Autosomal-dominant polycystic kidney disease (ADPKD): executive summary from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

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Autosomal Dominant Polycystic Kidney Disease (ADPKD): Executive Summary from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

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Abstract

Autosomal Dominant Polycystic Kidney Disease (ADPKD) affects up to 12 million individuals and is the 4th most common cause for renal replacement therapy worldwide. There have been many recent advances in the understanding of its molecular genetics and biology, and in the diagnosis and management of its manifestations. Yet, diagnosis, evaluation, prevention and treatment vary widely and there are no broadly accepted practice guidelines. Barriers to translation of basic science breakthroughs to clinical care exist, with considerable heterogeneity across countries. The KDIGO Controversies Conference on ADPKD brought together a panel of multi-

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disciplinary clinical expertise and engaged patients to identify areas of consensus, gaps in knowledge, and research and health care priorities related to diagnosis, monitoring of kidney disease progression, management of hypertension, renal function decline and complications, end-stage renal disease, extrarenal complications, and practical integrated patient support. These are summarized in this report.

Keywords

ADPKD; diagnosis; end-stage renal disease; management; patient support; polycystic kidney disease

INTRODUCTION

ADPKD, an inherited kidney disease that affects 12.5 million people worldwide in all ethnic groups, is responsible for up to 10% of patients in end-stage renal disease (ESRD), and is a major burden for public health.[1] It is characterized by relentless development and growth of cysts causing progressive kidney enlargement associated with hypertension, abdominal fullness and pain, episodes of cyst hemorrhage, gross hematuria, nephrolithiasis, cyst infections, and reduced quality of life (QOL).[2,3] Despite continuous destruction of renal parenchyma, compensatory hyperfiltration in surviving glomeruli maintains renal function within the normal range for decades.[4] Only when the majority of nephrons have been destroyed, renal function declines, typically after the fourth decade of life, and ESRD eventually ensues. ADPKD is a systemic disorder affecting other organs with potentially serious complications such as massive hepatomegaly and intracranial aneurysm (ICA) rupture.[1]

Mutations in the *PKD1* and *PKD2* genes account for the overwhelming majority of ADPKD cases. There is no convincing evidence for the existence of a third PKD gene.[5] Compared to *PKD1*, subjects affected with *PKD2* mutations have milder renal disease with fewer renal cysts, delayed onset of hypertension and ESRD by almost two decades and longer patient survival.[6,7] More recent studies have delineated a significant allelic effect in *PKD1* with milder disease associated with non-truncating compared to truncating mutations.[8–11] Gene linkage analysis of European families suggested that ~85% and ~15% of the cases were due to *PKD1* and *PKD2* mutations, respectively. However, two recent studies from Canada and United States have documented a higher *PKD2* prevalence of 26% and 36%, respectively.[12]

Polycystic kidney disease (PKD) has been known for over 300 years and was considered a rare and incurable disease. With medical advances, ADPKD is now diagnosed more frequently and there are several strategies through which QOL and life-span have improved. These include early detection and treatment of hypertension, lifestyle modifications, treatment of renal and extrarenal complications, management of chronic kidney disease (CKD)-related complications and renal replacement therapy (RRT). However, approaches to the diagnosis, evaluation, prevention and treatment of ADPKD vary substantially between and within countries and at present there are no widely accepted practice guidelines. Basic and translational research on PKD has increased exponentially in the last three decades, particularly after the discovery of the *PKD1* (1994) and *PKD2* (1996) genes. Molecular

genetic diagnosis is now available. Many therapeutic targets have been identified and tested in animal models, with clinical trials yielding encouraging results. The relatively low frequency of *de novo* mutations, dominant pattern of inheritance, accurate measurement of cyst burden through renal imaging, and slow disease progression make ADPKD an ideal candidate for nephroprevention.

The objective of this KDIGO conference was to assess the current state of knowledge related to the evaluation, management and treatment of ADPKD, to pave the way to harmonize and standardize the care of ADPKD patients, to identify knowledge gaps, and to propose a research agenda. The following sections summarize the areas of consensus and controversy discussed by a global interdisciplinary expert panel. The complete conference report is available in the Supplemental Appendix and supplementary meeting materials (e.g., slides) can also be found at the conference website (http://kdigo.org/home/conferences/adpkd/).

1. DIAGNOSIS OF ADPKD

Pre-symptomatic screening of ADPKD is not currently recommended for at-risk children. For at-risk adults the potential benefits of presymptomatic diagnosis usually outweigh the risks and it is most commonly performed by ultrasonography (US) which is inexpensive and widely available. The implications of a positive diagnosis vary from country to country and should be discussed beforehand with the test subject.

