MedicineToday 2014; 15(6): 16-27

PEER REVIEWED FEATURE
2 CPD POINTS

Management of autosomal dominant polycystic kidney disease

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Autosomal dominant polycystic kidney disease is the fourth most common cause of end-stage kidney disease in Australia. GPs play an important role in all aspects of management, including initial diagnosis, treatments to slow disease progression, monitoring for complications and screening of at-risk family members.

Key points

- **Autosomal dominant polycystic kidney disease (ADPKD) is a genetic condition characterised by the formation of multiple fluid-filled renal cysts and kidney enlargement.**
- **Complications of ADPKD include end-stage kidney disease, early-onset hypertension, nephrolithiasis, intracranial cerebral aneurysm and polycystic liver disease.**
- **Symptoms typically do not appear until after early to middle adulthood, and individual lifetime risk of renal failure varies markedly.**
- **Renal ultrasound examination remains the preferred imaging modality for diagnosis and family screening.**
- **Management includes referral to a nephrologist, genetic counselling, education, dietary and lifestyle treatments to slow progression of kidney disease, antihypertensives and monitoring for systemic complications.**
- **Disease-modifying treatments to slow cyst growth (e.g. tolvaptan) are in development.**

Autosomal dominant polycystic kidney disease (ADPKD) is a genetic condition characterised by the formation of multiple fluid-filled renal cysts and kidney enlargement. Potential complications of ADPKD include adult-onset end-stage kidney disease, early-onset hypertension and nephrolithiasis. ADPKD is also associated with systemic conditions including intracranial cerebral aneurysm and polycystic liver disease.[1]

GPs play an important role in all aspects of management of patients with ADPKD, including initial diagnosis, referral, genetic counselling and education, treatment of hypertension, prevention of kidney function decline, screening for systemic complications and screening at-risk family members.

HOW COMMON IS ADPKD?

ADPKD affects about one in every 500 to 1000 people of all races, and is the most common monogenic cause of chronic kidney disease (CKD). In Australia, it is the fourth most common cause of end-stage kidney disease, after diabetes, glomerulonephritis and hypertension, and accounts for around 5% of this population. Currently, approximately 2000 Australians with end-stage kidney disease caused by ADPKD receive renal dialysis or have had kidney transplantation.

CHARACTERISTICS OF ADPKD

ADPKD is usually diagnosed in adults. The hallmarks of ADPKD are:

- multiple renal cysts and kidney enlargement on ultrasound examination
- a family history of ADPKD.

In ADPKD, microscopic renal cysts form early in life (possibly in utero or in early childhood) and slowly grow by 10 to 20% per year, becoming detectable by renal ultrasound when they reach 1 cm in diameter. In the early stage, the kidney is near-normal in size with a few cysts.

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However, in established and late-stage ADPKD (usually in mid-adult life), the kidney can become markedly enlarged and abnormal in appearance, containing thousands of cysts varying in diameter from one to several centimetres and weighing up to 3 to 5 kg (Figures 1a to c).

Kidney failure develops when a critical number of cysts (possibly exceeding 1000) have enlarged sufficiently to disrupt the internal renal architecture and function. Mechanical compression of adjacent microvasculature by cysts and the release of proinflammatory molecules from cystic epithelial cells lead to interstitial inflammation and fibrosis, with loss of normal cortical parenchyma. Expanding cysts can cause discomfort owing to their size or pain if they bleed or become infected.

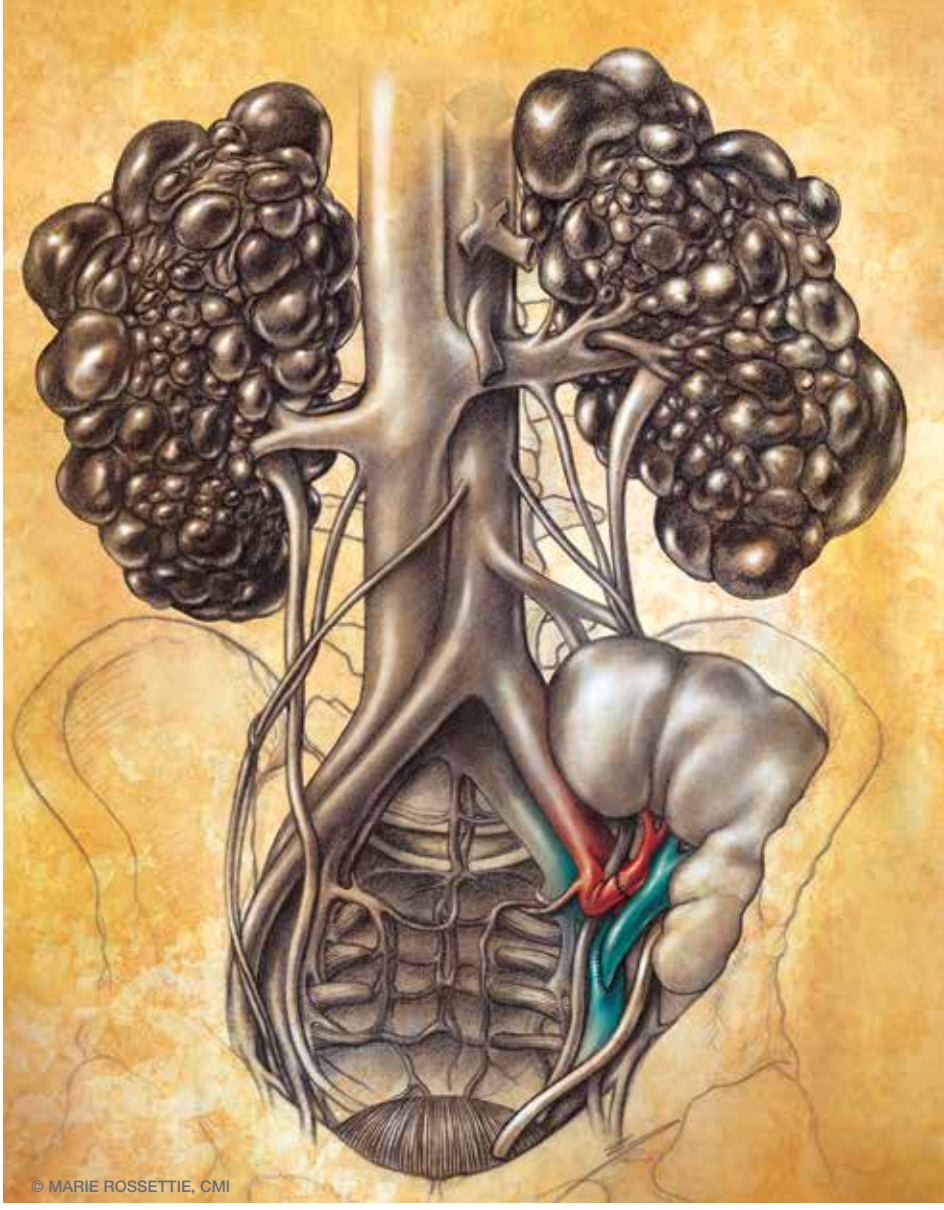
Other important features of ADPKD include:

- hypertension
- kidney stones
- cysts in other organs (mainly in the liver but occasionally in the pancreas, lungs and seminal vesicles)
- vascular abnormalities (e.g. intracranial arterial aneurysms, thoracic aortic dissection)
- rarely, colonic diverticulosis, hernias, mitral valve prolapse, bronchiectasis and male infertility (related to seminal vesicle and ejaculatory duct cystic dilatation causing azoospermia).

CAUSES OF ADPKD

What is the genetic basis?

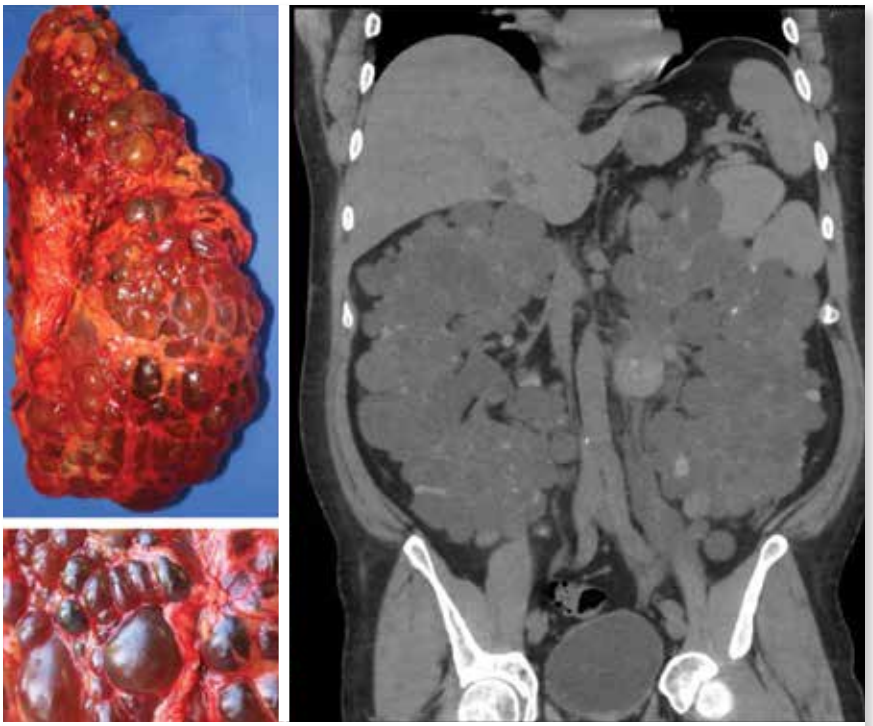
ADPKD is a dominant single-gene disorder with complete penetrance, which means that only one copy of the mutation (heterozygosity) is required for disease manifestation. Hence, each child of an affected parent has a 50% chance of inheriting the disease. In 85% of patients, ADPKD is caused by mutations in the polycystic kidney disease 1 (*PKD1*) gene, located on chromosome region 16p13.3. The remaining 15% of patients have a mutation in the *PKD2* gene located on chromosome region 4q21. Despite being a single-gene disorder, there is large inter- and intra-familial variability in disease phenotype and risk of renal failure, suggesting that unknown environmental factors also have a role in disease progression.



How do cysts form?

