REVIEW

Current management of autosomal dominant polycystic kidney disease

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Author contributions: Akoh JA solely contributed to this paper.

Conflict-of-interest statement: The author has no conflict of interest.

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Abstract

Autosomal dominant polycystic kidney disease (ADPKD), the most frequent cause of genetic renal disease affecting approximately 4 to 7 million individuals worldwide and accounting for 7%-15% of patients on renal replacement therapy, is a systemic disorder mainly involving the kidney but cysts can also occur in other organs such as the liver, pancreas, arachnoid membrane and seminal vesicles. Though computed tomography and magnetic resonance imaging (MRI) were similar in evaluating 81% of cystic lesions of the kidney, MRI may depict septa, wall thickening or enhancement leading to upgrade in cyst classification that can affect management. A screening strategy for intracranial aneurysms would provide 1.0 additional year of life without neurological disability to a 20-year-old patient with ADPKD and reduce the financial impact on society of the disease. Current treatment strategies include reducing: cyclic adenosine monophosphate levels, cell proliferation and fluid secretion. Several randomised clinical trials (RCT) including mammalian target of rapamycin inhibitors, somatostatin analogues and a vasopressin V2 receptor antagonist have been performed to study the effect of diverse drugs on growth of renal and hepatic cysts, and on deterioration of renal function. Prophylactic native nephrectomy is indicated in patients with a history of cyst infection or recurrent haemorrhage or to those in whom space must be made to implant the graft. The absence of large RCT on various aspects of the disease and its treatment leaves considerable uncertainty and ambiguity in many aspects of ADPKD patient care as it relates to end stage renal disease (ESRD). The outlook of patients with ADPKD is improving and is in fact much better than that for patients in ESRD due to other causes. This review highlights the need for well-structured RCTs as a first step towards trying newer interventions so as to develop updated clinical management guidelines.

Core tip: Autosomal dominant polycystic kidney disease

(ADPKD), the most frequent cause of genetic kidney disease affecting approximately 4 to 7 million individuals worldwide (7%-15% of patients on renal replacement therapy), is a systemic disorder mainly involving the kidney but cysts can also occur in other organs such as the liver, pancreas and arachnoid membrane. This paper discusses radiological evaluation of ADPKD, necessity for screening for intracranial aneurysms and current treatment strategies include reducing: cyclic adenosine monophosphate levels, cell proliferation and fluid secretion. It further discusses the role of surgery in managing ADPKD patients and highlights areas of new research.

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is a monogenetic disorder characterised by bilateral renal cysts and possibly kidney pain, urinary tract infection, haematuria, nephrolithiasis, hypertension and progressive renal failure due to progressive enlargement of cysts and fibrosis[1,2]. It is a leading cause of end-stage renal disease (ESRD) and the most common inherited kidney disease[3,4]. ADPKD is a systemic disorder mainly involving the kidney but cysts can also occur in other organs such as the liver, pancreas, arachnoid membrane and seminal vesicles[5]. In contrast to ADPKD, autosomal recessive polycystic kidney disease produces kidneys which are hugely enlarged due to multiple cysts, hypertension, and congenital hepatic fibrosis characterised by dilated bile ducts and portal hypertension[6]. Autosomal recessive polycystic kidney disease and other cystic lesions of the kidneys present a different set of challenges and will not be discussed further in this review.

The work of Thong *et al*[3] suggest that the age of diagnosis of ADPKD and mean kidney length can be used to predict ESRD at least 10 years in advance and thus enable patients at higher risk of developing it to be identified early for treatment. The quality of life (QOL) of patients with ADPKD is indirectly linked to the total kidney and liver volume by virtue of its close correlation with abdominal distention that exerts an important influence on QOL. Other associated symptoms of ADPKD such as pain, sleep disturbance, heartburn, fever, gross hematuria and anorexia (though not always correlated with total liver and kidney volumes) affected QOL[7]. Improving these symptoms and reducing abdominal distention can enhance the QOL of patients.

ADPKD remains a therapeutic challenge as effective treatment to retard the growth of kidney and liver cysts has not been achieved despite decades of basic and clinical research[4,8]. The Spanish Working Group on Inherited Kidney Diseases, in the absence of good evidence, only made recommendations relating to management of hypertension, pain, cyst infections and bleeding, extra-renal involvement including polycystic liver disease, intracranial aneurysms, ESRD, and management of children with ADPKD; but none on specific ADPKD therapies[9]. There are no clinical guidelines on management of this common cause of ESRD. The aim of this review is to present a concise account of the current status of managing patients with ADPKD including the surgical options.