Simple cysts occur more frequently with increasing age in the general population. Age-dependent US criteria for diagnosis and disease exclusion have been established for *PKD1*, and subsequently refined for at-risk adults of unknown gene type (see “Unified Criteria” in Table 1).[13] Conventional US is suboptimal for disease exclusion in subjects at risk for ADPKD younger than 40 years, often evaluated as potential living kidney donors. In this setting, the finding of a total of less than of 5 renal cysts by magnetic resonance imaging (MRI) is sufficient for disease exclusion.[14]

A positive family history is absent in 10–15% of patients with ADPKD due to *de novo* mutations, mosaicism, mild disease from *PKD2* and non-truncating *PKD1* mutations, or unavailability of parental medical records.[15] In the absence of other findings to suggest a different cystic disease, a patient with bilaterally enlarged kidneys and innumerable cysts most likely has ADPKD. Otherwise, the differential diagnosis needs to be broadened to include other cystic kidney diseases (see Table 2).

Newborns or children with renal cysts comprise a heterogeneous diagnostic group of cystic disorders. Although family history, imaging and clinical assessment for extrarenal manifestations may provide specific diagnostic clues, specialized consultation is strongly encouraged as genetic testing is often required.

Linkage-based diagnosis of ADPKD using polymorphic markers flanking the two disease genes, which requires multiple affected family members and can be confounded by *de novo* mutations, mosaicism, and bilineal disease,[5,16] is now rarely performed. Presently, direct mutation screening by Sanger sequencing of the *PKD1* and *PKD2* genes is the method of choice for molecular diagnosis of ADPKD. However, mutation screening for *PKD1* is

technically challenging, labor-intensive, and costly because of its large size and complexity (i.e., duplication of its first 33 exons in six pseudogenes with high DNA sequence identity)[17,18] In sequencing-negative cases, multiplex ligation-dependent probe amplification (MLPA) can be used as a follow-up test to detect large gene re-arrangements in less than 5% of cases.[19] Up to 15% of patients with suspected ADPKD are mutation-negative despite a comprehensive screen. The potential of Next-Generation Sequencing (NGS) technologies for high-throughput mutation screening of both *PKD1* and *PKD2* has recently been demonstrated.[20]

Molecular genetic testing is not required for most patients but may be considered in cases of: Equivocal or atypical renal imaging findings (e.g., early and severe PKD, markedly asymmetric PKD, renal failure without significant kidney enlargement, marked discordant disease within family, very mild PKD); sporadic PKD with no family history; early and severe PKD or PKD with syndromic features; and reproductive counseling.

Pre-Implantation genetic diagnosis (PGD) has been successfully applied in more than 300 genetic disorders, including ADPKD, to select healthy embryos created by in-vitro fertilization (IVF) for implantation.[21,22] PGD should be included in the discussion of reproductive choices with patients with ADPKD, although its availability and financial coverage vary from country to country.

2. MONITORING KIDNEY DISEASE PROGRESSION IN ADPKD

Treatments that extend kidney survival in ADPKD do not currently exist. Ideally, treatment should start early, when kidney parenchyma is relatively preserved. Kidney function may remain normal for several decades and is therefore not informative. By contrast, total kidney volume (TKV) in relation to age[2,3,23] can identify patients with progressive disease. TKV is an accurate estimate of kidney cyst burden and associates with pain, hypertension, gross hematuria, proteinuria or albuminuria, and loss of kidney function. TKV increases exponentially in virtually every ADPKD patient, with an average of 5–6%/year in adults.[2,24,25] Elevated TKV, particularly when used together with age and kidney function, identifies individuals who are at risk for progression to ESRD.[23]

TKV can be measured using US, CT and MRI. Precise measurements of TKV necessary in clinical trials to assess the impact of therapeutic interventions over short periods of time[26] can be obtained by planimetry or stereology analysis of MRI or CT images. However, CT imaging is associated with radiation exposure. MRI T2 weighted images provide information regarding total cyst volume and do not require gadolinium, eliminating the risk for nephrogenic systemic fibrosis.

