on the contralateral side was performed due to the 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 and 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 treating chronic renal pain in patients with end stage renal disease when other treatment 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 three month follow up in 18 patients studied,[43] with evidence of long-term pain relief at 31 months in a separate study.[44] The laparoscopic approach is generally preferred over an open procedure due to decreased blood loss, shorter recovery, and decreased pain.[44] Patients with extremely large kidneys with a volume greater than 3500cc are at an increased risk of

conversion to an open procedure, 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 compared to renal transplantation followed by bilateral laparoscopic nephrectomy.[45] Unpublished data from our institution suggests that transplant with concurrent unilateral nephrectomy in patients with ADPKD results in a greater decrease in the number of antihypertensive medications needed compared to transplant alone.

Transcatheter Arterial Embolization

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

Hepatic Cyst Treatment

There are a variety of surgical approaches that can be performed for pain associated with hepatic cysts including cyst fenestration, cyst fenestration with hepatic resection, liver transplantation, and transcatheter arterial embolization. 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 one 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 follow up of 9 years has been demonstrated with 75% of patients showing a normalized or improved functionality measured by the Eastern Cooperative Oncology Group Performance Status.[47]

Conclusions

The presentation of pain in patients with ADPKD can be variable, 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. There are a variety of conservative, medical, and non-invasive procedures that 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 be implemented to 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 is a procedure that 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.

FIGURE LEGEND

Figure 1. Diagram of extrinsic renal innervation based on human cadaveric dissections and animal models. The lighter text and arrows represents nerve conections found in only a minorty of human cadavers. [7, 10-12]

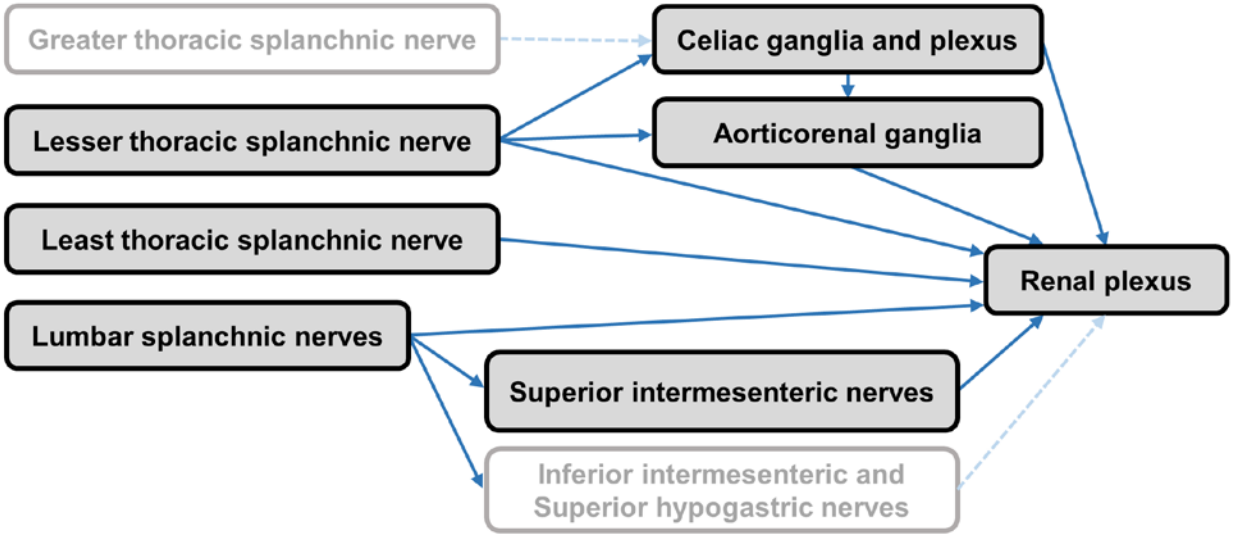


Figure 2. Illustration of renal innervation, based on the dissections of Mitchell GA.[10]

