PERSPECTIVES IN CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Gastrointestinal Manifestations of Autosomal-Dominant Polycystic Kidney Disease

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This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e10. Learning Objective–Upon completion of this activity, successful learners will be able to identify the various gastrointestinal manifestations of autosomal dominant polycystic kidney disease.

Autosomal-dominant polycystic kidney disease (ADPKD) is the most commonly inherited kidney disease, and the fourth most common cause of end-stage renal disease. ADPKD is a systemic disorder, associated with numerous extrarenal manifestations, including polycystic liver disease, the most common gastrointestinal manifestation, and diverticular disease, inguinal, and ventral hernias, pancreatic cysts, and large bile duct abnormalities. All of these gastrointestinal manifestations play a significant role in disease burden in ADPKD, particularly in the later decades of life. Thus, as ADPKD becomes more recognized, it is important for gastroenterologists to be knowledgeable of this monogenic disorder's effects on the digestive system.

Keywords: ADPKD; Cysts; Diverticulosis; Hernia.

Autosomal-dominant polycystic kidney disease (ADPKD) is the most prevalent monogenic disorder with lethal potential and the most commonly inherited kidney disease. It affects between 1/400 to 1/1000 people in the general population, equally in all ethnic groups, and is responsible for 10% of the patients younger than 65 years of age on renal-replacement therapy (RRT)[1,2] Mutations in 2 genes, *PKD1* and *PKD2*, account for most ADPKD; *PKD1* mutations affect 85%–90% of patients with ADPKD and *PKD2* mutations affect the remaining 10%–15%. Patients with *PKD2* disease tend to have a later onset of end-stage renal disease (ESRD) (mean age requiring RRT is 74.0 years vs 54.3 for *PKD-1* disease), with approximately 16 years of increased life expectancy.[1,3]

ADPKD is a systemic disorder that is associated with numerous extrarenal manifestations, many of which arise in the gastrointestinal tract (Table 1). With the subsequent improved survival of patients with ADPKD because of several therapeutic advances, these underappreciated extrarenal manifestations are increasingly being recognized as clinically relevant. Thus, it is critical for gastroenterologists to be able to adeptly identify the gastrointestinal manifestations of ADPKD, which can often adversely affect patients' quality of life, morbidity, and mortality. This review is the first to collectively summarize all of the reported associations between ADPKD and the digestive system.

Polycystic Liver Disease

Clinical Features

Liver cysts are the most common extrarenal manifestation of ADPKD; 58% of patients between the ages of 15 and 24 years old and 94% older than age 35 have cysts in the liver. Cyst burden (ie, cyst number and cyst volume) increases with age, and there is 0.9%–3.2% increase in liver size per year.[4,5] However, interestingly, hepatomegaly and increased liver parenchymal volumes are common before detection of liver cysts by imaging and is hypothesized to be secondary to microscopic cysts, biliary epithelial proliferation, or hepatocyte hyperplasia.[6]

Polycystic liver disease (PCLD) secondary to ADPKD should not be confused with isolated PCLD, which is also inherited in an autosomal-dominant manner and can be caused by mutations in *PRKCSH* and *Sec63*.[7] As compared with ADPKD PCLD, patients with isolated PCLD have more liver cysts that are larger in size (although it is unclear if there are differences in total liver volume) but less often require liver transplantation, perhaps because of the absence of kidney dysfunction in these patients.[8] However, despite these differences, most of the following information on ADPKD-associated PCLD is also applicable for isolated PCLD.