US has been used to measure disease progression in studies with long follow-up.[27] It is however operator-dependent, less reproducible and less precise, and can overestimate TKV compared to MRI and CT.[28,29] US measurement of TKV typically is calculated utilizing the ellipsoid equation based on orthogonal length, width and depth of the kidney.[27]

Advanced CT imaging can subdivide non-cystic tissue into fully enhanced parenchyma and hypoenhanced ("intermediate") compartment. The latter is thought to represent fibrotic, non-functional tissue.[30]

Renal blood flow (RBF), which can accurately be measured by MRI in ADPKD, is reduced and associates with disease progression.[31,32]

Imaging of the kidneys (preferably by CT or MRI) should be part of the initial evaluation in ADPKD patients. Radiology reports should be standardized and include maximum kidney length, width and depth measurements, and an estimate of TKV. In absence of approved treatment to slow disease progression, repeated TKV measurements in asymptomatic patients are not indicated. When approved disease-modifying therapies become available or if lifestyle modifications are shown to alter disease progression, repeat imaging may become an important management tool.

Glomerular filtration rate

Estimation of GFR using equations (eGFR) is in general acceptable for clinical care of ADPKD patients. Only in specific circumstances, measurement of GFR (mGFR) may be warranted. Whether the use of eGFR is also adequate for use in clinical trials remains debated.[33–35] Using mGFR may limit the feasibility of trials and it is unknown whether a limited number of mGFRs outperforms a larger number of eGFRs to assess change in kidney function over time. To date, using eGFR remains the standard to assess kidney function in randomized clinical trials in ADPKD. Of note, it should be established whether any novel treatment interfere with tubular creatinine secretion. When this is the case, baseline pretreatment eGFR should be compared with off-treatment eGFR after study completion, or mGFR should be used.

Proteinuria

Proteinuria (> 300 mg/day), occurs in ~25% of adults diagnosed with ADPKD, but typically does not exceed 1 gm/day.[36] Proteinuria associates with larger TKV, faster decline of renal function and earlier onset of ESRD. In patients with nephrotic range proteinuria, the presence of an additive disorder should be considered.

Patient reported outcomes (PROM) and QOL

There is no current validated PROM for ADPKD. Patients with ADPKD have not been found to score differently from the general population in standardized questionnaires (SF36) evaluating QOL.[37,38]

3. MANAGEMENT of HYPERTENSION, RENAL FUNCTION DECLINE and RENAL COMPLICATIONS

Treatment of hypertension in the adult ADPKD population

Patients with ADPKD are at increased risk for hypertension and cardiovascular events when compared to the general population.[39,40] Data supporting disease-specific BP targets are limited. The general advice of the 2012 KDIGO Clinical Practice Guideline for the

Management of BP in CKD can therefore be followed, suggesting a BP target ≤140/90 mmHg.[41,42] In accordance with this guideline, blood pressure targets should be individualized taking comorbidities into account.[41,42]

BP control can be achieved by lifestyle modification and medical treatment. Agents that interfere with the RAAS are first line BP-lowering agents in combination with a sodium-restricted diet.[39,40] There is controversy as to which second-line BP-lowering agents should be used. Large RCTs in non-ADPKD populations suggested that calcium channel blockers and diuretics may be preferred over beta-blockers for cardiovascular protection.[43] Theoretical concerns may argue against using these agents in ADPKD. Comorbid conditions should therefore influence the choice for a specific class.

Diagnosis and management of hypertension in pediatric patients

Cardiovascular abnormalities in ADPKD are evident from a young age onwards.[44] It is recommended to have children with a family history of ADPKD screened for hypertension from the age of 5 years onward, with an interval of 3 years in cases in which no hypertension is found. Diagnosis and treatment of hypertension in the pediatric population should follow prevailing pediatric guidelines, with the exception that RAAS blockade is preferred as first-line treatment.[45]

“Conventional” renoprotective treatments

Most ADPKD patients develop progressive renal insufficiency that eventually leads to ESRD. While several renoprotective strategies have been identified in non-ADPKD CKD (e.g., strict BP control, RAAS inhibition and low-protein diets), until recently no randomized, clinical trials of sufficient size and quality had tested such interventions in ADPKD.