The *PKD1* and *PKD2* genes encode the proteins polycystin-1 and polycystin-2, respectively, which are essential for maintaining the normal geometric structure of the distal nephron and renal collecting duct. Although all cells of a person with ADPKD carry the mutated allele, only a small proportion (about 1 to 2%) of the tubular epithelial cells lining the distal nephron start to proliferate, possibly because of a second 'somatic hit' to the unaffected allele, with loss of genetic heterozygosity, and/or age-related variations in gene dosage. Proliferation of these cells begins in utero or during early life and results in the formation of diverticular-like 'pouches' (Figures 2a and b). The segmental pouches expand and eventually grow to 100 µm in diameter or more, when they lose their tubular connection and form encapsulated cysts within the renal interstitium (Figure 2c).

The interstitial cysts continue to grow at different rates, as the lining epithelial cells



Figures 1a to c. Typical appearance of the kidney in late-stage autosomal dominant polycystic kidney disease, macroscopically (a and b, left) and on an abdominal CT scan (c, right). The kidneys are enlarged and the normal renal parenchyma has been almost completely replaced by hundreds of large renal cysts containing blood or urine-like fluid. By the time the kidneys have developed this appearance there would be associated renal scarring, impaired renal function and hypertension.

proliferate and secrete fluid (Figures 3a and b). This leads over decades to late-stage disease, with multiple cysts compressing the renal parenchyma within an enlarged and irregular kidney. The cysts are lined by a layer of flattened epithelial cells (similar to simple renal cysts), and are filled with discoloured fluid, which may be yellow similar to urine, or chocolate- or red-coloured from altered blood.

The *PKD* gene mutations also cause abnormalities in connective tissue and the basement membrane. These permit cyst growth and are responsible for systemic complications such as aneurysms, colonic diverticula and hernias.

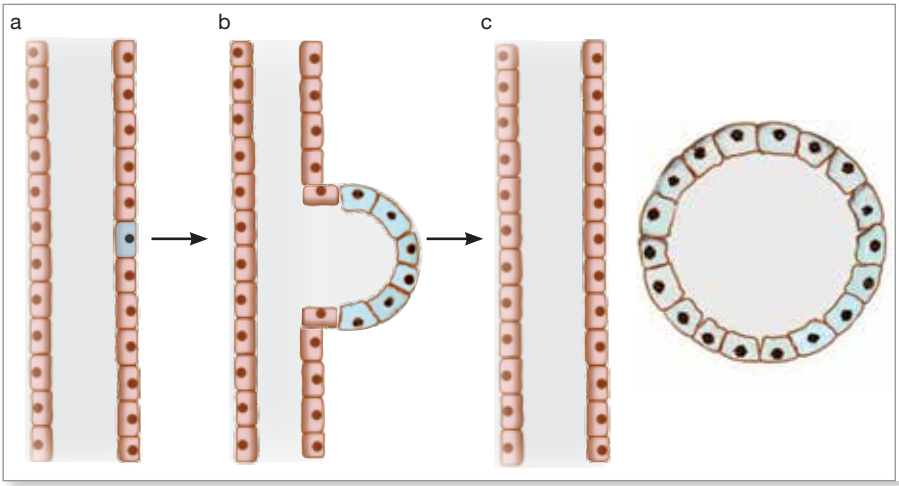
HOW DO PATIENTS WITH ADPKD PRESENT?

ADPKD is clinically silent in about half of affected people, and symptoms typically do not appear until after early to middle adulthood (age in the 30s to 60s). Rarely, it presents in utero or early childhood. Common asymptomatic and symptomatic presentations in adults are summarised in Box 1.

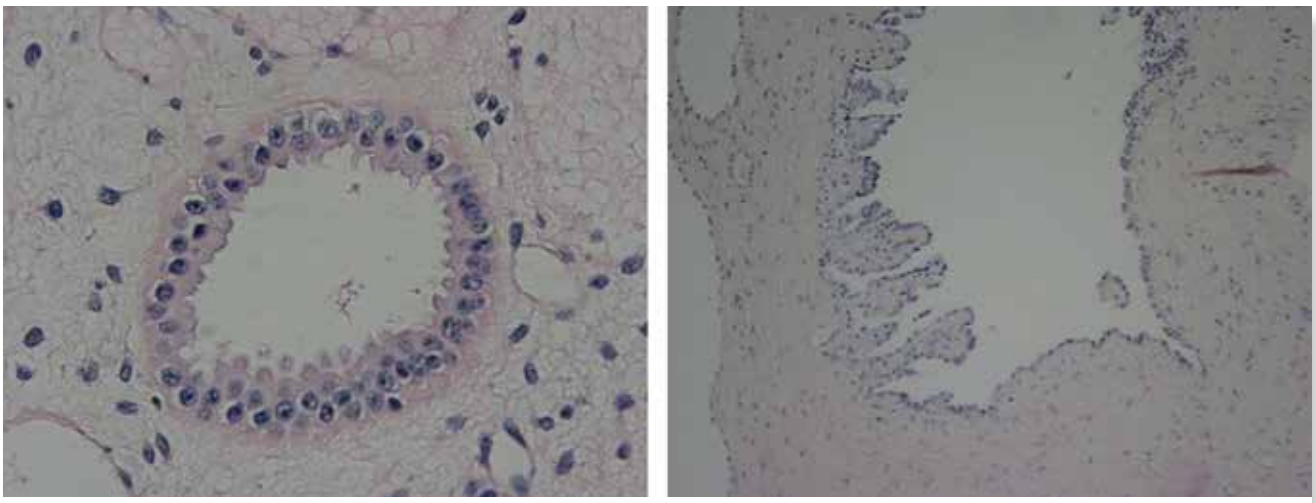
Symptoms associated with ADPKD include:

- macroscopic haematuria following abdominal trauma (such as during contact sports)
- spontaneous or provoked abdominal or loin pain from cyst rupture
- rarely, rupture of an intracranial cerebral (berry) aneurysm.