Abbreviations used in this paper: **ADPKD, autosomal-dominant polycystic kidney disease; CT, computed tomography; ESRD, end-stage renal disease; PCLD, polycystic liver disease; RRT, renal-replacement therapy.**

Most current article

1542-3565/$36.00
http://dx.doi.org/10.1016/j.cgh.2016.06.017

Table 1. Extrarenal Manifestations of ADPKD

Extrarenal Manifestations (frequency)
Gastrointestinal
• Liver Cysts (94% over the age of 35)
• Diverticular Disease (50-83% in ESRD patients)
• Hernias (45%)
• Pancreatic Cysts (9-36%)
• Choledochal Cysts (rare)
• Common Bile Duct Dilation (40%)
• Splenic Cysts (2.7%)[4]
Non-Gastrointestinal[12]
• Cardiac Valve Abnormalities (mitral valve prolapse- 25%)
• Pericardial Effusion (35%)
• Cerebral Aneurysms (9-12%)
• Arachnoid Cysts (8-12%)
• Spinal Meningeal Cysts (1.7%)
• Seminal vesicle Cysts (40%)
• Bronchiectasis (37%)
• Thyroid Cysts (not clearly defined)

Hepatic cysts are more prevalent in women, and the average volume of hepatic cysts is higher in women (5.27 mL) versus men (1.94 mL).[4,9] This difference in volume seems to widen with age, which may be explained by the observation that multiple pregnancies and exposure to oral contraceptive pills or estrogen-replacement therapy leads to worse disease.[5,10] A 19-patient prospective, nonrandomized study showed that polycystic volumes increased over 1 year in postmenopausal women taking estrogens.[10] Furthermore, progesterone has also been shown to stimulate the proliferation of cholangiocytes.[11] Thus, it has been recommended that oral, exogenous hormones or hormone-containing oral contraceptive pills should be avoided in women with symptomatic or severe PCLD.[12]

Approximately 20% of patients with PCLD develop symptoms, which can be the result of direct compression of nearby structures from the enlarged livers (can weigh up to 20 kg) or complications within the cysts themselves.[12,13] Abdominal distention, early satiety, nausea, emesis, esophageal reflux, dyspnea, and mechanical low back pain are all common compressive symptoms; furthermore, abdominal wall hernias, uterine prolapse, and symptoms related to compression of the hepatic veins (Budd-Chiari syndrome), inferior vena cava, portal vein, and bile ducts can rarely occur.[14]

Although vague, the previously mentioned symptoms can be very debilitating. Hogan et al[6,15] showed quality of life scores on the Short-Form 36 decreased with increasing (height-adjusted) liver volumes. Furthermore, symptoms are the most common reason patients are referred for treatment of their PCLD. Thus, in 2011, the PCLD complaint-specific assessment was established to assess the severity and impact of these patient complaints in a standardized, valid way to guide treatment decisions.[16] Notably, 9 of the 12 symptoms addressed in the PCLD complaint-specific assessment are related to effects of the liver size on the gastrointestinal tract.

Complications from the cysts themselves include infection, torsion, rupture, hemorrhage, or rarely cystadenoma or cystadenocarcinoma.[5,8,15,17–20] Cyst infection has a reported morbidity of 3% and mortality of 2% in patients with ADPKD on RRT.[21] The gold standard for diagnosis is a positive cyst aspirate culture with the presence of bacteria and/or neutrophils. However, this is not typically available to clinicians because the infected cysts cannot be identified or the cyst cannot be accessed percutaneously. Thus, these infections pose a great diagnostic challenge to clinicians because of the need to rely on a mix of indirect clinical, biochemical, and imaging data.[22] Patients classically present with fever, leukocytosis, and right upper quadrant pain. Blood cultures are positive in 10%–63% of patients, and *Escherichia coli* is the most common pathogen.[18,21,23] Carbohydrate antigen 19-9 levels can be markedly elevated (601–1644 U/mL) beyond what is seen in asymptomatic patients with ADPKD, and decrease in response to therapy.[24] A computed tomography (CT) scan or ultrasound can reveal findings suggestive of infection, but are often not specific enough to confirm the diagnosis.[21] ^{111}In-labeled leukocyte scanning and ^{18}F-fluorodoxygucose positron emission tomography scanning have both been shown to be reliable methods for diagnosis, but are costly and not widely available.[18,25–27] Intravenous antibiotics, such as fluoroquinolones, which have good cyst penetration because of their lipophilic properties, should be started for all patients. Also, drainage of the cysts in addition to intravenous antibiotics should be considered because this dual therapy has been shown to be more efficacious than antibiotics alone.[18,23]