Recently, the results of the HALT PKD clinical trials have been published.[25,46] In study A, 558 hypertensive patients with ADPKD (15 to 49 years of age, with an eGFR >60 ml per minute per 1.73 m^2) were randomly assigned to either a standard blood-pressure target (120/70 to 130/80 mm Hg) or a low blood-pressure target (95/60 to 110/75 mm Hg) and to either lisinopril plus telmisartan or lisinopril plus placebo.[25] In study B, 486 patients hypertensive patients with ADPKD (18 to 64 years of age, with eGFR 25 to 60 ml per minute per 1.73 m^2) were randomly assigned to receive lisinopril plus telmisartan or lisinopril plus placebo.[46] Both studies showed that an ACE inhibitor alone can adequately control hypertension in most patients justifying its use as first line treatment for hypertension in this disease. Study A showed that lowering blood pressure to levels below those recommended by current guidelines in young patients with good kidney function reduced the rate of increase in kidney volume by 14%, the increase in renal vascular resistance, urine albumin excretion (all identified in Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease as predictors of renal function decline), left ventricular mass index, and marginally (after the first four months of treatment) the rate of decline in eGFR. The overall effect of low blood pressure on eGFR, however, was not statistically significant, possibly because the reduction of blood pressure to low levels was associated with an acute reduction in eGFR within the first four months of treatment. Although these

results may not be unanimously viewed as positive, they do underline the importance of early detection and treatment of hypertension in ADPKD. The addition of an ARB (telmisartan) to an ACE inhibitor (lisinopril) was safe but did not confer additional benefit.

"Novel" ADPKD specific renoprotective treatments

Based on improved mechanistic knowledge, a large number of novel targets for lifestyle and medical interventions have been proposed. Various studies have shown a detrimental role of the antidiuretic hormone arginine vasopressin (AVP) in ADPKD. Patients therefore are advised to increase their water intake to suppress endogenous AVP, although the long-term feasibility and efficacy of this intervention remain unknown. Based on a potential effect on intracellular cAMP levels, avoiding high caffeine intake has been proposed. With respect to medical interventions three classes of drugs are especially promising. In a large scale RCT the AVP V2 receptor antagonist tolvaptan slowed the rate of growth of TKV and rate of eGFR decline in patients with ADPKD.[24] These data led to approval of tolvaptan by the regulatory authorities in Japan.[47] In the USA the FDA requested additional data to further evaluate the efficacy and safety of this drug.[48] Applications for approval are currently under review by the European Medicines Agency and Health Canada. With respect to somatostatin analogues, three placebo controlled RCTs suggested a beneficial renal effect, but these trials were of short duration and included a relatively small number of patients.[49–52] A recently published small-scale study[53] with three years of follow-up also suggested a beneficial effect.[54] Until the results of larger trials become available, somatostatin analogues should not be prescribed for renoprotection outside of a research study. Lastly, a RCT of HMG-CoA reductase inhibition with pravastatin in ADPKD children showed slower kidney volume growth and reduced loss of kidney function.[55] These data need confirmation, especially because a two-year RCT in the adult ADPKD population showed no effect of pravastatin treatment versus placebo.[56]

Hematuria and cyst hemorrhage

Cyst hemorrhage and gross hematuria are frequent complications of ADPKD. Gross hematuria can result from cyst hemorrhage, nephrolithiasis, infection and rarely, renal cell or urothelial carcinoma. Cyst hemorrhage can be associated with fever and differentiation from cyst infection may be difficult. Episodes of cyst hemorrhage or gross hematuria are usually self-limited and resolve within 2 to 7 days. If symptoms persist, a possible neoplasm should be excluded. Rarely, bleeding can be persistent or severe, sometimes with extensive subcapsular or retroperitoneal hematomas, requiring hospitalization. Temporary discontinuation of RAAS inhibitors and diuretics to avoid acute kidney injury during an episode of acute cyst hemorrhage has been suggested.[57]

Nephrolithiasis

Nephrolithiasis and cyst wall calcifications are common in ADPKD, favored by urinary stasis and metabolic factors (reduced urine pH, ammonium excretion and urinary citrate).[58,59] CT is the best imaging technique for detecting and evaluating kidney stones, and dual energy CT can differentiate uric acid from calcium containing stones.[60] Potassium citrate is the treatment of choice in the three stone-forming conditions associated with ADPKD: uric acid nephrolithiasis, hypocitraturic calcium oxalate nephrolithiasis, and distal

acidification defects. Extracorporeal shock wave lithotripsy and percutaneous nephrostolithotomy are successful in most cases without increased complications compared to patients without ADPKD.[61] Flexible ureterorenoscopy with laser fragmentation has also been used safely and effectively with less risk for traumatic nephron loss.[62,63]

Management of renal cyst infection

Recent meta-analyses highlight the course and successful management of both renal and liver cyst infections.[64] The presence of fever, abdominal pain, and high sedimentation rate or level of C-reactive protein (CRP) should raise the suspicion of a cyst infection, but the differential diagnosis is broad.[65,66] Blood and urine cultures may be negative. 18-Fluorodeoxyglucose positron emission tomography (FDG-PET) may be helpful in identifying infected cysts.[64] Lipid-permeable anti-microbial agents such as fluoroquinolones and trimethoprim-sulfamethoxazole, depending on sensitivity (if available), remain the standard treatment for cyst infections. There is wide variability regarding duration of treatment and indications and timing of percutaneous or surgical draining. Efficacy of antibiotic treatment is defined by the disappearance of fever, and at least two negative blood and/or urine cultures. Cyst infection may recur even after adequate periods of antibiotic therapy.