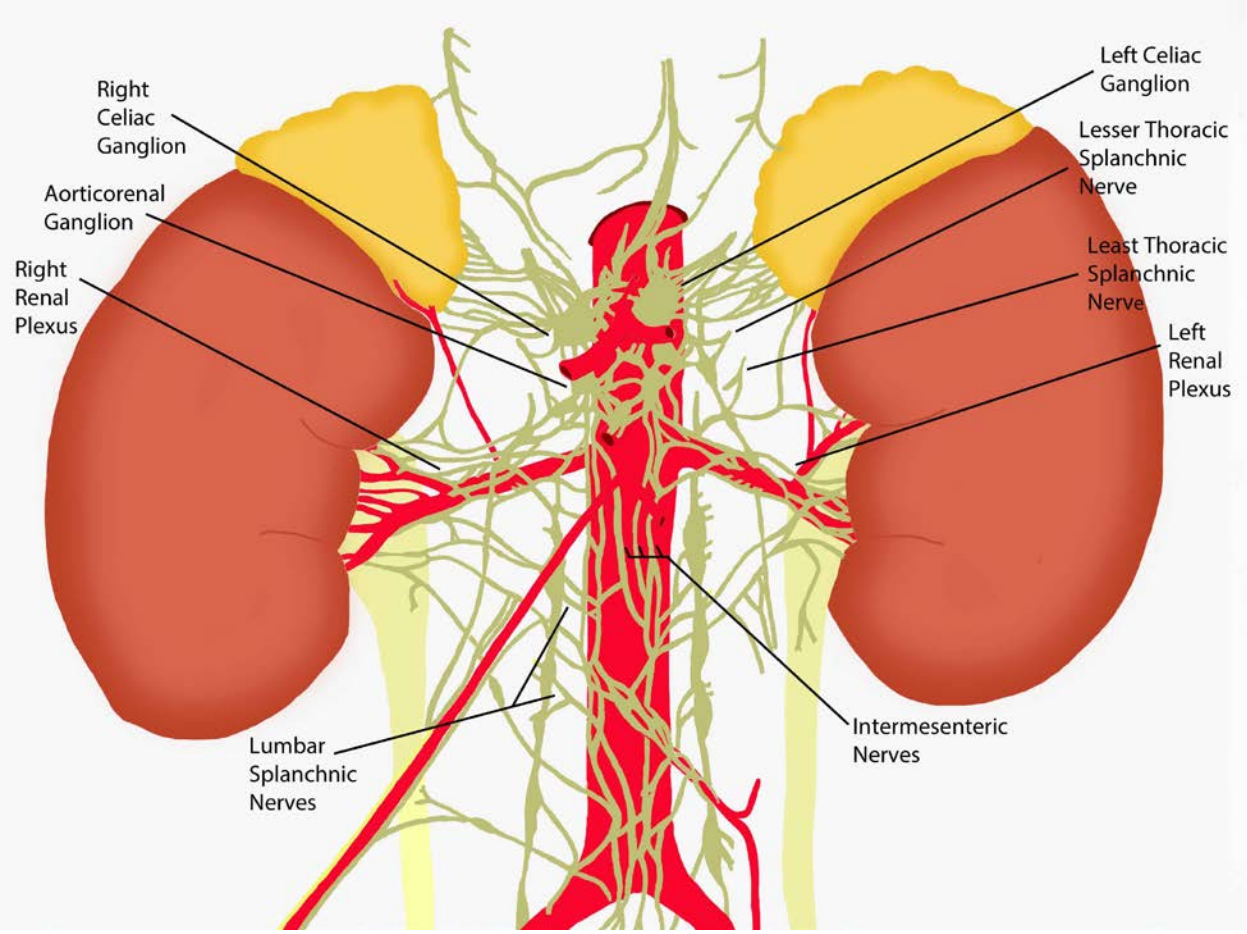
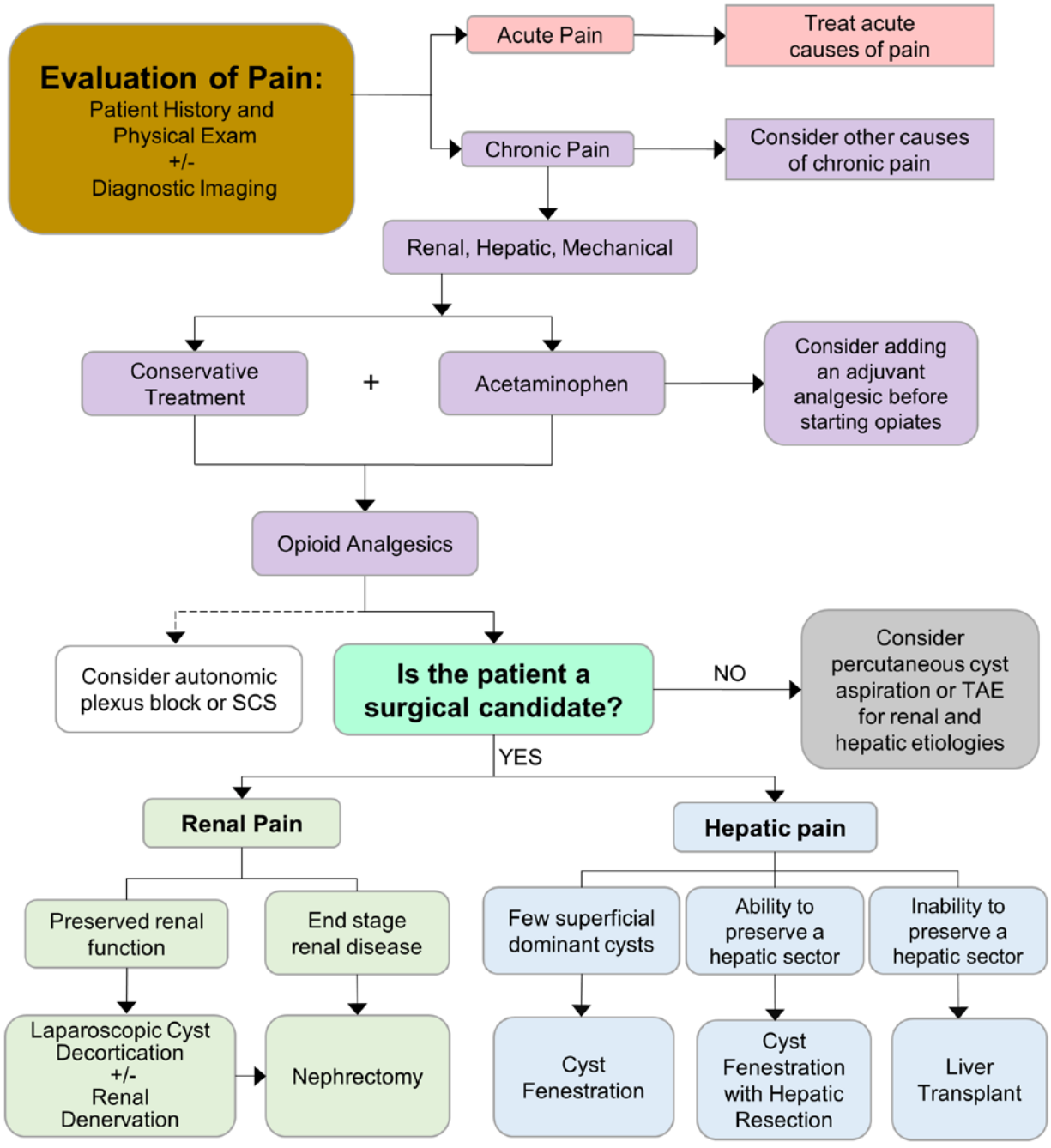


Figure 3. Flowchart of evaluation and treatment of chronic pain in ADPKD. SCS: spinal cord stimulation, TAE: transcatheter arterial embolization



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