Despite massive hepatomegaly, the displaced hepatic parenchyma is able to retain its overall function.[28] In fact, there have been cases where polycystic livers have been used for emergent transplantation.[29–31] Advanced fibrosis, portal hypertension, and the subsequent complications (eg, variceal bleeding, ascites) are rare and the result of either hepatic venous outflow obstruction or compression of the portal vein.[32]

Overall, laboratory abnormalities in PCLD are infrequent. In a cohort of 534 patients with ADPKD, only 2.3%, 2.7%, and 4.5% of individuals had levels of alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase above the upper limit of normal, and 5.1% had a serum albumin below the lower limit of normal (almost always from malnutrition rather than impaired synthetic function of the liver).[6] However, symptomatic patients undergoing evaluation for surgical intervention have laboratory aberrations more frequently.[14,21,33] In this group, γ-glutamyltransferase elevation is the most common, occurring in 60%–70% of patients (range, 1.5–7.0 times upper limit of normal). One potentially useful biomarker is carbohydrate antigen 19-9 because its serum levels are increased in 45% of patients with PCLD, and the degree of elevation positively correlates with polycystic liver volume.[24,34]

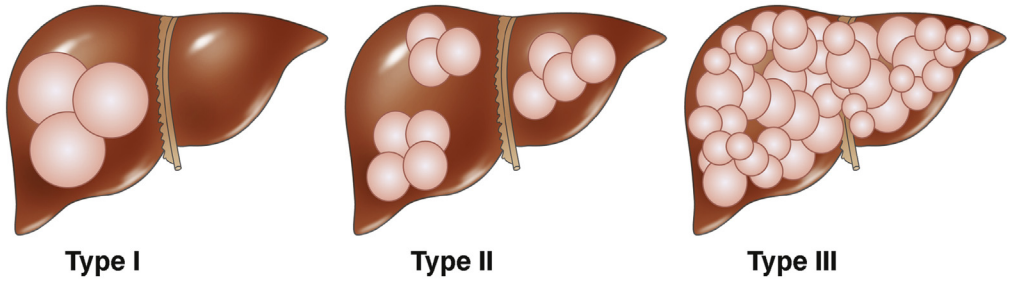

Figure 1. The Gigot Criteria for classifying polycystic liver disease. Type I is characterized by a liver that has <10 large (>10 cm) cysts. Type II is characterized by diffuse parenchymal involvement by multiple medium-sized cysts with large areas of noncystic parenchyma. Type III is characterized by large numbers of small and medium-sized cysts spread diffusely throughout the parenchyma with only minimal, normal areas.

According to the Kidney Disease Improving Global Outcomes ADPKD summary document, the use of radiographic imaging to determine the extent of liver cyst burden should be part of the initial assessment of all patients with ADPKD. Ultrasound or CT scan can be used, but magnetic resonance imaging is the most sensitive imaging modality for detecting cysts.[19,35] Because of the high water content in the cysts, there is a high signal intensity compared with hepatic parenchyma on T2 weighted images.[4,36,37]

Several classification systems to define the severity of hepatic cyst burden have been proposed. One such system is the Gigot Criteria, which categorizes patients according to number and size of liver cysts (Figure 1).[38] A second system, Schnelldorfer classification, aims to differentiate which patients would benefit from the different surgical therapies (Figure 2).[39]

Medical Treatment

The primary aim of the available medical and surgical therapies is to reduce symptoms by decreasing liver volume (Figure 2). There is no role for therapy in asymptomatic patients. Beyond limiting exposure to oral, exogenous hormones, medical therapy is centered on somatostatin analogues. These agents work by inhibiting cyclic adenosine monophosphate, a major promoter of hepatic cyst growth by increasing chloride and bicarbonate transport of fluid secretion across the apical membrane of cholangiocytes.[40,41]