Clinical signs of ADPKD include bilateral kidney enlargement on abdominal palpation or ballottement and hypertension. Systemic features, such as cardiovascular disease (e.g. mitral valve prolapse), intracranial cerebral aneurysms, inguinal hernias and diverticular disease, occur in up to 5% of people with ADPKD, as a result of associated connective tissue defects.



Figures 2a to c. Postulated mechanism of formation of renal cysts from the distal nephron and collecting duct in autosomal dominant polycystic kidney disease. a (left). A small number of cells lining the distal tubule of the nephron start to proliferate (blue-coloured cell). b (centre). This proliferation leads to the formation of a diverticular 'pouch'. c (right). With continued growth, the pouch detaches from the nephron and forms a cyst in the renal interstitium.



Figures 3a and b. Light micrographs of early-stage renal cysts in a patient with autosomal dominant polycystic kidney disease (haematoxylin and eosin stain). The epithelial cells lining the cyst are highly proliferative with evidence of hyperplasia (a, left), micropolyp formation (b, right) and de-differentiation (not shown).

DIAGNOSIS OF ADPKD

The diagnosis of ADPKD is based on a typical appearance on imaging, generally supported by a family history with an autosomal dominant pattern of inheritance. Although the family history is usually positive (an affected relative with confirmed ADPKD) or suggestive (first-degree relatives with renal failure resulting in dialysis or death), approximately 5 to 10% of patients with typical ADPKD on imaging have no family history despite careful radiological screening of both parents. These cases likely arise through spontaneous mutation or genetic mosaicism.

Renal ultrasound examination remains the preferred imaging modality for diagnosis of ADPKD and for family screening, as it is safe, reliable and inexpensive (Figure 4). The Pei-Ravine criteria for the diagnosis of ADPKD by renal ultrasound are summarised in the Table.[2] These criteria define age-specific thresholds for cyst numbers and can distinguish patients with ADPKD from those with multiple simple (Bosniak class 1) renal cysts, which can develop with ageing in normal individuals. ADPKD is characterised by larger numbers of renal cysts, kidney enlargement and earlier age of onset, often combined with a positive family history. When cyst numbers fail to meet the Pei-Ravine diagnostic criteria for ADPKD (designated 'indeterminate') in an at-risk person with a positive family history then repeating the renal ultrasound examination in one to two years is suggested.

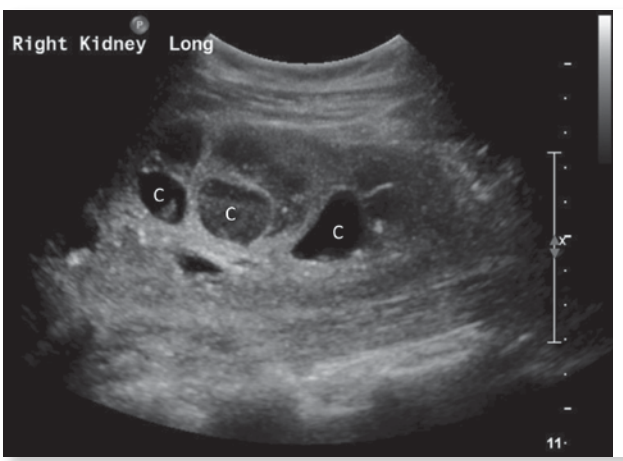


Figure 4. Ultrasound image of the right kidney showing multiple cysts of different sizes, typical of the appearance in autosomal dominant polycystic kidney disease. Larger cysts are labelled 'C'.

1. CLINICAL SCENARIOS FOR THE PRESENTATION OF ADPKD

Asymptomatic

- Screening of individual with a family history of ADPKD
- Incidental finding on imaging (ultrasound, CT or MRI) performed for another indication
- Early-onset hypertension (in an individual younger than 40 years)
- Reduced renal function and eGFR

Symptomatic

- Macroscopic haematuria in an individual younger than 40 years
- Abdominal or loin pain from cyst rupture
- Rupture of an intracranial aneurysm (rare)

ABBREVIATIONS: ADPKD = autosomal dominant polycystic kidney disease; eGFR = estimated glomerular filtration rate.

TABLE. PEI-RAVINE CRITERIA FOR THE DIAGNOSIS OF ADPKD BY RENAL ULTRASOUND EXAMINATION*[2]

Age (years)	Positive family history†	Number of renal cysts required to establish diagnosis	PPV, sensitivity	Number of renal cysts required to exclude diagnosis
15–29	Yes	≥3 (unilateral or bilateral)	PPV = 100%, sensitivity = 81.7%	Normal ultrasound does not exclude the diagnosis
30–39	Yes	≥3 (unilateral or bilateral)	PPV = 100%, sensitivity = 82–96%	Normal ultrasound does not exclude the diagnosis
40–59	Yes	≥4 (at least 2 in each kidney)	PPV = 100%, sensitivity = 90%	<2 (NPV = 100%, specificity = 98.2%)
≥60	Yes	≥8 (at least 4 in each kidney)	PPV = 100%, sensitivity = 100%	<2
Any age‡	No	≥10 cysts in each kidney with renal enlargement ± hepatic cysts		NA

ABBREVIATIONS: ADPKD = autosomal dominant polycystic kidney disease; NA = not applicable; NPV = negative predictive value; PPV = positive predictive value.
* Criteria based on the use of conventional 3-5 MHz ultrasound probe with cyst size typically being above 1 cm in diameter. CT, MRI and more sensitive ultrasound probes detect smaller cysts and therefore the above criteria are not applicable to these imaging modalities.
† Genotype unknown.
‡Criteria based on expert opinion.

