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An update on the pathophysiology and management of polycystic liver disease

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Abstract

Introduction: Polycystic liver disease (PLD) is characterized by the presence of multiple cholangiocyte-derived hepatic cysts that progressively replace liver tissue. They are classified as an inherited ciliopathy / cholangiopathy as pathology exists at the level of the primary cilia of cholangiocytes. Aberrant expression of the proteins in primary cilia can impair their structures and functions, thereby promoting cystogenesis.

Areas covered: This review begins by looking at the epidemiology of PLD and its natural history. It then describes the pathophysiology and corresponding potential treatment strategies for PLD.

Expert commentary: Traditionally, therapies for symptomatic PLD have been limited to symptomatic management and surgical interventions. Such techniques are not completely effective, do not alter the natural history of the disease, and are linked with high rate of re-accumulation of cysts. As a result, there has been a push for drugs targeted at abnormal cellular signaling cascades to address deregulated proliferation, cell dedifferentiation, apoptosis and fluid secretion. Currently, the only available drug treatments that halt disease progression and improve quality of life in PLD patients are somatostatin analogues. Numerous pre-clinical studies suggest that targeting components of the signaling pathways that influence cyst development can ameliorate growth of hepatic cysts.
1. Introduction

Polycystic liver disease (PLD) is an inherited ciliopathy / cholangiopathy characterized by multiple cysts which take up at least half of the volume of the liver parenchyma (1). PLD can occur as an extra-renal manifestation of autosomal dominant polycystic kidney disease (ADPKD) or less commonly, in isolation as polycystic liver disease (ADPLD).

During embryonic development, errors in genetic mechanisms and signaling pathways cause disruption in the biliary tree, leading to formation of cystic structures. The process of cyst formation in both ADPLD and ADPKD is complex, and cystogenesis involves defects in cilia lining the biliary epithelium as well as key proteins fundamental to cilia function. In ADPKD, the proteins are located in cilia which has led it to be classified as a ciliopathy (2). Conversely, hepatic cysts in ADPLD are lined by cholangiocytes and therefore ADPLD is classified as a cholangiopathy (3). Although popular belief is that cyst formation depends on excessive proliferation of biliary ducts, animal studies have shown it is related to increased and accelerated differentiation of hepatoblasts into cholangiocyte precursors (4). PLD has a heterogeneous set of structural changes of the biliary tree development.

Processes involved in cyst growth begin with ductal plate malformation which is compounded by abnormalities in cholangiocyte hyperproliferation and enhanced fluid secretion.

The cysts usually remain asymptomatic until adulthood, when they begin to grow under hormonal action and may potentially become symptomatic (5). Although exogenous estrogen and pregnancies appear to partake the pathophysiology of cyst formation in several retrospective studies (6-8), prospective studies exploring its role on the natural course of disease have been lacking. Current research suggests the role
of pregnancies may be limited as height-adjusted liver volume was similar in nulliparous females compared to multiparous females (9). Clinical manifestations of PLD are a result of either mass effect of the volume of hepatic cysts or to complications arising within the cysts. PLD rarely progresses to hepatic failure or clinical complications of portal hypertension. However the mass effect within the abdomen may have a significant effect on patients’ quality of life (QoL) and performance status (10-12).

This article provides an updated and clinically-focused summary of our current understanding of PLD. Management is largely focused at counseling patients and families and symptomatic management of complications. While most patients do not require any intervention, traditionally interventional radiology or surgery has been the preferred treatment option for mechanical destruction of cysts in advanced cases. However these options are invasive and cyst recurrence is not uncommon. Thus such approaches have significant limitations and are rarely indicated. There has been a impetus for drugs targeted at abnormal cellular signaling cascades to address deregulated proliferation, cell de-differentiation, apoptosis and fluid secretion. There has been progress in the development of pharmacologic treatments with demonstrated efficacy in animal models and human studies through the blockade of cyst secretion or inhibition of epithelial cells. However alternatives are needed, as a better understanding of the pathophysiology has the potential to identify promising drugs.
2. Epidemiology

The association between PLD and ADPKD was first described by Bristowe in 1856 (13). The polycystic liver is the primary presentation in ADPLD and polycystic kidneys are absent, whereas liver cysts develop in association with renal cysts in ADPKD (Table 1). Both ADPLD and ADPKD follow an autosomal dominant inheritance pattern (14, 15).

2.1. ADPKD

The epidemiology of ADPKD and associated PLD is well-studied. ADPKD is a major cause of chronic kidney disease and accounts for 7–10% of patients with end-stage renal disease. ADPKD is the most common monogenetic renal disease with a prevalence of 1:400–1:1000 (16) and is due to defects in either chromosome 16 (approximately 85% of patients) or chromosome 4 (approximately 15% of patients), thereby mutating the two transmembrane proteins; polycystin-1 (PC-1) or polycystin-2 (PC-2), respectively (17). These proteins are coupled in the ciliary membrane to form a functional complex (18, 19) to assist in mediating cell-cell adhesions in ciliated cells within the liver and kidney (20). Estimations of the prevalence of PLD in patients with ADPKD range from 20% to 94% (17, 21, 22).