Management of chronic pain

Kidney pain is the most common renal manifestation in ADPKD.[67,68] It may develop after an episode of acute pain and is likely maintained by aberrant activity of sensory and autonomic neurons innervating the kidney. Ongoing support to patients and a multidisciplinary approach are essential for the management of chronic pain. If needed, a sequential medication approach should be based on the WHO's pain relief ladder.[67,68] Diagnostic percutaneous cyst aspiration is helpful to determine whether a more permanent intervention such as cyst sclerosis or laparoscopic cyst fenestration is worth pursuing.[69,70] Celiac plexus blockade, radiofrequency ablation, and spinal cord stimulation have also been used.[71] Thoracoscopic sympathosplanchnicectomy may be helpful in some patients with disabling pain but it is invasive and has potential complications such as pneumothorax and orthostatic hypotension.[72] Laparoscopic renal denervation has been helpful in a small series of patients.[73] Recently, percutaneous transluminal catheter-based denervation has also been shown to be effective in case reports and deserves further evaluation.[74,75]

Reproductive issues

All women of reproductive potential should receive counseling including potential aggravation of polycystic liver disease (PLD) with exogenous estrogen or progesterone exposures.[76] In general, ADPKD women with normal BP and kidney function have a favorable course during pregnancy. Pregnancy induced hypertension and preeclampsia occur more frequently. Preeclampsia is a known risk factor for future development of ESRD in the general population, but its contribution to disease progression in ADPKD has not been studied.[77] Multiple pregnancies (> 3) have been reported to be associated with a greater risk for decline in kidney function in ADPKD. Preemptive discontinuation of RAAS inhibitors is necessary due to the potential teratogenicity and increased risk of acute renal failure in the developing fetus.

4. MANAGEMENT of ESRD

Optimal choice of RRT

Transplantation is the optimal choice of RRT in appropriate patients with ADPKD[78–82] Living kidney donation, ideally preemptive, is likely to be associated with best outcomes.[83] The limited number of potential donors in affected families raises the question about donation priorities, requiring individual and family counseling.

When transplantation is not an option, or for those waiting for transplantation, either hemodialysis (HD) or peritoneal dialysis (PD) are suitable modalities. Although intra-abdominal space restrictions, increased risk for abdominal wall hernias and increased prevalence of colonic diverticula may pose challenges, ADPKD is not a contraindication for PD.[84,85]

Preparation for transplantation

Kidneys should not be routinely removed prior to transplantation, since nephrectomy in ADPKD patients is associated with significant morbidity and mortality.[86–89] Indications for nephrectomy include recurrent and/or severe infection, symptomatic nephrolithiasis, recurrent and/or severe bleeding, intractable pain, suspicion of renal cancer and space restrictions prior to transplantation, taking into account that kidney size typically declines after transplantation.[90] Hand assisted laparoscopic nephrectomy is better tolerated.[91–93] While practices vary widely, on average less than one third of patients in published series undergo pre-transplant nephrectomy.[86,94–96] Experience with prior and simultaneous nephrectomy has been reported[95,97] but both practices have not been directly compared.

The risk-benefit relationship for screening patients for ICA and diverticular disease prior to transplantation remains unknown. Interpretation of BMI needs to take into account the weight of severely enlarged organs.

Post-transplant complications in ADPKD patients

Post-transplant morbidity appears not to be increased in ADPKD patients as compared to other, non-diabetic transplant recipients. Specific complications have been reported to be more frequent, including new onset diabetes,[94] gastrointestinal (GI) complications,[98,99] erythrocytosis,[94] urinary tract infections,[94,100] thromboembolic complications,[94] and hemorrhagic stroke.[101]

Use of kidneys from ADPKD patients for transplantation

Transplantation of ADPKD kidneys with acceptable kidney function and size from deceased donors can be an option, provided there is fully informed consent.[102]

Risk for renal cancer in ADPKD with renal failure

The incidence of clinically significant renal cell carcinoma (RCC) in ADPKD patients with renal failure is not increased as compared to patients with other kidney diseases,[103–105] although in some studies removed ADPKD kidneys revealed a 5% to 8% incidence of RCC, most measuring ≤2 cm in diameter.[106,107] Except in case of repeated hematuria (see above),

systematic screening is not recommended and optimal management of suspicious lesions (i.e., observation vs. intervention) remains unknown.