EPIDEMIOLOGY

ADPKD is the commonest cause of genetic renal disease affecting approximately 4 to 7 million individuals worldwide and accounting for 7%-11% of patients on renal replacement therapy (RRT) in Europe[5,10-13] and about 10%-15% of patients requiring dialysis in the United States[14].

According to the Danish National Registry on Regular Dialysis and Transplantation, 693 patients with ADPKD reached ESRD between 1990 and 2007. Analysis of the data showed that progression to ESRD increased from 6.45 per million people in 1990-1995 to 7.59 per million people in 2002-2007. In addition, the mean age at onset of ESRD increased by 4.7 years and patient survival improved by 38%[15]. In a study of the Catalan registry (1984-2009), Martínez *et al*[11] found 1586 (7.9%) of 20033 ESRD patients with ADPKD. The survival rate of ADPKD patients on renal replacement therapy was significantly higher than that of non-ADPKD patients. Review of the United States Renal Data System shows that of the 375152 patients initiated on ESRD therapy between 1992 and 1997, 5799 (1.5%) had polycystic kidney disease. As with the Catalan registry, patients with polycystic kidney disease had lower mortality compared to patients with other causes of ESRD[16].

In a retrospective comparison of clinical characteristics of 837 patients with ADPKD between 1961-1990 and 1991-2011, Helal *et al*[17] reported an earlier age of disease diagnosis (29 years *vs* 35 years), lower mean blood pressure (129/82 mmHg *vs* 142/91 mmHg), better estimated glomerular filtration rate (eGFR) (63.6 mL/min *vs* 44.6 mL/min), and more use of renin-angiotensin-aldosterone system (RAAS) inhibitors (42.5% *vs* 13.6%) during the later period.

PATHOLOGICAL CONSIDERATIONS

In 85%-90% of cases, ADPKD results from a mutation in the *PKD1* gene, and the other 10%-15% of cases are accounted for by mutations in *PKD2*. *PKD1* and *PKD2* encode for polycystin-1 and polycystin-2 proteins (polycystin signaling complex) which regulate different signals including 3',5'-cyclic adenosine monophosphate (cAMP), mammalian target of rapamycin (mTOR) and

epidermal growth factor receptor pathways. Abnormal activation of these signals causes an increased cell proliferation which is an important component of this disease[18]. ADPKD is characterized by the progressive development of cysts in renal tubular epithelial cells that gradually compress the parenchyma and compromise renal function. There is considerable interest in the primary cilia as a site of the proteins that are involved in renal cystogenesis in ADPKD[19,20]. Research on primary cilia has increased significantly during the last decade[21]. Cyst enlargement is thought to result from increased fluid secretion; and abnormal cell replication by the epithelium lining the cyst[22]. The processes underlying the decline in renal function include disruption of glomerular filtration and urine concentrating mechanisms, coupled with compression of adjacent nephrons in the cortex, medulla and papilla. Cyst-derived chemokines, cytokines and growth factors cause fibrosis that is similar to development of other progressive ESRD[23]. This concept that attributes important roles to tubular cell ciliary functioning, cell proliferation and fluid secretion, alterations in levels of intracellular calcium, cAMP and activation of cellular kinases, including mTOR[12] is the basis of potentially effective treatments discussed below.

Animal studies indicate that excessive activation of the alternative complement pathway is associated with ADPKD progression, probably mediated through cyst-lining cell proliferation, tubulointerstitial inflammatory cell infiltration and fibrosis. Regulating activation of the complement system might represent a new treatment strategy for ADPKD[24]. Cyst expansion causes ischemia within the kidney and activation of RAAS leading to the development and/or maintenance of hypertension. The features of disease progression in ADPKD include increasing total kidney volume (TKV), hypertension, cardiovascular complications, proteinuria and progression to ESRD[25].

Extrarenal manifestations
Apart from renal cysts, patients often have extra-renal disease encompassing cysts in the liver (94%), seminal vesicle (40%), pancreas (9%), arachnoid membrane (8%), and spinal meninges (2%); and connective tissue abnormalities such as mitral valve prolapse (25%), intracranial aneurysms (8%), diverticular disease (20%-25%) and abdominal hernia (10%); hypertension and left ventricular hypertrophy[26-28]. Recognition of extrarenal manifestations (ERM) reduces diagnostic uncertainty and may influence choice of treatment option[29].

Cardiovascular system
Other cardiovascular abnormalities include aortic aneurysms, arachnoid aneurysms, cerebral artery dolichoectasia, mitral regurgitation, aortic insufficiency, and tricuspid regurgitation. There is evidence to suggest that ADPKD is associated with an increased incidence of coronary aneurysms and dissection[30,31]. Cardiovascular

complications are responsible for 80% more deaths in ADPKD than ESRD. Furthermore, intracranial aneurysms affect 4%-41.2% of ADPKD patients, with a risk of rupture about five times higher than in the general population[2,32].