2.2. ADPLD

In contrast, the prevalence of ADPLD is likely to be underestimated as most patients are asymptomatic and thus unlikely to ever receive a diagnosis. In approximately 80% of patients with presumed ADPLD, no genetic mutation is identified. In a minority of patients, a mutation on the short arm of chromosome 19 affecting protein kinase substrate 80 K-H (PRKCSH), that encodes for hepatocystin, or a mutation on the
short arm of chromosome 6 affecting Sec63, is found (23, 24). Hepatocystin and Sec63p are components of the molecular machinery involved in the translocation, folding and quality control of newly synthesised glycoproteins in the endoplasmic reticulum (25, 26). Interest in genetically unresolved subjects have resulted in whole-exome sequencing which have identified new missense mutations, such as LRP5 (27) and GANAB missense mutation (28).

3. Pathophysiology

The clinical course of PLD is distinctly heterogeneous. Part of this heterogeneity may be explained by Knudson’s somatic ‘second-hit’ hypothesis. Subjects carrying a germline mutation (the ‘first hit’ in a PLD gene) are susceptible. However it is the second somatic event, a second loss-of-function, which is required for individual cysts to develop. These two events eliminate a key functional gene complex (PC-1 and PC-2), which then modifies secretory responses and initiates focal proliferation and cyst formation from the affected epithelial cell (Figure 1). Somatic hits can range from missense mutations to loss of heterozygosity (29). Hence while ADPKD is phenotypically autosomal dominant, at the cellular level, it is likely to be a recessive disease requiring a second somatic event (30, 31).

Processes involved in cyst growth begin with ductal plate malformation and abnormal biliary cilia. This is compounded by factors including cholangiocyte hyperproliferation, fluid secretion and cyst expansion. In addition, proposed altered intracellular signaling pathways involved include (i) Ca^{2+} signaling, (ii) cAMP signaling and (iii) mammalian target of rapamycin (mTOR) signaling. (32-34).
3.1. Ductal malformations

Hepatic cystogenesis likely begins in embryological phase as the formation of the ductal plate is required for development of healthy bile ducts. Incomplete remodeling of the ductal plate in PLD results in the persistence of embryonic bile duct structures that do not communicate with normal bile ducts. These complexes of disconnected and ectatic bile ductules, also termed von Meyenburg complexes, are subject to progressive dilatation since they do not undergo apoptosis resulting in the formation of multiple cysts (21, 35, 36).

3.2. Abnormal biliary cilia

Primary cilia are mechanosensory organelles which can moderate intracellular levels of cAMP and Ca$^{2+}$ when bent by bile flow. The PC is a solitary non-motile organelle which is different to normal cilia on many epithelial cells. The structures are immotile but sense fluctuations in osmolality and composition of bile (37-39). It has been recently recognized that they also transduce molecular signals including Hedgehog and wnt pathways. PC-1 and PC-2 are located in the primary cilia. When their genes are mutated, the absence of their protein products results in defects in ciliary structure as well as their sensory and transducing functions. This causes a decreased Ca$^{2+}$ level and an increased cAMP level resulting in hyperproliferation, abnormal cell-matrix interactions, an imbalance in fluid secretion and absorption; and ultimately cystogenesis (40).

3.3. Hepatic cyst growth

Two main signaling pathways implicated include cAMP-mediated activation of the extracellular regulated kinase (ERK) pathway (41) and the mTOR-mediated signaling
cascade (42) (Figure 2).

3.3.1. Cholangiocyte proliferation/ Biliopathy

Cholangiocytes (which are normally quiescent) start to proliferate by releasing cytokines, growth factors, neuropeptides, and hormones to regulate interaction with the surrounding environment and maintain biliary homeostasis. Cystogenesis in PLD involves overexpression of growth-factor receptors and loss of adhesion (20, 43, 44). Estrogens act not only directly but also by promoting the synthesis and release of growth factors from cyst epithelium (45-47).

3.3.2. Fluid secretion

The fluid homeostasis is in flux as secretin promotes fluid secretion in hepatic cysts (32, 48). Secretin, the major cAMP agonist in cholangiocytes, stimulates the insertion of multiple transporters and channels into the apical membrane of cholangiocytes. Biliary epithelia maintain a cAMP-dependent Cl\(^-\) and HCO\(_3\)^- secretion that facilitates fluid secretion (49, 50). Somatostatin, which has an antisecretory activity, reduces cyst volume in rat models and in patients (48, 50, 51).

3.3.3. Cyst expansion

Metalloproteases, highly elevated in liver cyst epithelium, remodel the extracellular matrix surrounding the cysts (52). Cyst expansion also requires vascular supply, supported by numerous cytokines (IL-6 and IL-8) and growth factors such as vascular endothelial growth factor (VEGF) (20). Inhibition of VEGF attenuated the progression of liver cysts in an experimental mouse model of ADPKD (53). Similar pharmacological inhibition of the VEGF signalling pathway in humans could prove to be an important therapeutic target for treatment of PLD. While VEGF is secreted by
cholangiocytes and cysts lining the biliary epithelium, VEGF receptors are also expressed in these same cells (47, 53, 54), creating autocrine loops.

3.4. Altered intracellular signaling pathways
Defects in primary cilia function cause a reduced cytoplasmic level of Ca\(^{2+}\) (40). Proliferation of cholangiocytes is a Ca\(^{2+}\)-dependent process (40). It has been suggested that the disturbed intracellular Ca\(^{2+}\) homeostasis in ADPKD accounts for the increased cAMP levels. High levels of cAMP causes activation of two cAMP effectors (55) which upregulate the ERK1/2 pathway, resulting in cholangiocyte proliferation and fluid secretion (41, 55, 56).