Role of genetic testing

Linkage analysis and direct DNA sequencing can determine the type of mutation (*PKD1* or *PKD2*) a patient with ADPKD carries, with detection rates varying between 65 and 85%. However, DNA sequencing is time-consuming and expensive because the *PKD1* gene is large and complex, displaying pronounced allelic heterogeneity, meaning that most detected mutations are unique. Because of the diagnostic simplicity of renal ultrasound examination combined with family history, and the lack of therapeutic impact of mutation typing, genetic testing is not routinely used in clinical practice.

Direct-to-consumer DNA genetic testing is not recommended. Prenatal and pre-implantation genetic testing are of increasing interest, but there are currently no consensus guidelines on their use. Counselling for prenatal testing should be multidisciplinary, involving clinical geneticists, fertility physicians and nephrologists, and should take into account the wide phenotypic variability in progression of ADPKD to renal failure, with at least half of patients experiencing a benign course during life.

SCREENING OF FAMILY MEMBERS

Screening of family members of affected patients is a complex issue. Given the robustness of renal ultrasound examination as a diagnostic test for ADPKD, this investigation should be considered equivalent to a pre-symptomatic genetic test. Counselling should be offered to at-risk first-degree family members following the guidelines recommended for other genetic diseases, including a discussion of the risks and benefits of making the diagnosis.[3]

Potential benefits of screening include early detection and treatment of complications (particularly hypertension), prevention of decline in renal function and possible help with future family planning. However, the psychosocial impact of a diagnosis of ADPKD for the individual and possible effect on future life insurance applications and employment need to be taken into account. Referral to a clinical geneticist and an adult or paediatric nephrologist should be considered.

Screening methods used for ADPKD include measurement of blood pressure and a renal ultrasound examination. A normal appearance on ultrasound does not exclude the diagnosis of ADPKD in people younger than 40 years.

For the children of people with ADPKD, early screening before cysts have time to develop is often not helpful as they are less likely to have treatable complications such as hypertension; a normal ultrasound result does not exclude disease; and there are no disease-modifying therapies currently available to prevent disease progression. A better approach may be to wait until these children reach adulthood and can make their own informed decision about screening. This is in contrast to the inherited childhood-onset recessive variant of polycystic kidney disease, which has an earlier age of onset; early screening is likely to reveal renal abnormalities and hypertension may be present.

MANAGEMENT OF ADPKD

Management of patients with ADPKD is summarised in Box 2.[4] Web resources providing useful information for patients about ADPKD are listed in Box 3.

Counselling about future end-stage kidney disease

The possibility of end-stage kidney disease (CKD stage 5) can cause significant

2. MANAGEMENT OF PATIENTS WITH ADPKD

Assess for the presence of risk factors for renal function decline

- History of end-stage kidney disease in family member
- Hypertension
- Impaired eGFR
- Total kidney volume to height ratio > 600 mL/m on ultrasound as assessed by the ellipsoid method; consider repeating every five years
- Macroalbuminuria (urine ACR >25 mg/mmol for males and >35 mg/mmol for females)

Treat to help slow decline in kidney function and reduce hypertension risk*

- Lifestyle changes
  - Smoking cessation
  - Dietary salt restriction
  - Moderate alcohol consumption
  - Maintain BMI between 18.5 and 24.9 kg/m^2 through diet and exercise
  - Avoid more than two caffeinated drinks per day
- Blood pressure: assess and maintain blood pressure <130/80 mmHg with ACE inhibitor or ARB
- Cholesterol: maintain total cholesterol level <4.0 mmol/L with diet and statin
- Blood glucose (for patients with concurrent diabetes): aim for HbA_{1c} <7.0%
- Avoid nephrotoxic drugs and episodes of acute kidney injury

Assess and manage other renal complications

- Chronic kidney disease (monitor eGFR and refer to nephrologist)
- Renal pain: symptom review
- Kidney stones: maintain adequate fluid intake (1 to 2 litres per day) for primary prevention
- Haematuria: symptom review
- Urinary tract and cyst infection: symptom review

Assess and manage other systemic complications

- Consider screening for intracranial cerebral aneurysms
- Consider avoiding oral contraceptive pill and hormone replacement therapy in women with severe polycystic liver disease
- Discuss participation in ongoing local and multicentre trials

Consider screening at-risk family members

ABBREVIATIONS: ACR = albumin to creatinine ratio; ADPKD = autosomal dominant polycystic kidney disease; ARB = angiotensin-receptor blocker; BMI = body mass index; eGFR = estimated glomerular filtration rate; HbA_{1c} = glycated haemoglobin.