Hypertension: Hypertension develops in about 50%-70% of patients with ADPKD and is associated with an increased risk of progression to ESRD. Stimulation of RAAS plays a significant role in the development of hypertension. The presence of cardiovascular changes such as carotid intima-media thickness, and arterial stiffness in young normotensive patients with ADPKD suggests that cardiovascular involvement starts early in these patients. Early diagnosis and treatment of hypertension with RAAS inhibitors, has the likely benefit of reducing the cardiovascular complications and slowing the progression of kidney dysfunction[33].

Left ventricular hypertrophy: Left ventricular hypertrophy (LVH) has been recognised as an early complication in patients with ADPKD. LVH is associated with arrhythmias, congestive heart failure, and increased cardiac mortality. Observational studies using echocardiography have estimated the prevalence of LVH in adults to range from 20%-40%[34]. The recently observed decline in the incidence of LVH may be as a result of earlier detection, treatment and more rigorous control of blood pressure including the increasing use of RAAS antagonists.

Miscellaneous
Another cited ERM is thoracic aortic dissection, which can cause high mortality and morbidity rates[35]. Also pulmonary dysfunction should be recognised as one of the extrarenal complications of ADPKD due to the demonstrable improvement in lung function following renal transarterial embolism[36].

Complications of ADPKD
Complications in ADPKD usually result from kidney involvement and include cyst bleeding and cyst infection. However, serious extrarenal features such as subarachnoid haemorrhage can also occur[5].

Cyst infection/Urinary tract infection Idrizi et al[37] studied 180 patients with ADPKD (2003 to 2008) and reported urinary tract infections caused by gram negative enteric organisms in 60% (108 patients). The episodes of isolated cyst infections (negative urine culture and no urinary white blood cell casts) were more frequent than those of acute or chronic pyelonephritis (urinary sediment containing white blood cell casts). The key challenge is how to distinguish between cyst infection and acute or chronic pyelonephritis. Hepatic pyocyst is an uncommon but potentially life-threatening complication of ADPKD. With extensive hepatic cystic disease, localization of a pyocyst and targeted aspiration or drainage is often a diagnostic challenge. Two ADPKD patients with recurrent gram-negative sepsis were

investigated with ^{67}Ga SPECT/CT to look for the source of infection - with accurate localisation in both cases[38].

Screening/surveillance

Ultrasonography remains the first choice imaging modality for diagnosing ADPKD[26]. However, computed tomography (CT) scanning is particularly useful in assessing pain, complex renal or hepatic cysts and in cyst aspiration[39]. New magnetic resonance imaging (MRI) methods developed by the Consortium for Radiologic Imaging for the Study of Polycystic Kidney Disease allow accurate estimates of change in TKV over time in ADPKD patients with intact renal function. PKD1 status, male sex, hypertension, reduced renal blood flow, and proteinuria are associated with increased renal volume and change in renal volume over time[25]. MRI has advantages when there is suspicion of malignancy and similar to CT, is useful in the assessment of living kidney donors[39].

Following a comprehensive literature review of articles published from 1998 to 2013, Ellimoottil *et al*[40] concluded that CT and MRI with/without contrast enhancement remained the gold standard for evaluating cystic lesions of the kidney. However, diffusion-weighted MRI and contrast enhanced ultrasound have surfaced as new tools for assessment of complex cysts. In a retrospective analysis, Israel *et al*[41] reported that findings on CT and MRI were similar in 81% of lesions. MRI may depict septa, wall thickening or enhancement leading to upgrade in cyst classification that can affect management.

Kawano *et al*[42] explored urinary biomarkers in ADPKD in human and in an animal model using gene expression analysis of the kidney from DBA/2FG-pcy mice (ADPKD model animals) to identify prospective biomarkers. Their study suggests that NGAL, M-CSF, MCP-1 are potential candidates for urinary biomarkers in ADPKD.