To date, 3 randomized controlled trials have been performed with somatostatin analogues (Table 2). Caroli et al[42] performed a post hoc analysis of a double-blind, crossover, placebo-controlled study of 6 months of long-acting octreotide, 40 mg every 28 days, in 12 patients with ADPKD, which demonstrated a mean liver volume reduction of 4.0% (as assessed by CT) in the octreotide arm versus 1.25% increase with placebo ($P < .005$). Hogan et al[43] conducted a randomized double-blind, placebo-controlled trial of 42 patients (36 of whom had ADPKD-associated PCLD, 6 of whom had isolated PCLD) with monthly injections of long-acting octreotide (40 mg) for 1 year. This study

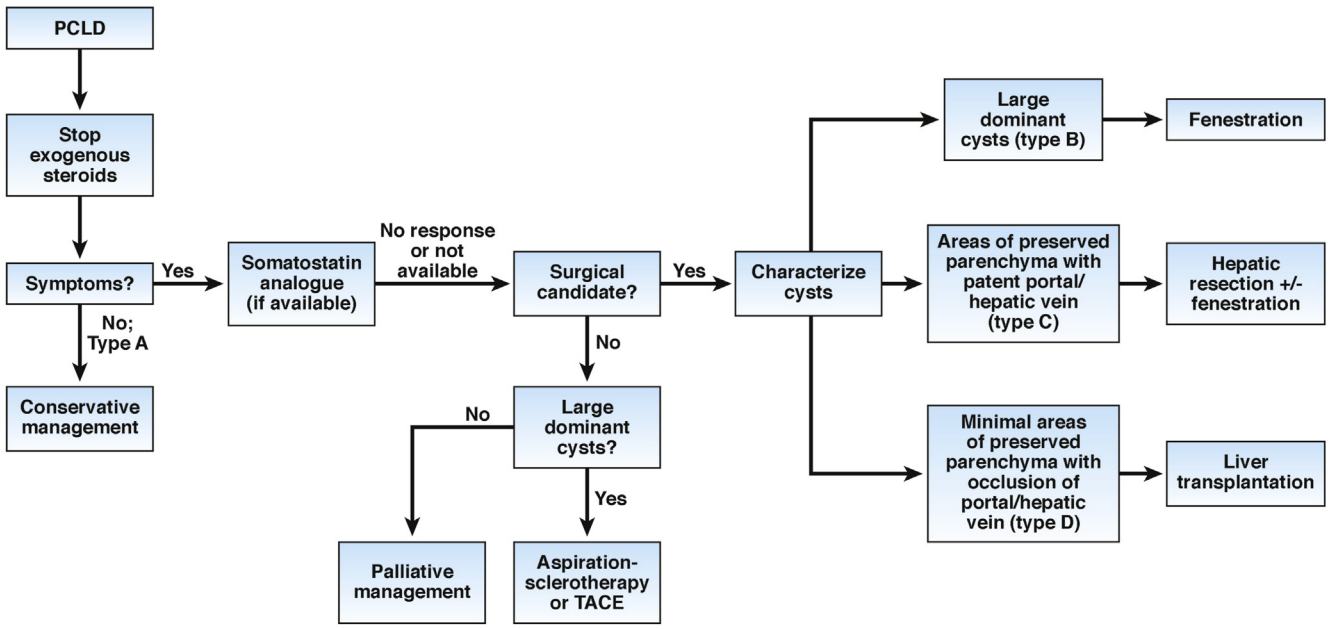

Figure 2. Algorithm for the medical and surgical management of polycystic liver disease, which incorporates the Schnelldorfer classification (types A–D).TACE, transarterial chemotherapy embolization.

Table 2. Summary of the 3 Randomized Controlled Trials Involving SAs

Study	Population	SA	Mean liver volume change with SA	Mean liver volume change with placebo	Imaging study used
Caroli et al[42]	N = 12 (all had ADPKD)	Octreotide	4.0% decrease in 6 mo	1.25% increase in 6 mo	CT
Hogan et al[43]	N = 42 (36 had ADPKD)	Octreotide	4.9% decrease in 1 y	0.9% increase in 1 y	MRI
LOCKCYST (van Keimpema et al)[45]	N = 54 (32 had ADPKD)	Lanreotide	2.9% decrease in 1 y	1.6% increase in 1 y	CT