Hemoglobin, BP, and lipid targets in ADPKD patients on dialysis

Therapeutic targets should not be different in ADPKD compared to other patients on dialysis. Anemia is on average less severe in ADPKD patients[108] and some patients spontaneously maintain high hemoglobin levels.

Anticoagulation

There is insufficient evidence to recommend a specific management of anticoagulation in ADPKD patients with ESRD. Whether and to what extent the risk and/or severity of bleeding from ICA or kidney cysts are increased by systemic anticoagulation is unknown.

5. Management of extrarenal complications

Intracranial aneurysms

Intracranial aneurysms (ICA) occur in 9–12% of patients with ADPKD compared with 2–3% in the general population.[109–111] There are no clear risk factors for ICA rupture in patients with ADPKD, other than family history of rupture.[112] Mean age at rupture is lower than in the general population (41 vs 51 years). Overall there appears to be no difference in the rate of rupture between ADPKD and the general population.

This panel does not recommend widespread screening for ICA because (i) it yields mostly small ICAs with a low risk of rupture and (ii) prophylactic repair of an unruptured ICA (UIA) may be risky. Indications for screening in patients with good life expectancy include family history of ICA or subarachnoid hemorrhage, previous ICA rupture, high-risk professions (e.g., airline pilots) and patient anxiety despite adequate information. Time-of-flight (TOF) MRA without gadolinium enhancement is the screening method of choice.

Management of UIAs should be discussed with a multidisciplinary team at an expert center. Individuals with small, untreated UIAs should be re-evaluated every 6 to 24 months.[109,113,114] Smoking cessation and control of cardiovascular risk factors are strongly recommended. Patients with a family history of ICA and a negative screening should be re-screened at 5–10 years intervals.[113]

Polycystic liver disease (PLD)

Liver cysts occur in more than 80% of adults with ADPKD.[115] The cyst burden increases with age and is greater in women especially in those with multiple pregnancies or those who have taken exogenous estrogens.[116] Liver imaging to determine the extent of polycystic liver disease (PLD) should be a part of the initial assessment of all ADPKD patients.

Most patients with PLD are asymptomatic, while about 20% of them will suffer compressive symptoms including abdominal pain and distension, back pain, early satiety and gastroesophageal reflux.[117–119] Treatment options for severe PLD include surgical and medical therapy.[120] Surgical options encompass aspiration/sclerotherapy, fenestration,

partial or segmental hepatectomy and liver transplantation.[110–121] Somatostatin analogues were shown to reduce or stabilize liver volume in severe PLD: their use is currently restricted to either clinical trials or compassionate use.[122–124]

Liver cyst infections typically manifest with localized pain and fever accompanied by laboratory data reflecting inflammation.[64,125,126] PET-CT was recently reported to be the most sensitive tool for identifying infected cysts.[127–129] A prolonged course of a fluoroquinolone, combined with early, percutaneous cyst drainage provide the best treatment results.[125] Recurrence of liver cyst infection is frequent.

Additional extrarenal manifestations

Additional extrarenal manifestations mainly encompass cysts in other organs (seminal vesicle: 40%, pancreas: 10%, arachnoid membrane: 8%, spinal meningeal: 2%) and connective tissue abnormalities (mitral valve prolapse, abdominal hernia and diverticular disease).[1] They are rarely symptomatic and do not justify routine screening. Their recognition may spare the patient from additional testing (Table 3; see full report in Supplemental Appendix).

6. PRACTICAL INTEGRATED PATIENT SUPPORT

First diagnosis

There is an unmet need for all ADPKD patients to have access to nephrologists knowledgeable about the disease. Checklists for both the patient and doctor are required for first diagnosis consultation and follow-up. In addition to treatment options and extrarenal complications, these checklists must cover practical implications such as potential impact on work, insurance, lifestyle, family planning, and psychological health.

Family planning

Key issues include genetic counseling and PGD/IVF access which, despite cost concerns, imply potentially significant societal savings. Consensus was reached that these decisions are for the patients and/or parents to make. World-wide access to these modalities is desired.

Screening children

There are three options for at-risk but undiagnosed children: 1) screen the children as young as possible and disclose the results to the entire family; 2) screen and disclose results only to the parents; 3) do not screen. In the full conference report, each option is explored based on unique conditions. Ultimately, the approach taken should be the parents' decision.