Intracranial aneurysms

Though the prevalence of IA is higher in patients with ADPKD than the general population (4%-41.2% *vs* 0.4%-6%), the mortality rate of aneurysm rupture is similar. Levey *et al*[43] showed that routine arteriographic screening for cerebral aneurysms in patients with ADPKD was not of significant benefit. Butler *et al*[44] reexamined this question by comparing an MRI screening strategy with a non screening strategy. Aneurysms detected by MRI screening were managed neurosurgically whereas the patients in the non screening arm received cerebrovascular care only in the event of subarachnoid hemorrhage. Taking into consideration a host of factors including the prevalence of asymptomatic aneurysms in ADPKD patients (15%); the annual incidence of aneurysmal rupture (1.6%); the morbidity and mortality rates associated with subarachnoid haemorrhage (70% and 56%, respectively); and the life expectancy of patients with ADPKD, the model predicted that the screening strategy would provide 1.0 additional year of life without neurological disability to a 20-year-old patient with ADPKD. Furthermore, a financial analysis showed that a screening strategy is likely to be more cost effective. Rozenfeld *et al*[10] performed a critical appraisal of the estimated value of screening for IA in the setting of ADPKD noting the variable length of the preclinical phase of aneurysm development and the fact that the clinical phase (symptoms to haemorrhage or death) can be quite short, they recommended only screening patients who have a family history of aneurysm or subarachnoid haemorrhage, high risk occupation, undergoing major surgery, exhibiting severe anxiety about the issue or if anticoagulation is contemplated for any reason.

Jiang *et al*[45] screened and followed up unruptured intracranial aneurysms (UIAs) and concluded that 3.0 T 3D-TOF (time of flight) MRA was feasible for UIAs follow-up in ADPKD patients. However, the risk of enlargement and rupture of UIAs in ADPKD patients was not higher than in the general population. The jury is therefore out on whether to screen ADPKD patients or not. A pragmatic way forward may be to define the population at risk and screen those.

Sixty-eight adults, pre-dialysis ADPKD patients underwent both screening for intracranial aneurysms with MRI of the brain and ambulatory blood pressure monitoring with a view to establishing an association between these in ADPKD. Ten of the 68 patients had intracranial aneurysms while 58 had none. The night time maximum diastolic blood pressure, maximum increase in diastolic BP from measurement to measurement at night, and the standard deviation of the daytime mean arterial pressure were significantly higher in patients with aneurysm. Additionally, those over 45 years of age with aneurysm had significantly worse parameters. They concluded after a series of analyses that hypertensive ADPKD patients with substantial fluctuations in BP assessed by automated blood pressure monitoring, especially those after 45 years-of-age, should become candidates for screening for intracranial aneurysms[46].

TREATMENT OF ADPKD

There is presently no effective treatment for ADPKD and management measures are focused mainly on managing the complications of the disease, not on slowing cyst development or preventing progression to kidney failure. Current treatment strategies include: lowering cAMP levels; inhibiting cell proliferation; and reducing fluid secretion[47]. Many clinical trials have been undertaken to study the effect of diverse drugs on the growth of renal and hepatic cysts, and on deterioration of renal function. The drug classes that have been tested in randomised clinical trials (RCT) include mTOR inhibitors (sirolimus and everolimus), somatostatin analogues (octreotide, lanreotide, pasireotide), and most recently, vasopressin V2 receptor antagonist,

tolvaptan. Other drugs being tested include bosutinib [sarcoma proto-oncogene Abelson murine leukaemia oncogene (SRC-ABL) tyrosine kinase inhibitor] and triptolide, a traditional Chinese herbal medication. Additional therapeutic strategies to retard cyst growth aim at blood pressure control *via* inhibition of RAAS and the sympathetic nervous system[8]. Also, targeting up or down regulated molecules in the renal epithelial cells are being tested[5].

Overactivity of both mTOR and cystic fibrosis transmembrane conductance regulator is thought to contribute to the progressive expansion of renal cysts in ADPKD. Recent research has established that AMP-activated kinase can suppress the activity of each of these proteins. Clinical AMP kinase activators such as metformin and berberine may thus have potential in the clinical management of ADPKD. The use of berberine in diarrhea may be due to the inhibitory impact of AMPK on chloride extrusion by small intestinal enterocytes[48].

Drug therapy for ADPKD

Rapamycin: He *et al*[49] conducted a meta-analysis of 4 RCTs (564 patients) regarding mTOR inhibitor therapy in patients with ADPKD investigating changes in patients' GFR, urinary protein, TKV, cyst volume, parenchymal volume, lipid profile and the frequency of adverse events. Their main findings were that though mTOR inhibitor therapy was associated with a smaller TKV than the control group, it did not slow down the decline of renal function. This agrees with the findings of a randomised, crossover study (The SIRENA Study)[50]. However, another meta-analysis of RCTs (5 studies, 619 patients) that used mTOR inhibitors to halt the progression of ADPKD failed to demonstrate any significant reduction in TKV or GFR between the TORI-treated and control groups[51]. These findings, in addition to a significantly higher level of proteinuria in the mTOR inhibitor-treated group than in the control group, were similar to those of another meta-analysis[52].