Another pathway involved is mTOR; which has diverse roles in protein translation, cell growth and cell proliferation. It also has anti-apoptotic and pro-angiogenic effects (57). PC-1 usually attenuates the activity of mTOR by forming a complex with tuberin to block the inactivation of mTOR through phosphorylation by ERK and Akt kinases. Defects in PC-1 result in abnormal upregulation of mTOR. As expected, the expression of mTOR is increased in the epithelium that lines the cysts in PLD (42). Rapamycin, as an mTOR inhibitor, retards the development of renal cysts and the rate of decline in renal function in rodent models of polycystic kidney disease (58).

4. Natural history
Patients with PLD may stay asymptomatic for most of their lives. Symptoms predominantly arise from the compression imposed by hepatomegaly from massive cysts (17). Symptoms can manifest in the form of dyspnea, early satiety, and gastroesophageal reflux (Table 2). In ADPKD, hepatic cysts are the most common extra-renal manifestation. The hepatic cysts are often incidental discoveries and
clinically insignificant. The growth rate of polycystic livers is estimated at 1.8% in 6-12 months (1, 48, 51).

One study found that patients with ADPLD have greater numbers of liver cysts and cysts with larger volumes than those with ADPKD who have polycystic livers (59). A retrospective study on patients with ADPKD found that risk factors for the presence of hepatic cysts include older age, female gender, and history of multiple pregnancies (60). In women, under hormonal influence, the cysts can progress rapidly and can result in liver parenchyma atrophy (21). The promotion of liver cyst growth by estrogen may be related to the expression of α- and β-estrogen receptors by cholangiocytes (61).

4.1 Hepatic complications

It has been predicted that about half of the patients with advanced hepatic disease have had cyst hemorrhage, cyst rupture or a cyst infection (26, 62). Cyst infections are a serious complication because of its indolent course, and high risk of recurrence. Spontaneous cyst rupture is extremely rare and has been associated with hemodynamic compromise (63). If intra-peritoneal fluid leakage persists, surgical intervention is required for hemostasis control (64).

In advanced stages there are two processes that may result in portal hypertension. First, there is reduction of hepatic vein outflow (HVO) which manifests with abdominal pain, hepatomegaly and ascites. Hepatic vein thrombosis is a recognized cause of HVO obstruction (65) and is associated often with intrahepatic collateral venous drainage as well as greater mortality (66). Massive hepatomegaly may also compress the inferior vena cava (IVC), which is characterized by increased renal
outflow pressure that provokes development of ascites and lower extremities edema (66). Secondly, portal vein inflow may be reduced in advanced disease due to the volume effect of cysts (67). While it has been estimated that hepatic cysts accounts for 10% of deaths in patients with ADPKD on hemodialysis, liver failure and death from isolated ADPLD is rare (22).

4.2 Renal involvement
The main distinguishing feature between ADPLD and ADPKD is the presence of polycystic kidneys (59). ADPKD results in renal dysfunction in the majority of patients. A strong correlation between renal dysfunction and hepatic cysts has also been demonstrated in observational studies (22, 60, 68). In contrast, renal cysts are found in 28-35% of ADPLD patients and renal failure does not occur (21, 26).

4.3 Malnutrition
In advanced cases, the mass effect and pressure within the abdomen leads to a significant loss of appetite, nausea and early satiety, leading to poor protein and energy intake. These symptoms are exacerbated by renal dysfunction (69-71). The consequence may be the onset of quite significant protein-calorie malnutrition with loss of muscle mass and fat stores. Such effects in themselves may jeopardize outcomes. Sarcopenia is highly prevalent is patients with symptomatic PLD (42%) (72). Therefore, assessment of nutritional status even in the early stages of PLD is recommended to ensure timely interventions (10, 27). Traditional anthropometric parameters, such as body mass index and body weight, are of limited value because of the fluid-filled kidneys and liver. A study found that height-adjusted total kidney and liver volume was the sole significant predictor of malnutrition after adjusting for other
risk factors, including renal function (73). Temmerman et al (2015) described how low dose lanreotide reduced liver volumes – however, patients continued to lose weight and muscle mass (74). Research into whether treatment modalities facilitate weight gain and muscle mass may prove to be informative.

In addition, a devastating consequence to severe PLD is poor body image, depression, loss of function, and overall poor QoL (75). Patients with severe PLD are often too incapacitated to independently perform activities of daily living. Indeed, patients with severe ADPLD often describe their condition as equivalent to being heavily pregnant.

5. Diagnosis
The most common methods for the diagnosis of PLD are Ultrasonography (US) and computed tomography (CT) due to their ability to image the liver, widespread availability, and acceptable cost (76, 77). MRI is more sensitive and specific and can also provide information that is especially useful for operative planning (22). On US, hepatic cysts are non-enhancing and well-circumscribed. If cysts have higher attenuation value, aggregated fibrin deposits and internal septa of hematomas (64, 78) bleeding, infection, or neoplasm should be considered. Currently, agreed radiological diagnostic criteria for ADPLD are lacking. Uniform diagnostic criteria are lacking. In addition, the US criteria for ADPKD should not be met (26, 79). However, in patients from families with ADPLD, ≥4 liver cysts can be sufficient for diagnosis (80). Clinical differentiation from ADPKD remains a challenge in patients without a positive family history, as patients with ADPLD may
have incidental renal cysts and patients with ADPKD might have polycystic livers as a predominant feature.