Lifestyle modifications

Consensus was reached on many recommendations (see full report in Supplemental Appendix). More comprehensive patient education, with focus on positive messages about diet and lifestyle are required to motivate patients' adherence.

Exercise and sports

Evidence is lacking on the impact of sports on ADPKD patients. While it might “make sense” to avoid hard contact sports, there is a lack of evidence that contact sports do indeed represent an unacceptable risk to the majority of ADPKD patients.

Patient psychological care

Anxiety and depression are highly prevalent in CKD patients, and reported by >60% of those with ADPKD. Since these disorders are related to lowered life expectancy, physicians must actively listen and have empathy for psychological and emotional concerns of ADPKD patients, including anxiety about lifestyle, body image, and sexual dysfunction.

Financial impacts

ADPKD is handled inconsistently by financial institutions and employers. A global PKD community initiative should produce a ‘standardized’ and endorsed statement about ADPKD that patients could use when dealing with banks, insurers, employers and health payers.

Support

Due to the current lack of up-to-date ADPKD information worldwide in all languages and for all cultures, collaboration between worldwide patient groups is encouraged, including creation of a global ‘PKD Portal’ to enable and empower patients to become advocates of their own care. A list of supporting websites for several countries is provided in Table 4.

PKD Centers of Excellence

Evidence supports a multitude of patient benefits through access to a multidisciplinary team approach to care, with all relevant specialties in one center or clinic to ADPKD patients. And despite the likely continuing uneven geographical distribution of expertise and patients, the growth in telemedicine holds great promise for the expert treatment of ADPKD in the future.

CONCLUSION AND PERSPECTIVES

The KDIGO controversy conference on ADPKD represents the first global initiative that brought together a panel of multi-disciplinary clinical expertise and engaged patients from 20 countries to perform a detailed analysis of the literature and to identify areas of consensus, gaps in knowledge, and research and healthcare priorities. To this end, this conference report has proposed an extensive research agenda with the goal to close up these said gaps and resolve outstanding controversies (see Table 5 in Supplemental Appendix). Current knowledge and the large volume of ongoing clinical trials and large collaborative studies warrant the development of practice guidelines/best practice policies for ADPKD. Facing the identification of priorities for clinical research, there is a need for a global, academic network to prioritize, facilitate, coordinate and avoid duplication of such trials. Patient support organizations play a key role in closing the gap between disease understanding and the development of effective education tools, new treatments, and improved health policies.[130]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Performance of ultrasound-based unified criteria for diagnosis or exclusion of ADPKD

Diagnostic confirmation			
Age (years)	**PKD1**	**PKD2**	**Unknown gene type**
15–29	A total of ≥3 cysts *: PPV=100%; SEN=94.3%	PPV=100%; SEN=69.5%	PPV=100%; SEN=81.7%
30–39	A total of ≥3 cysts *: PPV=100%; SEN=96.6%	PPV=100%; SEN=94.9%	PPV=100%; SEN=95.5%
40–59	≥2 cysts in each kidney: PPV=100%; SEN=92.6%	PPV=100%; SEN=88.8%	PPV=100%; SEN=90%
Disease exclusion			
Age (years)	**PKD1**	**PKD2**	**Unknown gene type**
15–29	No renal cyst: NPV=99.1%; SPEC=97.6%	NPV=83.5%; SPEC=96.6%	NPV=90.8%; SPEC=97.1%
30–39	No renal cyst: NPV=100%; SPEC=96%	NPV=96.8%; SPEC=93.8%	NPV=98.3%; SPEC=94.8%
40–59	No renal cyst: NPV=100%; SPEC=93.9%	NPV=100%; SPEC=93.7%	NPV=100%; SPEC=93.9%

Abbreviations: NPV, negative predictive value; PPV, positive predictive value; SEN, sensitivity; SPEC, specificity.

* Unilateral or bilateral.