The above studies of mTOR inhibitor treatment of ADPKD showed no clear benefit on the primary endpoint of TKV or eGFR. Another trial evaluated two levels of rapamycin on the 12-mo change in (125)I-iothalamate GFR (iGFR) as the primary endpoint and TKV secondarily[53]. In a study of 30 adult patients with ADPKD randomised to low-dose rapamycin (trough level, 2-5 ng/mL; *n* = 10), standard-dose rapamycin trough level (> 5-8 ng/mL; *n* = 10), or standard care (SC group, *n* = 10), Braun *et al*[53] showed that patients receiving low dose rapamycin demonstrated a significantly better iGFR but without a significant effect on TKV after 12 mo.

Somotatostatin analogues: Therapy with somatostatin analogues is meant to regulate the activity of the tubular epithelial lining the cysts *via* secondary chloride transport thereby shrinking the renal cysts. A randomised, cross-over, placebo-controlled trial compared the risk/benefit profile of a 6-mo treatment with long-acting somatostatin (octreotide-LAR, 40 mg intramuscularly every 28 d) or placebo in ADPKD patients with mild-to-moderate renal insufficiency showed a significantly slower increase in TKV for patients on somatostatin compared to placebo[54]. The work of Hogan *et al*[55] agrees with this. In another study involving long term treatment with octreotide, Caroli *et al*[56] assessed the effect of 3 years of octreotide-LAR treatment on kidney and cyst growth and renal function decline in participants with ADPKD. They performed a multicentre, randomised, single-blind, placebo-controlled, parallel-group trial in five hospitals in Italy between 2000 and 2008 on adult (> 18 years) patients with eGFR of 40 mL/min per 1.73 m^2 or higher who were randomly assigned on a 1:1 ratio to 3 year treatment with two 20 mg intramuscular injections of octreotide-LAR (*n* = 40) or 0.9% sodium chloride solution (*n* = 39) every 28 d. The mean ± standard error of mean increase in TKV in the treatment group (220.1 ± 49.1 mL) was lower than in the placebo group (454.3 ± 80.8 mL) but the difference was not statistically significant. They reported four cases (10%) of cholelithiasis or acute cholecystitis in the octreotide-LAR group that were probably treatment-related.

Vasopressin 2 receptor antagonist: Blockade of vasopressin V2 receptor is thought to limit cyst growth, thereby delaying progressive renal dysfunction. Vasopressin antagonists and somatostatin analogues lower intracellular cAMP levels and though associated with limited clinical benefits, they have significant side effects[28]. Torres *et al*[57] conducted a large (1445 patients between 2007 and 2009) well-structured prospective study of Tolvaptan, a selective vasopressin 2 receptor antagonist in young patients (≤ 50 years) with ADPKD with reasonably good kidney function (eGFR > 60 mL/min), and with MRI-measured TKV > 750 mL. They compared TKV, kidney function, albuminuria, kidney pain and vital signs. The TEMPO (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes) trial showed that tolvaptan was effective in slowing the expansion of kidney volume and deterioration of kidney function[58]. Tolvaptan has been reported to prolong the median age at ESRD onset by 6.5 years and increase life expectancy by 2.6 years. Even if the benefits of tolvaptan persist in the longer term, it would still not be cost effective treatment[59]. Tolvaptan has significant adverse effects including polyuria, nocturia, polydipsia and elevation of aminotransferase enzyme concentrations with the potential for acute liver failure. In the TEMPO 3:4 trial, 8.3% of patients in the treatment arm had severe tolvaptan-related aquaresis leading to drug discontinuation[28]. Appropriate patient selection is critical to optimize long-term benefits while minimizing adverse effects and hepatotoxic risk factors[4].

Combined drug treatment such as the use of low doses of rapamycin, tolvaptan, and AEterna-Zentaris

slows the progression of PKD with limited side effects, suggesting the use of combined therapies also in clinical trials[60]. Although not targeting the causative mechanisms of cyst formation and growth, the HALT-PKD study examined the effects of dual blockade of the RAAS and aggressive blood pressure control on the rate of progression of ADPKD[61]. In summarising the various trials of drug therapy for ADPKD, Myint et al[62] called for further well-designed and suitably powered trials of longer duration using new biomarkers or therapeutic agents with better tolerance are required.

Hypertension

Patch et al[63] undertook a cohort study of 2085 patients with ADPKD between 1991 and 2008 to determine the association between antihypertensive therapy and mortality in patients with ADPKD. The proportion on antihypertensive drugs increased from 32% in 1991 to 62% in 2008. Also, use of drugs acting on the RAAS increased from 7% of participants to 46% by 2008. These changes were associated with a reducing mortality. Effective BP control prevents an increase in LVM index and reduces urinary albumin excretion, indicating the relative importance of good BP control in slowing cardiac and renal organ damage in ADPKD[64]. RAAS inhibitors cause regression of LVH and play an important role in the cardiovascular risk management of ADPKD patients[34].