*Interventions to prevent the decline of kidney function and risk for hypertension in ADPKD follow broad principles recommended in Kidney Health Australia guidelines for the management of CKD.[4] Direct evidence for these interventions in ADPKD, however, is limited.

3. WEB RESOURCES FOR FURTHER INFORMATION ON ADPKD

PKD Foundation of Australia
(http://pkdaustralia.org)*

Kidney Health Australia
(www.kidney.org.au)

Renal Resource Centre
(www.renalresource.com)

Centre for Genetics Education
(www.genetics.edu.au)

* To be launched in the second half of 2014.

anxiety to patients with ADPKD. However, it is important for clinicians to highlight that the individual lifetime risk of renal failure varies significantly (even within the same family because of variations in penetrance), and a diagnosis of ADPKD does not necessarily mean a progression to ultimate renal dialysis.

Clinical predictors of renal failure include:

- a relative with early-onset end-stage kidney disease (before the age of 55 years)
- the presence of 'large' cystic kidneys (i.e. total kidney volume corrected for height greater than 600 mL/m)
- impaired estimated glomerular filtration rate (eGFR).

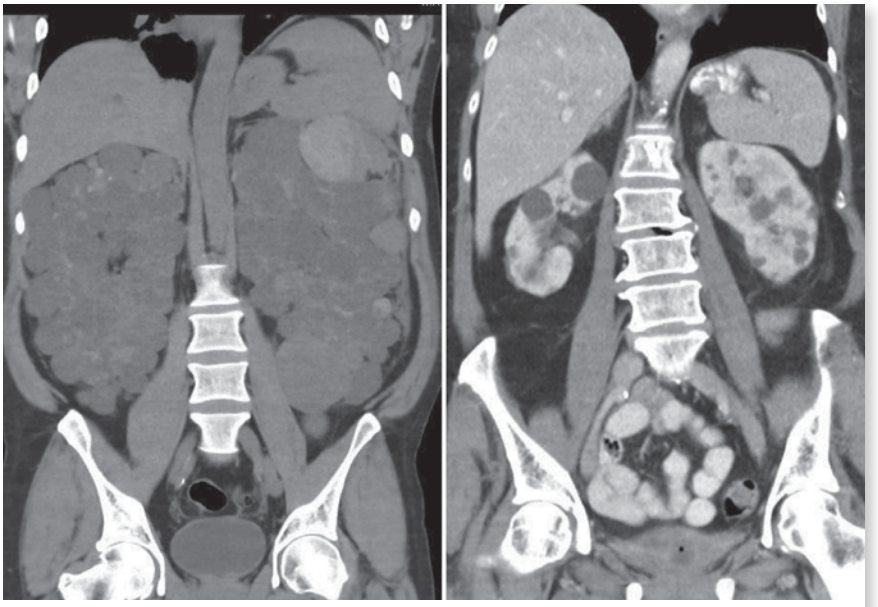
Patients with ADPKD typically display long periods of stable or mildly abnormal GFR until the fourth to sixth decade of life, because of hyperfiltration by unaffected nephrons, which maintains overall GFR. When the kidneys become significantly enlarged, renal function progressively and inexorably declines, at a rate of 4 to 6 mL/min/1.73 m^2 loss of eGFR per year.

Individuals with *PKD1* mutations have larger kidneys and more renal cysts and almost all develop end-stage kidney disease before the age of 70 years (Figure 5a). In contrast, patients with *PKD2* mutations have milder disease, and most maintain adequate renal function during their lifetime (Figure 5b).

Preventing decline in kidney function and cyst growth in CKD stages 1 to 3

Dietary and lifestyle treatments to slow progression

There are no dietary guidelines specifically for patients with ADPKD. However, generic interventions to reduce cardiovascular risk (i.e. regular exercise, smoking cessation, a body mass index below 25 kg/m^2 and dietary salt restriction) are suggested. Low-protein diets have not been shown to slow decline in renal function in ADPKD.



Figures 5a and b. CT scans in two patients with autosomal dominant polycystic kidney disease illustrating the variation in severity of renal disease. a (left). Large cystic kidneys with little normal renal parenchyma in a 47-year-old man with a serum creatinine level of 300 µmol/L, estimated glomerular filtration rate (eGFR) of 20 mL/min/1.73 m^2 and chronic kidney disease (CKD) stage 4. This patient probably has a mutation in the *PKD1* gene and has a high risk of end-stage kidney disease. b (right). Incidental finding of a much smaller number of renal cysts in a 72-year-old woman with a serum creatinine level of 77 µmol/L, eGFR of 66 mL/min/1.73 m^2 and CKD stage 2. Milder disease is typical of a mutation in the *PKD2* gene.

Patients with ADPKD have an increased risk of kidney stones and should maintain adequate fluid intake. Caffeine stimulates cyst growth in cells in vitro, and patients are advised to limit their intake to no more than two caffeinated drinks per day, although clinical evidence supporting this recommendation is sparse.

Antihypertensives

Hypertension occurs in 60% of patients with ADPKD before impairment of GFR, at an average age of 30 to 35 years. It is almost universal in late-stage ADPKD (CKD stages 4 and 5). Over the past decades, effective antihypertensive treatment has significantly reduced the incidence of hypertensive cardiovascular disease and left ventricular hypertrophy. Hypertension is mediated by increased intrarenal angiotensin II production and local ischaemia secondary to compression of intrarenal microvessels by expanding cysts. Hence, either an ACE inhibitor or angiotensin receptor blocker (ARB) is the preferred first-line agent for patients with ADPKD and hypertension, with a suggested target blood pressure below 130/80 mmHg. Additional antihypertensive drugs can be introduced as needed, but there is no evidence supporting combined treatment with an ACE inhibitor and ARB.