The Gigot criteria are used to crudely determine the severity and distribution of cysts in patients with PLD(81) (Table 3). They are based on the number and size of hepatic cysts and the amount of residual liver parenchyma. Moreover, the Gigot classification is subjective and does not account for vascular compromise or sectoral (sectional) liver parenchymal sparing. Other classification criteria includes Schnelldorfer criteria (Table 4) which better identifies patients who would benefit from resection or transplantation(82). The extent of the disease is more accurately assessed by CT or MRI volumetry (83, 84).

In most patients with PLD, liver function tests are usually normal (85). In advanced disease it has been observed that alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), aspartate aminotransferase (AST), and total bilirubin are commonly elevated between 15% to 70% (11). The elevated ALP and GGT levels probably reflect activation of cholangiocytes (59, 60). Bilirubin is rarely elevated but in advanced cases jaundice may arise due to compression of the common bile duct secondary to a strategically located cyst. Ca 19-9 can be elevated in PLD as it is produced by the epithelial lining of the cyst wall. However there are currently no guidelines for levels that predict symptomatic disease (86). The level is elevated in 45% of ADPLD patients and is not associated with the presence of malignancy (86). Markedly raised levels should prompt one to consider hepatic cyst infection. With resolution of infection, the levels should decline (87).
6. Non-pharmacologic interventions

The majority of patients will not require treatment; instead reassurance and avoidance of repeated abdominal imaging (to restrict cumulative radiation doses and minimize unnecessary patient anxiety) is recommended. Symptomatic patients may require treatment when they experience organ dysfunction due to the raised hepatic volume or when there are complications from their cysts such as torsion, infections or hemorrhages. The goal of management is to decrease the total liver volume to provide abdominal decompression. Higher liver volumes were associated with a lower QoL (88, 89). The pharmacological and non-pharmacological options are listed out in Table 5.

Percutaneous treatment options for PLD include cyst aspiration and sclerotherapy, cyst fenestration and transcatheter arterial embolization. Surgical interventions including hepatic resection and liver transplantation. In general, several factors have to be considered before any surgical intervention is recommended: (1) The amount of cystic burden; (2) The location of the cysts; (3) The vicinity of the cysts to the main biliary ducts and portal and hepatic vein branches and (4) the availability of liver transplantation. Despite the traditional widespread use of radiological and surgical procedures, such procedures are now uncommonly used due to cyst recurrence leading to limited and transient benefits, and significant complications. Furthermore there are no controlled trials with most practices relying on center-dependent experience (59).

6.1. Cyst aspiration & sclerosis

Aspiration-sclerotherapy involves aspiration and puncture of a cyst followed by injection of a sclerosing agent that causes destruction of the epithelial lining inhibiting
fluid production (90, 91). The main indication for aspiration-sclerotherapy is the presence of a dominant large symptomatic liver cyst; Gigot’s type I. The most commonly used sclerosing agent is ethanol (92, 93). Complications encountered include pain during ethanol instillation, probably due to peritoneal irritation (1). Cysts totally regressed in 22-55% (94, 95) with an 80% recurrence rate and 50% for retreatment for recurrent symptoms (96). However most patients with polycystic disease have too many cysts or cysts are of insufficient size to warrant this approach.

6.2. Fenestration

Unlike aspiration, fenestration is favored in patients who have multiple cysts in close proximity (97). Fenestration involves both aspiration and surgical unroofing of multiple superficial large cysts. This treatment is recommended in Gigot type I–II PLD and after unsuccessful outcomes with aspiration–sclerotherapy. While it is usually performed laparoscopically, conversion to open technique is sometimes required (97), although is associated with prolonged hospitalization and morbidity. Immediate outcome including symptom relief is achieved in the majority of cases (92%), but cyst recurrence (24%) and symptoms recurrence (22%) is considerably high. Re-operation is required for management for the majority of patients with recurrences (1). Complications of fenestration include ascites, pleural effusion, hemorrhage and bile leakage (98).

6.3. Trans–catheter arterial embolization

Trans-catheter arterial embolization (TAE) aims to selectively embolize the hepatic artery branches that supply the major liver cysts (99) using microcoils or polyvinyl alcohol particles (100). The goal of TAE is to limit the presumed source of cystic-
fluid accumulation (99, 101). A recent series showed that treatment failure rate may be as high as 70% (102). For patients with advanced PLD and multilobal disease, TAE can be technically challenging. Further evidence is required to establish if TAE serves as a safe and effective option for PLD treatment.

6.4. Hepatic resection
For patients with severely symptomatic polycystic liver disease with preserved liver and renal function and more than one sector of normal liver parenchyma, hepatic resection is a safe and feasible strategy which provides symptomatic relief and prolongs the need for a liver transplant (103, 104). The use of post-operative long-acting somatoatstin analogue has the ability to halt the growth of remaining cysts and prevent new cysts from developing (103). Most hepatic resections are either non-anatomical if minor (< 3 segments), or major (4 or more segments) with fenestration.