MRI, magnetic resonance imaging; SA, somatostatin analogue.

demonstrated a mean volume decrease of 4.9% on magnetic resonance imaging with octreotide and an increase of 0.9% with placebo ($P = .048$). Furthermore, an open label extension of long-acting octreotide for 1 more year showed unchanged liver volume (the beneficial effects of the first 12 months were maintained).[44] Finally, the LOCKCYST trial, a double-blind, placebo-controlled trial of lanreotide, 120 mg monthly for 6 months, or placebo for 54 patients (32 with ADPKD-associated PCLD, 22 with isolated PCLD) demonstrated a 2.9% mean liver volume decrease on CT in the lanreotide arm as compared with a 1.6% increase with placebo ($P < .01$).[45] An open label extension of the study showed stability of the liver volume over the next 6 months in the lanreotide arm, and recurrence of growth (4%) once lanreotide was stopped.[46] The latter 2 randomized controlled trials also reported an improvement in quality of life in the patients exposed to somatostatin analogues. However, despite these beneficial effects, somatostatin analogues have not been approved for treatment of PCLD and can only be used in a clinical trial or in compassionate, off-label use.

The response to somatostatin analogues seems to be dose-dependent. For example, 120 mg of lanreotide for 6 months had a greater decrease in liver volume than patients treated with 90 mg, but more side effects were reported (LOCKCYST II trial).[47] Furthermore, looking at a pooled analysis for LOCKCYST I and II, 3 major findings emerged: (1) treatment with somatostatin analogues is equally effective for patients with ADPKD-associated and isolated PCLD, (2) efficacy does not depend on the size of a polycystic liver, and (3) women 48 years old or younger had a greater response to therapy when compared with older women (8.0% vs 4.1% reduction in liver volume).[48] The most common adverse events experienced with lanreotide, 120 mg, were abdominal cramps (51%) and diarrhea (63%), both of which resolved after several doses. Injection granulomas were infrequently reported.

Although 1 small retrospective study suggested that sirolimus in the post–kidney transplant setting may slow progression of liver cyst burden, the addition of everolimus in a prospective fashion to octreotide did not confer any benefit.[49,50] Pasireotide, a more potent somatostatin analogue with broader receptor specificity, has been shown to be more effective in inhibiting hepatorenal cystogenesis in mice with polycystic kidney and liver disease (PCK rats and *Pkd2*$^{WS25/-}$).[51] A prospective, double-blinded randomized controlled trial studying pasireotide is currently underway.

Surgical Treatment

Aspiration-sclerotherapy is a technique characterized by aspiration of a cyst followed by injection of a sclerosing agent that causes destruction of the epithelial lining to prevent fluid production. This technique is useful for patients who have 1 or a few large, dominant cysts with diameters greater than 5 cm and are also high-risk surgical candidates. The most commonly used sclerosing agent is ethanol, but minocycline and tetracycline have also been used. Cysts totally regress in 22% of patients, partially regress in 19% of patient, and recur in 21% of patients; symptoms from the cysts resolved or were reduced in most of patients.[52–54] In 1 series of 9 patients, a continuous decrease in the volume of liver cysts was seen over 4–6 months after the procedure, suggesting that patients should not be scheduled for a repeat one until 6 months have passed.[55] The most common complication was pain during the injection of the sclerosing agent, likely from peritoneal irritation.[54]

Transcatheter arterial embolization aims to selectively embolize the branches of the hepatic artery that supply major cysts, thereby disrupting the source of cystic fluid accumulation.[56,57] Two small case series revealed an improvement in symptoms and a decrease in total liver volume and intrahepatic cyst volume.[58,59] Larger studies are still needed before this can be routinely incorporated into clinical practice.