Chronic pain

Chronic pain defined as pain existing for > 4-6 wk, is a significant cause of morbidity in patients with ADPKD. Chronic pain in ADPKD patients is often severe, impacting physical activity and social relationships and frequently difficult to manage[65]. Analysis of 171 questionnaires completed by patients with polycystic kidney disease of varying levels of renal function showed the order of frequency of pain as: low back pain, abdominal pain, headache, chest pain and leg pain. The severity of pain, documented by the visual analogue scale was 4 to 5/10 in the majority of patients[66]. MRI will differentiate between mechanical low back pain caused by cyst enlargement from cyst rupture or infection. Also, the increased incidence of uric acid nephrolithiasis as a factor in producing renal colic must be considered when evaluating acute pain in the population at risk. If stone disease is suspected, then abdominal CT scan and/or ultrasound should be the method of investigation.

Approaches to chronic pain management must include measures that help patients to adapt to chronic pain thereby limiting its interference with their life style[67]. Management ranges from non pharmacologic therapy to high-dose opioid therapy and more invasive procedures, including surgical intervention. Celiac plexus neurolysis and intercostal nerve radiofrequency ablations offer temporary respite. Dorsal column neurostimulation is a more permanent step, affording superior analgesia with better QOL[65,68]. The use of open or laparoscopic cyst decortication procedures for control of pain and infection in those with preserved renal function does not result in further renal dysfunction[14].

ESRD/dialysis

The key issues relating to peritoneal dialysis in patients with ADPKD are: a higher incidence of abdominal wall hernias, the increased risk of diverticulitis; and peritoneal space problems due to enlarged kidneys[69]. However, the little evidence available showed no real difference between ADPKD and non ADPKD patients[69,70].

SURGICAL OPTIONS

Cyst procedures

Anecdotal report of successful intracystic infusion of ciprofloxacin that achieved a sufficiently high antibiotic level in infected renal cysts so as to completely eradicate S. choleraesuis in a 52-year-old male with ADPKD refractory renal cyst infection with multiple pyocysts[71] has highlighted a potential salvage therapy for refractory renal cyst infection especially when surgery is contraindicated. Transcatheter renal artery embolisation is performed to reduce kidney volume in ADPKD patients with nephromegaly and improve lung function by reducing the splinting effect on the diaphragm[36]. Open transperitoneal bilateral renal cyst reduction surgery in patients with symptomatic ADPKD has been shown to be a relatively safe and effective treatment for individuals in whom more conservative therapies have failed[72].

Cyst decortication is highly effective in the management of disease-related chronic pain for the majority of patients with ADPKD and may alleviate hypertension and preserve renal function[73]. The technique of retro-peritoneoscopic decortication as described by Hemal et al[74] is preferred in the presence of infected cysts so as to prevent intraperitoneal contamination.

Transplantation

When patients with ADPKD are assessed for renal transplantation, the key issues relate to native nephrectomy, liver cysts, screening for intracranial aneurysms and living-related kidney donation. Prophylactic native nephrectomy is indicated in patients with a history of cyst infection or recurrent haemorrhage or to those in whom space must be made to implant the allograft[75]. Other issues include anaemia management, the potential benefits of select immunosuppressive agents, the role for combined kidney-liver transplantation and complications of ADPKD after transplantation[76].

Few studies have investigated whether the TKV and liver volume in patients with ADPKD decrease after renal transplantation. Yamamoto et al[77] analysed changes in the volume of native kidney (bilateral: $n = 28$; unilateral: $n = 5$) and liver (concomitant polycystic disease: $n = 18$) in 33 patients with ADPKD, who underwent renal transplantation. Volumetry was retrospectively conducted using simple CT scan data 6

mo before transplantation, at the time of transplantation, and one, three, and five years after transplantation. Kidney volumes were significantly reduced in all but one patient after renal transplantation, decreasing by 37.7% and 40.6% at 1 and 3 years, respectively. In contrast, 16 of 18 patients showed significant increase of liver volumes after renal transplantation with the mean rates of increase of 8.6% and 21.4% at 1 and 3 years, respectively. In the light of these findings, native nephrectomy would be unnecessary if the space for an allograft is available in the absence of infection, bleeding, or malignancy. When ADPKD is combined with polycystic liver disease, the possibility of intolerable symptoms caused by growing liver cysts should be considered[75,77].

Nephrectomy

More recent data suggests that about a fifth of ADPKD patients undergoing renal transplantation would require native unilateral or bilateral nephrectomy[78-80]. Brazda et al[81] reported a higher rate of native nephrectomy (35.4%) and advocated that if native nephrectomy is needed, it would be better before transplantation than after.