The extent of the resection is based on the location of cysts and varies from a single segment to an extended lobectomy. The significant distortion of the intra-hepatic vasculature and biliary tree makes these procedures technically very challenging. In select cases, a combination of segmental resection with fenestration of remaining cysts can be considered. Symptom relief is achieved in 86% of cases although cyst recurrence is expected in one third of patients (1). Compared to radiological options, segmental resection is associated with high morbidity (51%) which includes ascites, pleural effusion, biliary leakage, and hemorrhage (1) as well as mortality (82). Another disadvantage of hepatic resection is the risk of subsequent adhesions which increases the technical difficulty or recipient hepatectomy and may make future liver transplantation difficult.
6.5. Liver transplantation

If liver transplantation is available, then this is the preferred option for patients with advanced disease rather than using it as a last resort in patients who have failed radiological or surgical interventions (75, 80, 96). Schnelldorfer et al. (82) classified PLD into four types; liver transplantation is recommended for type D that is marked by severe symptoms, absence of normal liver parenchyma and the occlusion of the isosectoral portal or hepatic veins. Malnutrition and nutritional deficiencies are important additional drivers to transplantation (105). Placement on a transplant waiting list, prioritization and allocation rely on the careful consideration of a multidisciplinary panel. Exceptions to the current organ allocation system based on the Model for Endstage Liver Disease (MELD) score occur (106, 107) as hepatic functioning is usually normal. For patients undergoing liver transplantation for PLD, perioperative morbidity is 40%-50%, whereas overall mortality is 10%-17% (1). Hence risks of surgery need to be carefully considered as even severe PLD is not associated with excess mortality when left untreated (1, 108, 109). Despite this, 91% of patients had a substantial improvement in health-related QoL measures (75).

7. Pharmacologic interventions

In recent years, several randomized clinical trials have been performed to study the effects of drugs on the growth of hepatic cysts (12, 110, 111). Unlike the existing standard of care, these treatments are designed to attenuate the progression of the disease in target tissues and to prevent the onset of organ failure. New potential pharmacological therapies are based upon discoveries of the molecular and cellular signaling cascades that are involved in ADPKD, resulting from the loss of PC-1/PC-2
function (2). Drugs that have been tested include the mTOR inhibitors, sirolimus and everolimus (112), somatostatin analogues such as octreotide (51, 113, 114), lanreotide (48, 74), pasireotide (115), the vasopressin V2 receptor antagonist; tolvaptan (116), and most recently, ursodeoxycholic acid (117).

7.1. Somatostatin analogues

While there are presently no approved medical treatments for PLD, there have been recent advancements with somatostatin analogues (118). There are 5 somatostatin receptors SSTRs (SSTR-1 to -5), and each has unique affinity for somatostatin, octreotide, lanreotide, and pasireotide. Somatostatin analogues are cAMP level inhibitors and decrease fluid secretion and cell proliferation through the Gi α subunit (50), providing a novel opportunity to modulate cystogenesis. They also inhibit the expression of IGF-1, VEGF, and other cytogenetic growth factors as well as the downstream signaling of these receptors (119). Its use was first demonstrated in the pck (PKHD1, fibrocystin) rat model of PLD (119) where cAMP concentrations in cholangiocytes were 2 times greater than the control. Octreotide lowered cAMP concentration in cholangiocytes and serum and suppressed hepatic disease progression, resulting in reductions in liver weight and cyst volume. Several RCTs have demonstrated a reduction in total liver volume in the treatment group compared to an increase in the placebo group; using octreotide (51, 114) and lanreotide (48).

Hogan demonstrated a 4.95 ±6.77% reduction in liver volume at one year (51) and, Van Keimpema et al demonstrated a 2.9% reduction in liver volume at 6 months, and a median reduction in liver volume of 4% at the end of one year of lanreotide treatment (48). This effect is dose dependent; patients treated with 120 mg lanreotide demonstrated a greater reduction in liver volume (decrease of -123 mL) than patients
treated with 90 mg of lanreotide (decrease of -82 mL) or placebo (increase of +36 mL) (120). Effects of somatostatin analogues beyond 1 year are also promising. In a study with a 2-year open-label extension study, therapy with long-acting octreotide over 4 years in selected patients arrested PLD progression, ameliorated symptoms and improved QoL (121). Cessation of therapy resulted in immediate recurrence of liver growth, indicating that continuous treatment is necessary to maintain the beneficial effect (121), same as a previous study (122). Whether alternating treatment periods may prove to be more cost effective of chronic somatostatin inhibition therapy is worth studying.

In the PKD rat model, pasireotide, a more potent somatostatin analogue with broad receptor specificity, was significantly more effective in diminishing hepatic and renal cystogenesis than octreotide (115). Pasireotide is also more stable (12-hour half-life) than octreotide (70–113 minutes). It is used for the treatment of Cushing’s disease, and is currently being investigated for management of acromegaly and neuroendocrine tumors. A clinical trial (NCT01670110(123)) assessing the efficacy of pasireotide in PLD is now underway at Mayo Clinic. In the abovementioned trials, there were minimal side effects with somatostatin analogues (122); they were mainly abdominal cramps and mild diarrhea with loose, pale stools (48, 51). These adverse events waned with repeated injections, after administration of pancreatic enzymes or after reduction of the dose (124). Somatostatin analogues have been found to improve health-related QoL in symptomatic PLD and hepatomegaly and improve general health perception (125). Pooled data from three RCTs on somatostatin analogues identified women, particularly young women (<48 years of age), who had the greatest reduction in total liver volume (8%) (p < 0.001) (126). The reasoning for this is unknown, but estrogen has been found to boost the response to somatostatin for
pituitary tumors and other conditions. This may be due to estrogen-induced modification of intracellular signaling pathways, such as JAK-STAT, ERK, or AP1. This data suggests that treatment should be directed towards women.