Other treatments to slow renal progression

Beneficial generic interventions used in other types of CKD should be considered in patients with ADPKD. For example, renal cysts in ADPKD are strongly positive for components of the renin–angiotensin system, and its blockade by ACE inhibitors or ARBs may slow cyst growth. This hypothesis is currently being tested in the multicentre clinical HALT-PKD trial.[5]

Similarly, a recent study of pravastatin (20 to 40 mg/day) in 110 patients with ADPKD aged between 8 and 22 years found that three years of treatment mildly attenuated the increase in total kidney volume (21% vs 30% compared with baseline, p=0.02).[6]

Finally, experimental data suggest that patients with ADPKD have an increased risk of acute kidney injury, which exacerbates cyst growth. Hence, patients should avoid dehydration and limit their exposure to nephrotoxic NSAIDs or COX-2 inhibitors, radiocontrast agents and aminoglycosides. Severe haemodynamic compromise should be appropriately treated.

Investigational disease-modifying drugs

There are currently no drugs approved to stop the early formation of renal cysts or to slow cyst growth in patients with ADPKD. However, the results of several promising randomised controlled trials of specific disease-modifying treatments should be available within the next decade.

The pituitary hormone vasopressin promotes water reabsorption in the renal collecting duct but also stimulates cyst growth in ADPKD. The vasopressin receptor antagonist tolvaptan reduced cyst growth by almost 50% in patients with early-stage disease over three years in a recent randomised controlled trial.[7] However, tolvaptan treatment for patients with ADPKD remains in clinical trials, following requests for further data by the US Food and Drug Administration.

Interestingly, a high fluid intake can also attenuate vasopressin, but a recent nonrandomised clinical trial of this treatment in patients with ADPKD had inconclusive results, and further studies are needed.[8] Other novel drugs currently under evaluation include target of rapamycin complex inhibitors (sirolimus and everolimus), somatostatin analogs, bosutinib and the traditional Chinese herbal medication triptolide.

Managing ADPKD with late-stage CKD

Patients with CKD stages 4 and 5 should be managed according to Kidney Health Australia guidelines.[4] These patients require regular monitoring of eGFR, screening for uraemia complications, predialysis counselling, timely creation of long-term dialysis access and consideration for pre-emptive kidney transplantation by living kidney donation.

Managing other renal complications

Polyuria and nocturia

These common symptoms occur even in the early stages of ADPKD as a result of cystic disruption of the inner renal medullary architecture, which impairs urinary concentrating ability. There is no specific management apart from patient awareness.

Chronic renal pain

Mild diffuse discomfort in the loin or anterior abdomen, present on most days, is reported by 60% of patients with enlarged kidneys confined within the abdominal cavity. The discomfort is typically mild and does not require analgesia, but occasionally chronic pain is severe and disabling. Imaging of the kidney and/or spine is required to identify the aetiology of the pain, followed by chronic pain management strategies, including lumbar strengthening exercises, and occasionally intervention, such as aspiration of one or more large cysts or renal denervation.

Acute renal pain

The sudden onset of acute pain requires careful evaluation through history-taking, physical examination and renal imaging, generally by CT scan. The differential diagnosis includes the following.

Cyst haemorrhage: This can present with a sudden onset of sharp, localised, unilateral abdominal pain and/or macroscopic haematuria, either secondary to renal trauma (e.g. contact sports) or spontaneous (as the cysts are surrounded by neoangiogenesis that can bleed). Symptomatic episodes occur in about half of patients with ADPKD, but the true incidence of cyst bleeds is probably far higher because hyperdense cysts (reflecting blood or high protein content) are commonly seen in renal CT scans of asymptomatic patients. Most episodes are self-limiting and resolve within two to seven days. Management typically entails increased fluid intake, simple analgesia and bed rest. Prolonged symptoms (lasting more than a week) or an initial episode occurring after the age of 50 years warrant additional investigations of the renal tract to exclude neoplasm.

Urinary tract and cyst infection: Pyelonephritis or an infected cyst usually present with subacute onset of kidney pain, associated with fever, chills and rigors. Microbiological confirmation of infection within a contained cyst is difficult, as urine culture is generally negative. Suspected cyst infection is best treated with lipid-permeable antibiotics (e.g. norfloxacin or trimethoprim–sulfamethoxazole) which can penetrate cysts. Occasionally, CT-guided aspiration to drain an infected cyst is required if antibiotics are not effective.

Nephrolithiasis: Kidney stones occur in 30% of patients with ADPKD, compared with 8 to 10% of the general population. The stones are usually composed of uric acid or calcium oxalate, a result of reduced excretion of citrate (an inhibitor of stone formation) and altered tubular urine flow. The clinical features are those of classic renal colic, and urological management is comparable to that of patients without ADPKD.