Indication/timing: As highlighted above, the indications for nephrectomy include pain/discomfort, space for transplantation, ongoing haematuria, recurrent infections, and gastrointestinal pressure symptoms (early satiety)[82,83]. Another argument in favour of nephrectomy in those with complex cysts is the risk of malignancy as exemplified by two cases of renal cell carcinomas in 157 ADPKD patients undergoing nephrectomy before or after transplantation - an incidence of 1.3%[79]. Fuller et al[78] evaluated the indications for and outcome of pre-transplant, concomitant and post-transplant native nephrectomy in patients with ESRD due to ADPKD. Between 1992 and 2002, 32 (18.7%) of 171 patients with ESRD due to ADPKD who received a kidney transplant underwent native nephrectomy - 25 bilateral and 7 unilateral. They observed that the predominant indication for native nephrectomy depended on its timing - haematuria, a renal mass and chronic pain in the pretransplant group; lack of space in the concurrent group; and urinary tract infection in the posttransplant group[78]. Bilateral nephrectomy performed either before or during transplantation has the advantage of removing future complications of ADPKD while not significantly increasing immediate general complications[80]. Nunes et al[84] studied 159 renal transplants in patients with ADPKD divided into two groups according to the need for a unilateral native nephrectomy owing to enlarged kidneys (n = 143) vs those not needing it at the time of transplantation (n = 16). They reported no differences in rates of delayed graft function, acute rejection and chronic allograft dysfunction.

Song et al[85] assessed the transplant outcome of ADPKD patients who underwent concurrent bilateral nephrectomies during kidney transplantation. Their study compared 31 patients undergoing concurrent bilateral nephrectomy with 32 patients without and reported a significantly longer operation time (300 ± 30.85 min vs 120 ± 20.78 min, P < 0.01), higher need for blood transfusion (4.31 ± 1.05 U vs 1.35 ± 0.23 U, P < 0.01) and higher rate of adjacent organ injury (22.58% vs 0%, P < 0.01) during operation in the concurrent bilateral nephrectomy group. This was hardly surprising.

Tyson et al[86] examined population level data on 2368 patients with ADPKD and performed unadjusted, multivariable and propensity score adjusted analyses of postoperative outcomes of 271 patients (11.4%) who underwent simultaneous kidney transplantation and bilateral native nephrectomy compared to bilateral native nephrectomy alone. They concluded that except for increased rates of intraoperative bleeding, blood transfusion and urological complications there were no significant differences in postoperative adverse outcomes[86]. In patients with ADPKD native nephrectomy of massively enlarged kidneys may be safely performed during the transplant procedure with no repercussions on the length of hospital stay, graft short- and long-term function and patient survival. Concomitant native nephrectomy of enlarged kidneys at the time of renal transplantation is reasonable and safe for patients with ESRD due to ADPKD[87,88]. It must be bourne in mind however, that native nephrectomy in ADPKD is a major undertaking associated with significant morbidity and mortality. Kirkman et al[82] reported that two of 20 patients in the bilateral nephrectomy pre-transplant group and one in the bilateral nephrectomy post-transplant group died in the immediate post-operative period.

Nephrectomy technique: Historically, nephrectomy for ADPKD was performed by an open technique. Eng et al[89] performed a study to compare outcomes (operative time, complications, transfusion requirement, and length of stay) in hand-assisted laparoscopic nephrectomy (n = 56) with open nephrectomy (n = 20). Overall complication rates were similar but patients undergoing open bilateral nephrectomy were more likely to receive transfusion, and the length of stay was longer in the open group [5.9 d vs 4.0 d for unilateral (P = 0.013) and 7.8 d vs 4.6 d for bilateral]. The most frequent complications associated with hand-assisted laparoscopic nephrectomy were incisional hernia at the hand-port site and thrombosis of arteriovenous fistulae. Compared to open bilateral nephrectomy, the laparoscopic approach resulted in significantly shorter hospital stay, decreased morbidity and quicker recovery. With an average weight of 3 kg, these were really only moderately large kidneys[90,91]. For patients considering renal transplantation, avoidance of transfusion is important to prevent sensitisation which limits access to compatible organs. Laparoscopic nephrectomy is technically safe and feasible in patients with ADPKD but progressive cyst aspiration is a critical step, facilitating the identification of vital structures and the creation of

enough abdominal cavity space to operate[90].