Fenestration is open or laparoscopic surgical deroofing of superficial and deep cysts with subsequent drainage of their contents into the intraperitoneal cavity. The major advantage of this approach is that multiple cysts can be drained at the same time. The best candidates are patients with Gigot type I and select patients with type II PCLD (those with a limited number of superficial, large cysts). Patients with most cysts in right posterior segments (VI, VII) or at the dome of the liver are better candidates for an open approach because they are poorly visualized with laparoscopy.[60] In 92% of both

open and laparoscopic cases, immediate symptom relief occurred, but cysts and symptoms recurred in 24% and 22% of patients, respectively. One series suggests that there is a higher recurrence rate with the laparoscopic approach versus the open approach (71% vs 20%), but another series revealed similar recurrence rates (11% in laparoscopic group vs 13% in the open group).[61,62] The overall mortality rate is 2% and morbidity rate is 23%, with complications that include ascites, pleural effusion, arterial and venous bleeding, and biliary leakage.[61]

Segmental hepatic resection should be considered for patients in whom fenestration alone is unlikely to significantly reduce liver volume, who are not candidates for liver transplantation, who harbor cyst rich segments but have at least 1 segment with predominantly normal liver parenchyma, and who are incapacitated by massive hepatomegaly.[54,63] The extent of resection ranges from a single segment to lobectomy, but at least 30% of normal liver parenchyma (with patent branches of hepatic and portal veins) needs to remain to prevent severe hepatic dysfunction postoperatively.[64] To preserve parenchyma, this approach is often combined with extensive fenestration of cysts in the remaining segments. Overall, symptom relief occurs in 86% of patients, and the rate of cyst recurrence is 34%.[54] In a retrospective study of 124 patients (111 of which had ADPKD), Eastern Cooperative Oncology Group performance status had normalized or improved in 75% of patients and 73% (of the 78 patients surveyed) had returned to work full-time during a mean of 9 years follow-up. The average reduction in hepatic volume in this study was 57%.[39] Collectively, the mortality rate of this procedure is 3% and the morbidity rate is 51%, which includes such complications as ascites, pleural effusion, biliary leakage, worsening kidney function, hemorrhage, and distortion of the intrahepatic vasculature and biliary system.[39,54]

Finally, liver transplantation is the only curative therapeutic option and should be limited to patients with type II/III with diffuse, small cystic disease that would not benefit from the previously described therapies.[63] Starzl et al[65] described "a syndrome of lethal exhaustion," which is characterized by intractable pain, cachexia, and fatigue as the major indication for transplantation. Further indications include recurrent cyst infections and untreatable complications, such as portal hypertension and nutritional compromise.[63] Model for end-stage liver disease exception criteria are used because synthetic function is rarely compromised, and malnutrition is the waiting list endpoint.[66] The overall morbidity rate reported is 41% and the 30-day mortality rate is 5%. The 1- and 5-year survival for combined liver-kidney transplant is 86% and 80%, respectively; liver transplant alone is 93% and 92%.[54] These data are similar to the 734 patients in the European Liver Transplant Registry who received a liver transplant for symptomatic PCLD from 1988 to 2009 and had a 5-year 85% survival rate.[67] It is important to note that 38% of the explantations in these patients were difficult secondary to adhesions from prior therapy. Furthermore, the quality of life improved in most (91%) patients who received a liver or liver-kidney transplant.[68]

Diverticular Disease

There is an association between ADPKD and diverticulosis in the presence of ESRD. Scheff et al[69] described 83% (10/12) of patients with ADPKD disease on RRT had colonic diverticulosis compared with 32% (10/31) of patients with ESRD without ADPKD and 38% (45/120) of control patients without ESRD. In a similar study, colonic diverticulosis was found in 50% (7/14) of patients with ESRD with ADPKD, whereas it was only found in 15% (13/86) of non-ADPKD ESRD control subjects.[12,70] Additionally, 1 case series described that 8 patients with ADPKD (4 with ESRD) also had duodenal diverticulosis.[71] In contrast, patients with ADPKD who had not reached ERSD had no significant increase in colonic diverticulosis as compared with age- and gender-matched control subjects (47% vs 59%).[72]

It is hypothesized that smooth muscle dysfunction from the *PKD1* and *PKD2* mutations may render these patients susceptible to developing diverticulosis.[73] Another hypothesis is that diverticulosis is related to abnormal extracellular matrix production, which has been observed in ADPKD.[74]