7.2. mTOR inhibitors

mTOR inhibitors have immunosuppressive effects (127) and are thought to have antiproliferative effects on cysts in polycystic liver and kidney disease. In animal models of PKD, mTOR inhibition reduced kidney size and cyst volume and slowed disease progression (128-130). Unfortunately, mTOR inhibitors in clinical trials have been disappointing. Sirolimus and Everolimus were studied in Phase-II prospective randomized control trials but neither drug showed substantial therapeutic effects in renal cystogenesis (131-133). In contrast, in a case series in which kidney transplant recipients with ADPKD who received sirolimus had a mean reduction in liver volume by 11.9%, as compared with a 14.2% increase in liver volume in the patients who received tacrolimus (42). The side effects of mTOR inhibitors increase risk of infection and malignancy with long-term use are serious. Other side effects can include dyslipidemia, vascular thromboses and pulmonary disease. Everolimus did not enhance the beneficial effect of octreotide in reducing liver volume in patients with ADPLDs (134). Overall, the role of mTOR inhibitors in the treatment of patients with ADPLDs has not fulfilled expectations and is not currently recommended (117).

7.3. Ursodeoxycholic acid

Ursodeoxycholic acid (UDCA) is a Ca\(^{2+}\) agonist in hepatocytes and cholangiocytes and was shown to halt liver disease in a rat model of PLD. Its mechanism of action is by inhibiting cystic cholangiocyte hyperproliferation and decreasing the level of
cytotoxic bile acid species in the liver. An RCT demonstrated an increase in total liver volume increased by 4.6 ± 7.7% after 24 weeks of UDCA treatment compared to 3.1 ± 3.8% in the control group (p = 0.493). However, UDCA inhibited liver cyst volume growth in ADPKD patients compared to controls (p = 0.049) (117).

7.4. Vasopressin-2-receptor antagonists

The vasopressin-2-receptor (V2R) is located on renal tubular epithelia and upregulates cAMP which enhances both secretion and proliferative responses (135). Blockade of vasopressin on the Gs protein-coupled receptor V2 in the kidney using tolvaptan has been shown to decrease cAMP levels inhibit renal-cyst enlargement and improve renal function in the pck rat model (127, 136). Preliminary results of a controlled trial of tolvaptan (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and its Outcomes, TEMPO trial; ClinicalTrials.gov Identifier: NCT00428948) (116) show a significant protective effect against kidney growth in the first year of treatment. However, the V2R is not expressed in cholangiocytes, implying that V2R antagonists will probably be ineffective in treatment of liver cysts although research is needed in this area (116).

8. Conclusion

PLD may occur in isolation or as the major extra-renal manifestation of ADPKD. PLD is a progressive disease, and a substantial minority of patients will develop severe symptoms. Management of patients with PLD should begin with advice to avoid estrogen-containing hormone therapies. For highly symptomatic cases with massive hepatic cystic disease, radiologic or surgical interventions may be considered but have limited efficacy due to recurrence of cysts and symptoms, significant
morbidity and even mortality. If available, liver transplantation should be considered for those with major impairment to their QoL secondary to a pronounced mass effect within the abdomen. Advances in the understanding of signaling pathways involved in polycystic disease has stimulated investigators to pursue new medical treatments. Although the exact pathophysiology of cyst formation remains to be unraveled, it is clear that the intracellular signalling routes that involve cAMP, calcium concentration, VEGF or mTOR are aberrantly regulated in polycystic livers. These signaling routes are promising targets for therapeutic intervention in PLD. In particular the use of long-acting somatostatin analogues has been the medical mainstay in the treatment of liver cysts. Future directions include identifying other targets and determining whether a combination of drugs which act on different pathways may have a synergistic effect on volume reduction. Ultimately these efforts should provide treatment recommendations that are individualized.

9. Expert Commentary
Apart from liver transplantation and somatostatin analogues, traditional methods of treatment have not been shown to change the natural course of the disease. There is currently no consensus on thresholds for treatment and several questions remain unanswered; who needs therapy and when should therapy be initiated? Most clinical studies involve patients with severe hepatomegaly with a median total liver volumes range of 4500 to 6500 mL. Earlier observations suggested that patients with very enlarged livers responded to treatment more efficiently than those with smaller livers (51). However a study by Pisani used relatively small median liver volumes at baseline (1477mL) and demonstrated a substantial reduction of 7.8% in total liver volumes in response to octreotide (113). As such, initiating medical therapy early
during the course of the disease before QoL has been influenced is a logical step. Early treatment may also help stop progression to more severe and irreversible stages of the disease that may require surgical interventions and impact on patient QoL. The results of clinical trials in PLD suggest that lifelong treatment with somatostatin analogues might be necessary to maintain its effects. However, this is complicated by the expense of treatment as it is currently used off-label or in the context of clinical trials. The high costs make it infeasible to provide routine treatment in asymptomatic patients. Rather the decision to treat should be selectively based on relative rapid cyst growth rate as well as patient-specific factors to prevent the development of highly symptomatic disease. As a result, it is imperative to explore factors which predict response as well as characteristics that would warrant long-term therapy. These findings will help us to individualize treatment in PLD patients (137).