Nephrectomy/transplant outcome

Jacquet et al[92] reported the outcome of a longitudinal study on renal transplantation in patients with ADPKD comparing 534 ADPKD patients with 4779 non-ADPKD patients. This comprehensive French study performed using DIVAT (Donnees Informatisees et VAlidees en Transplantaion) demonstrated that renal transplantation is associated with better graft survival but patients had more thromboembolic and metabolic complications, and an increased incidence of hypertension. And from Italy, Mosconi et al[93] analysed the results of 1800 patients with ADPKD and 12505 ESRD patients from other causes during 2002-2010. Among patients with long term follow-up, ADPKD patients had better graft survival compared with other kidney diseases (86% vs 82% at 5 years; $P < 0.01$); and mortality was not different (92% vs 79% at 1 year). ADPKD is a risk factor for the development of new onset diabetes after transplantation (OR = 2.41, $P = 0.035$)[94].

Dinckan et al[88] compared the outcome of renal transplantation in ADPKD patients undergoing concurrent unilateral ($n = 38$) or bilateral ($n = 125$) native nephrectomy with 161 randomly selected controls. Despite additional surgery and a higher complication rate, the long-term results of patients with complications were not affected negatively and graft survival was similar in the two groups. Following bilateral native nephrectomy, hypertension control was better and the incidence of lower urinary tract infection was lower postoperatively[85]. Overall one year patient and graft survival were 94%-97% and 92%-96% respectively[81,88,95]. Surgical complications, which might be associated with simultaneous nephrectomy requiring re-operation, occurred in 12% of patients[95]. One wonders whether the outcome of the 38% who received kidneys from living donors might have been different if they had pre-transplant native nephrectomy.

RESEARCH POINTERS

Interventions to halt progression of ADPKD

The potential role of glucose metabolism in the pathogenesis of ADPKD may provide a new perspective for the understanding of the pathobiology of ADPKD and open potential new avenues for therapeutical interventions[96].

Treatment aimed at preventing or reducing cyst formation or slowing cyst growth is a reasonable strategy for prolonging useful kidney function in patients with ADPKD[23]. The findings of Caroli et al[56]'s study provide the background for large randomised controlled trials to test the protective effect of somatostatin analogues against deterioration in kidney function and progression to ESRD. Advances in research into molecular mechanisms of cystogenesis will help develop new targeted ADPKD therapies[28].

Meijer et al[97] have designed DIPAK 1 study (Deve-loping Interventions to Halt Progression of ADPKD 1) to examine the efficacy of the somatostatin analogue lanreotide on preservation of renal function. The DIPAK 1 study is a multicenter, randomised controlled, clinical trial designed to show whether subcutaneous administration of lanreotide every 4 wk slows down disease progression in patients with ADPKD.

Vitamin D is increasingly being recognised for a number of other important physiological functions, including reducing blood pressure and proteinuria as well as kidney inflammation and fibrosis. Vitamin D deficiency is associated with proteinuria, increased mortality and may mediate the progression to kidney failure. Based on the prediction that cholecalciferol will attenuate hypertension, proteinuria and reduce the urinary excretion of a biomarker, monocyte chemoat-tractant protein-1 (MCP-1, a surrogate inflammatory marker of progression in ADPKD). Rangan et al[98] have designed a study to provide evidence as to whether a simple intervention such as vitamin D repletion, in either deficient or insufficient states, is a treatment to prevent kidney failure in ADPKD.

QOL with ADPKD

Particular emphasis needs to be placed on performing clinical trials with the goal of improving outcomes and QOL of patients with ADPKD[76].

OUTCOME

ADPKD patients have good graft and patient survival[13]. Haynes et al[99] performed a retrospective cohort study of all patients with ADPKD who received RRT between 1971 and 2000 at the Oxford Kidney Unit. Age at start of RRT and presence of a functioning transplant were associated with improved survival in unadjusted analyses. After adjustment for age the period of treatment also became a significant predictor of overall survival. Survival on RRT appears to have improved and exceeds that observed in the general population, such that RRT now provides almost two-thirds of the life expectancy of the general population, compared to about half in earlier decades.

Data were retrieved from three Danish national registries (1993-2008) on about 823 patients of whom 431 had died during the study period. A multivariate competing risk model comparing the two 8-year periods, adjusted for age at ESRD, gender and treatment modality, showed that deaths from cardiovascular disease decreased by 35% and deaths from cerebrovascular disease decreased by 69% from the first to the second time period[100].

LIMITATIONS

The absence of large RCT on various aspects of the disease and treatment, and the preponderance of case series and observational studies is a significant limitation. Though these reports are valuable, there

still remains considerable uncertainty and ambiguity in many aspects of ADPKD patient care as it relates to ESRD. To a large extent our knowledge is based on small numbers in various trial, single centre retrospective data and numerous review articles.

CONCLUSION

The outlook of patients with ADPKD is improving and is in fact much better than that for patients in ESRD due to other causes. This review highlights the need for a well-structured RCT as a first step towards trying newer interventions so as to develop updated clinical management guidelines.

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