Patients with ESRD secondary to ADPKD also seem more prone to developing complications related to the diverticulosis. Scheff et al[69] also described 40% (4/10) of the patients with ADPKD on RRT developed diverticulitis compared with 0% (0/10) in the patients with ESRD without ADPKD and 0% (0/45) in the control patients without ESRD.[69] A separate study demonstrated that 20% (12/59) of patients with ADPKD ESRD had acute diverticulitis (6 of whom required surgical intervention), whereas only 3% (4/125) of ESRD control subjects developed diverticulitis.[75] Furthermore, in the posttransplant period, patients with a history of ADPKD accounted for 46% of the reported cases of complicated diverticulitis despite only accounting for 9% of the total transplant population.[76] Kidney Disease Improving Global Outcomes does not recommend routine screening for diverticulosis in patients with ADPKD ESRD at this time.

Hernias

The prevalence of hernias is also higher in patients with ADPKD. One retrospective study demonstrated that 45% (38/85) of patients with ADPKD ESRD developed hernias as compared with only 16% (7/85) of age- and sex-matched patients with other etiologies of renal failure and 4% (3/85) of general surgical control subjects. In fact, there were significantly greater numbers of inguinal ($P < .001$), incisional ($P = .019$), and paraumbilical ($P = .007$) hernias in patients with ADPKD. Interestingly, 18 patients were diagnosed before the

detection of renal disease. It has been hypothesized that the hernias are the result of abnormal extracellular matrix production and/or increased intra-abdominal pressure from cyst burden.[77]

This propensity to develop hernias is especially important to remember in patients with ADPKD on peritoneal dialysis. One study revealed that 46.2% (6/13) of male patients with ADPKD developed bilateral inguinal hernias while undergoing peritoneal dialysis as compared with only 3% (1/30) males on peritoneal dialysis secondary to other etiologies of renal failure.[78]

Pancreatic Cysts

Mice models with mutations in *PKD1* and *PKD2* have established a causal relationship between the genetics of ADPKD and pancreatic cysts.[79,80] According to autopsy data from patients with ADPKD, pancreatic cysts were found in 9% (6/67) of individuals.[81] In a study using ultrasound screening, 9% (16/173) of patients with ADPKD older than age 30 had pancreatic cysts, which were often a single, unilocular cyst. The presence of pancreatic cysts was related to increasing age and female sex and were exclusively found in PKD1 patients.[82] In a recent study, 36% (40/110) of patients with ADPKD had at least 1 pancreatic cyst on magnetic resonance imaging as compared with 23% (25/100) control subjects. In contrast to the previous findings, this study demonstrated that patients with ADPKD with a pancreatic cyst were 5.9 times more likely to have a PKD2 mutation.[83] Patients with ADPKD with pancreatic cysts are usually asymptomatic, but rarely these cysts can cause pancreatitis from compression of the pancreatic duct or may evolve into malignancies (eg, intraductal papillary mucious tumors or cystadenocarcinomas).[84–87]

Large Bile Duct Involvement

There have been multiple case reports describing the presence of Caroli disease, which is multifocal cystic dilation of the larger intrahepatic bile ducts, in patients with ADPKD.[88–90] Additionally, 1 study found that 40% (22/55) of patients with ADPKD had a dilated common bile duct on CT scan (defined as >7 mm in diameter) as opposed to just 9% (5/55) in patients without ADPKD.[91] Hogan et al[6] also demonstrated that common bile duct diameter positively correlates with height-adjusted liver volume and liver parenchymal volume. Common bile duct dilation is also postulated to be secondary to abnormal extracellular matrix production. Awareness of its association with ADPKD is necessary to prevent unnecessary diagnostic procedures.

Conclusions

ADPKD is the most common inherited kidney disease and is associated with numerous extrarenal manifestations. It is becoming increasingly important for gastroenterologists recognize the hepatobiliary, pancreatic, and luminal manifestations of this disease, which have significant effects on the quality of life, morbidity, and mortality of these patients.

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Conflicts of interest
The authors disclose no conflicts.