The answer to these questions may also lie in determining the factors responsible for the phenotypic variability of PLD as well as exploring the pathways involved in genotype-to-phenotype expression. Extending upon the “two-hit” hypothesis, a question that arises is what factors manipulate somatic mutations to result in different phenotypes? It appears that epigenetic modifications and modifier genes may have key roles. Epigenetic alterations are a phenomenon that modifies gene expression and activity without changing DNA sequence. Only recently, has epigenetics been associated with the pathogenesis of renal cysts in ADPKD, however it has not been studied in PLD (138).

PLD is a heterogeneous disease; there are large variations in the extent and speed of cyst development amongst patients. In addition, there is a significant proportion of patients (15%) who do not respond to therapy (48). It is therefore important to
identify patients who are most likely to progress and develop severe PLD and to benefit most from therapy. We know from a recent study that genotype is not a predictor of severity of liver cysts, in contrast to the renal phenotype (9). This indicates modifiers beyond the disease gene significantly influence the phenotype.

Many generic patient-reported questionnaires are not validated in PLD or lack specificity for PLD as they do not include items that address extra-abdominal symptoms such as increased abdominal girth or dyspnea. As a result, it is difficult defining clinical response in patients receiving experimental therapies. Focus has shifted towards developing patient-reported outcome tools which are sensitive to changes in PLD-specific symptoms, with the development of; polycystic liver disease complaint-specific assessment (POLCA) tool (139) as well as PLD-Q (140).

10. Five-year view

Many novel pre-clinical agents are being explored in ADPKD and are in the research pipeline. The VEGFR2 inhibitor, SU5416, has been shown to blunt liver cyst growth in animal models (53, 57). Others include bosutinib, a Src-ABL tyrosine kinase inhibitor; triptolide, an active ingredient in traditional Chinese medicine and histone deacetylase. New discoveries into gene mutations in genes involved in disease susceptibility have also identified new signaling pathways to be targeted.

Perhaps something closer on the horizon is the use of combination pharmacological therapies and/or radiological modalities. This concept has been explored in a trial compared the efficacy of combining everolimus and octreotide with octreotide monotherapy. Whilst everolimus did not enhance the beneficial effect of octreotide in reducing liver volume in patients with ADPLDs (134), perhaps a combined treatment
with different compounds simultaneously blocking multiple signaling pathways may be successful. In fact, combined inhibition of mTOR and ERK displays synergism and better efficacy than single target therapy in preclinical models for cancer (141, 142). Other considerations include sequential therapy with a somatostatin analogue after aspiration sclerotherapy to avoid incomplete cyst reduction and re-accumulation of cyst fluid. An RCT is currently investigating if pasireotide, two weeks prior to and two weeks following aspiration sclerotherapy can decrease fluid re-accumulation (143).

11. **Key issues**

1. There are two phenotypes of polycystic liver disease; isolated (ADPLD) and in association with polycystic kidney disease (ADPKD). Mutations in PRKSCH and Sec63 for ADPLD and PKD-1 and PKD-2 for ADPKD are the respective genes identified to be responsible.

2. Alterations in the proteins translated from these mutated genes affect signal transduction pathways linked to the primary cilium of biliary epithelial cells. Abnormal regulation of these signaling pathways result in epithelial secretion, growth and proliferation and cyst formation.

3. Understanding these pathways has been pivotal in identifying new potential targets for therapy.

4. The current mainstays of treatment for symptomatic cases are radiologic or surgical interventions. Apart from liver transplantation, none of these treatment options are curative and often retreatment is often required secondary to cyst recurrence.
5. Of the pharmacological therapies, somatostatin analogues have the most evidence to decrease the volume of polycystic livers, although combination therapies are on the horizon.

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**Declaration of interest**

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* RCT comparing sirolimus with tacrolimus in ADPKD patients


* RCT exploring lanreotide vs placebo in PLD


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**Figure legends**

**Figure 1** Genotype–Phenotype correlation in PLD. Two hit mechanism of ADPKD: the germline mutation predisposes biliary epithelium to cystic transformation, but a second somatic mutation is required to initiate cystogenesis within a single cell. This is followed by clonal expansion, detachment, followed by cystic growth and expansion. Environmental factors such as female gender, age <48, estrogen use and multiple pregnancies increase the risk of developing a severe phenotype. Adapted from Everson, 2008 (137) and D’Agnolo, 2016 (138)