Table 2

Differential diagnosis of other renal cystic diseases

Disorder	Inheritance	Family history	Clinical features
Autosomal recessive polycystic kidney disease (ARPKD)	AR	Siblings (25%)	~ 1 in 20,000. Neonatal deaths in 30%; Potter's phenotype; biliary dysgenesis (congenital hepatic fibrosis, intrahepatic bile duct dilatation), resulting in portal hypertension and cholangitis.
Renal cysts and diabetes syndrome (RCAD/MODY 5/ HNF-1B [*]	AD	Spontaneous mutations (often deletions) in 50%	Renal cysts or malforfation in 90%, diabetes mellitus in 45%, hypomagnesemia in 40%, genital tract abnormalities in 20%, hyperuricemia in 20%, elevated liver enzymes in 15%
Tuberous sclerosis complex (TSC)	AD	Absent in two thirds of families	~1 in 10,000 live births. Skin lesions (facial angiofibromas, periungual fibroma, hypomelanotic macules, Shagreen patch), >90%; cerebral pathology (cortical tuber, subependymal giant cell astrocytoma), 90%; renal (polycystic kidneys, angiomyolipoma), 50–70%; retinal hamartomas, 50%; lymphangioleiomyomatosis.
PKD1-TSC contiguous gene syndrome	AD	Spontaneous presentation frequent	Presentation of severe ADPKD at an early age, with polycystic kidneys with renal angiomyolipomas frequently present after the first year of age.
von Hippel-Lindau syndrome	AD	~ 20% de novo	~1 in 36,000. Cerebellar and spinal hemangioblastoma; retinal angiomas; serous cystadenomas and neuroendocrine tumors of pancreas; pheochromocytoma; renal cell carcinoma.
Medullary cystic kidney disease (MCKD [**])	AD	rare	Slowly progressive kidney disease; medullary cysts (but uncommon in families with type 2 MCKD [now known as ADTKD-*UMOD*]); hyperuricemia and gout (in type 2 MCKD [now known as ADTKD-*UMOD*]); small to normal sized kidneys.
Medullary sponge kidney (MSK)	Unclear	Familial clustering reported	~1 in 5000. Medullary nephrocalcinosis; kidney stones; "brush" or linear striations on intravenous pyelogram.
Simple renal cysts	Acquired	None	Common; increase in number and size with age. Normal renal function; normal-sized kidneys.
Acquired cystic kidney disease (ACKD)	Acquired	None	Common in patients with chronic renal failure or ESRD; multiple cysts associated with normal- or small-sized kidneys

Abbreviations: AD, autosomal dominant; ADTKD, autosomal dominant tubulointerstitial kidney disease; AR; autosomal recessive; ESRD, end-stage renal failure; MODY 5, maturity onset diabetes mellitus of the young type 5

[*] Current designation is ADTKD-*HNF1B*

[**] Use of the term MCKD is discouraged; formerly MCKD Type 1 should now be referred as ADTKD-*MUC1* and formerly MCKD Type 2 should now be referred as ADTKD-*UMOD*.

Table 3

Other extrarenal manifestations of ADPKD

Manifestation	Associated	% Affected	Screen	Comment
Cardiac valve abnormalities	Yes	Mitral valve prolapse 25%	No	Screen only if cardiovascular signs/ symptoms
Pericardial effusion	Yes	Up to 35%	No	Screen only if cardiovascular signs/ symptoms
Extracranial aneurysms	Yes, case reports	Unknown	No	Clinicians should be aware of vascular phenotype in some patients
Arachnoid cysts	Yes	8–12%	No	Possible increased risk for subdural hematoma.
Spinal meningeal cysts	Yes	1.7%	No	Rare cause of spontaneous intracranial hypotension
Pancreatic cysts	Yes	10%	No	Usually asymptomatic
Diverticular disease	Possibly in association with ESRD	~20–50% in ESRD	No	Increased incidence in patients who have reached ESRD
Abdominal hernias	Yes	Unknown	No	
Seminal vesicle cysts	Yes	~40%	No	Does not correlate with abnormal semen parameters
Male infertility	Unknown	Unknown	No	Abnormal semen parameters reported
Bronchiectasis	Possibly	37% in one series vs. 13% controls	No	One study only; mild, no clinical consequence
Congenital hepatic fibrosis	Yes, case reports, usually affecting only one generation within a family with ADPKD	Rare	No	Rare but potentially life-threatening; early diagnosis in siblings with ADPKD can be lifesaving with appropriate monitoring and treatment.

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ESRD, end-stage renal disease

Table 4

List of support information websites for ADPKD by country

Australia	http://pkdaustralia.org
Canada	http://www.endpkd.ca
France	http://www.polykystose.org
Germany	http://www.pkdcure.de
Italy	http://www.renepolicistico.it
Japan	http://www.pkdfcj.org
Netherlands	http://www.nvn.nl/nierziekten-en-behandeling/nierziekten/cystenieren
Spain	http://airg-e.onmedic.org
Switzerland	http://www.swisspkd.ch
UK	http://www.pkdcharity.org.uk
USA	http://www.pkdcure.org