**Figure 2** Polycystic liver diseases signaling pathways linked to secretion, growth or proliferation of polycystic epithelial cells and potential interventions. Defects in the polycystin-1 (PC-1) and polycystin-2 (PC-2) complex in the primary cilium reduce Ca2+ influx. Low intracellular Ca2+ inhibits adenyl cyclase (AC) and activates phosphodiesterase (PDE). This increases levels of cAMP and thus activation of protein kinase A (PKA). AC is inhibited by somatostatin through the somatostatin receptor (SSTR) and inhibitory regulatory G-protein (Gi). Low Ca2+ also allows PKA to activate the extracellular signal-regulated kinase (ERK) pathway, which promotes proliferation. PC-1 binds tuberin, a component of the tuberous sclerosis complex (TSC) which normally inhibits mTOR, a regulator of growth and proliferation. A defect in PC-1 promotes mTOR activity, resulting in cell growth and upregulation of the cyclin/CDK pathway. Vascular endothelial growth factor (VEGF) is secreted into the cyst lumen where it can activate ERK. ERK can inhibit tuberin and thus further activate mTOR, creating a feedback loop. Estrogen, acting through membrane and
cystolic/nuclear receptors (ER) can also stimulate proliferation. Potential therapeutic interventions are targeted at specific loci within signalling pathways. Somatostatin analogues that bind to the somatostatin receptor and V2R antagonists inhibit AC, reducing cAMP concentrations. mTOR inhibitors arrest the cell cycle of replication and reduce VEGF secretion. Green ovals: pathways upregulated. Red ovals: pathways downregulated. Adapted from Everson, 2008 (137) and Everson, 2013 (139)

**Table 1** Comparative epidemiological and genetic mutation characteristics of autosomal dominant polycystic kidney disease associated polycystic liver disease and isolated polycystic liver disease

**Table 2** Symptoms and complications of PLD

**Table 3** Gigot classification

**Table 4** Schnelldorfer classification
Tables

Table 1: Comparative epidemiological and genetic mutation characteristics of autosomal dominant polycystic kidney disease associated polycystic liver disease and isolated polycystic liver disease

<table>
<thead>
<tr>
<th></th>
<th>ADPKD</th>
<th>PCLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>0.20%</td>
<td>&lt;0.01%</td>
</tr>
<tr>
<td>Type of inheritance</td>
<td>AD</td>
<td>AD</td>
</tr>
<tr>
<td>Gene mutated</td>
<td>PKD1; PKD2</td>
<td>PRKCSH; SEC63</td>
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<td>Encoded product</td>
<td>Polycystin-1; polycystin -2</td>
<td>Hepatocystin; Sec63 protein</td>
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<td>Chromosome locus</td>
<td>216p13.3; 4q21</td>
<td>19p13.2; 6q21</td>
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<tr>
<td>Renal involvement</td>
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Table 2: Symptoms and complications of PLD

<table>
<thead>
<tr>
<th>Symptoms due to mass effect</th>
<th>Complications related to mass effect</th>
<th>Complications related to the cysts</th>
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<tbody>
<tr>
<td>Abdominal distention</td>
<td>Hepatic venous-outflow obstruction</td>
<td>Infection</td>
</tr>
<tr>
<td>Early satiety</td>
<td>Inferior vena cava syndrome</td>
<td>Torsion</td>
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<tr>
<td>Postprandial fullness</td>
<td>Portal vein compression</td>
<td>Rupture</td>
</tr>
<tr>
<td>Gastro-esophageal reflux</td>
<td>Bile duct compression</td>
<td>Hemorrhage</td>
</tr>
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<td>Back pain</td>
<td>Malnutrition</td>
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<td>Lower limb edema</td>
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<td></td>
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<td>Dyspnea</td>
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Table 3: Gigot classification

<table>
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<th>Number of cysts</th>
<th>Cyst size</th>
<th>Liver involvement</th>
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<tr>
<td>I</td>
<td>&lt;10</td>
<td>Large (&gt;10cm)</td>
<td>&lt;25%</td>
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<tr>
<td>II</td>
<td>Multiple</td>
<td>Small, medium</td>
<td>25-50%</td>
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<tr>
<td>III</td>
<td>Multiple</td>
<td>Small, medium</td>
<td>&gt;75%</td>
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Table 4: Schnelldorfer classification

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<th>Type B</th>
<th>Type C</th>
<th>Type D</th>
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<tr>
<td><strong>Symptoms</strong></td>
<td>Absent or mild</td>
<td>Moderate or severe</td>
<td>Severe (or moderate)</td>
<td>Severe (or moderate)</td>
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<tr>
<td><strong>Cyst characteristics</strong></td>
<td>Any</td>
<td>Limited No. large cysts</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td><strong>Areas of relative normal liver parenchyma</strong></td>
<td>Any</td>
<td>&gt;2 sectors</td>
<td>&gt;1 sector</td>
<td>&lt;1 sector</td>
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<tr>
<td><strong>Isosectoral portal vein or hepatic vein occlusion of preserved sector</strong></td>
<td>Any</td>
<td>Absent</td>
<td>Absent</td>
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Table 5: Non pharmacological and pharmacological management options

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<tr>
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<th>Pharmacological options</th>
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<tbody>
<tr>
<td>Cyst aspiration &amp; sclerotherapy</td>
<td>Somatostatin analogues</td>
</tr>
<tr>
<td>Cyst fenestration</td>
<td>mTOR inhibitors</td>
</tr>
<tr>
<td>Transcatheter arterial embolization</td>
<td>Ursodeoxycholic acid</td>
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<tr>
<td>Segmental hepatic resection</td>
<td>Vasopressin-2-receptor antagonists</td>
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<td>Liver transplantation</td>
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