Managing systemic complications

Treatment of liver cysts

Liver cysts occur in up to 80% of patients with ADPKD but are generally asymptomatic and liver function tests have normal results. Rarely, some patients develop severe polycystic liver disease that requires multidisciplinary care by a hepatologist, nephrologist and hepatobiliary surgeon. Severe hepatic cystic disease more commonly affects women, and risk factors include multiple pregnancies and the use of oral contraceptives or hormone replacement therapy, suggesting that female sex hormones can promote cyst growth. Clinical trials suggest that somatostatin analogs slow liver cyst growth, but further studies are required.

Screening for intracranial cerebral aneurysms

The lifetime prevalence of intracranial cerebral aneurysm in patients with ADPKD approximates 5 to 10% (and 20% in those with a family history of intracranial aneurysm), compared with 1 to 2% in the general population. Rupture of an intracranial cerebral aneurysm has a 60% mortality rate and can lead to significant morbidity in survivors. Rupture occurs at an earlier age than in the general population (39 *vs* 51 years of age). However, most aneurysms detected on screening are small (75 to 90% less than 10 mm in diameter) and have a low annual risk of rupture (0.05 to 0.7%). Genetic factors are likely to predispose to these aneurysms, as suggested by familial clustering.[9,10]

There are no consensus guidelines on screening and re-screening for intracranial cerebral aneurysm in patients with ADPKD. Traditional criteria for screening include:

- a family history of intracranial aneurysm or subarachnoid haemorrhage
- symptoms (e.g. severe headache, transient ischaemic attack, cranial nerve palsy)
- imminent major surgery (e.g. renal transplantation)
- imminent start of long-term anticoagulation with warfarin
- patient request or anxiety after discussing the risk
- prior history of intracranial aneurysm rupture
- high-risk occupation (e.g. pilot, bus driver).[9,10]

However, it is also reasonable to offer

baseline screening to all patients, regardless of the above criteria, at the time of initial diagnosis of ADPKD, in the expectation that the vast majority will have reassuringly negative results.

Cerebral CT with low-dose contrast or cerebral magnetic resonance angiography are suitable screening tests for intracranial cerebral aneurysms.

Re-screening in patients with an initial negative result is recommended in high-risk patients (e.g. family history of intracranial cerebral aneurysm or subarachnoid haemorrhage) every five to 10 years and in low-risk patients perhaps once, in 10 years.[10]

Management in pregnancy

The risk of adverse events during pregnancy in women with ADPKD is similar to the risk in those with other types of CKD and depends on underlying kidney function and the presence or absence of hypertension. Multidisciplinary management involving an obstetrician and a nephrologist should be considered.

PATIENT MONITORING

Clinical and laboratory investigations

Clinical monitoring and laboratory testing should follow the Kidney Health Australia CKD guidelines, tailored to the GFR.[4] Targeted clinical monitoring of patients with ADPKD should include:

- periodic review of symptoms (e.g. pain from cyst rupture)
- blood pressure measurement
- cardiovascular risk assessment
- assessment for systemic complications.

Routine investigations include:

- measurement of serum urea, creatinine and electrolytes, and eGFR
- full blood count
- urine microscopy
- quantitation of proteinuria (spot urine protein to creatinine ratio).

Proteinuria is usually mild and evident only in the middle and late stages of disease (quantified as 150 to 1500 mg/day by 24-hour urine collection; or spot urine protein to creatinine ratio 15 to 150 mg/mmol).

In patients with late-stage ADPKD (CKD stages 4 to 5), eGFR should be closely monitored to help predict when renal replacement therapy will be needed and when complications are likely, such as anaemia, metabolic acidosis and

secondary hyperparathyroidism. Patients with ADPKD often display minimal CKD-related anaemia because the cyst epithelial cells secrete erythropoietin, maintaining haemoglobin levels.

Imaging

A combined renal and abdominal ultrasound examination is essential for initial diagnostic evaluation of liver and renal cysts. In addition, the total kidney volume (of both kidneys) can be used as a biomarker of disease severity and stage, estimated by renal ultrasound using the ellipsoid formula (kidney volume = kidney length x depth x width/610). Kidney dimensions are easily measured on ultrasound imaging if specifically requested.

Longitudinal studies suggest that a ratio of total kidney volume to patient height exceeding 600 mL/m predicts future decline in renal function. Serial monitoring in total kidney volume (e.g. every three years) is more accurate when performed with renal MRI, but in the absence of disease-modifying treatments this technique is currently confined to research studies. Monitoring of asymptomatic patients by serial renal CT scans should be avoided because of the dangers of radiation exposure.

SHARED CARE BETWEEN GP AND SPECIALIST

The GP has a vital role in long-term management of patients with ADPKD as most are relatively healthy and asymptomatic. Patients should be referred to a nephrologist when the diagnosis is known or suspected, for initial evaluation including assessment of disease severity and renal and extrarenal complications, screening of family members and patient education.

In patients with early-stage or mild disease, visits to a nephrologist are usually infrequent (at three- to five-year intervals). Visits become more frequent in late-stage or severe disease (CKD stages 3 to 5), when management of the complications of renal failure, treatment of hypertension and eventually timely preparation for renal replacement therapy are needed.

CONCLUSION

ADPKD is an important genetic cause of CKD that should be considered in young patients with new-onset hypertension, macroscopic haematuria or impaired renal function. The risk of progressive renal failure is highly variable, and generic treatments that slow functional loss, including control of hypertension, are recommended.

Targeted specific therapies for ADPKD are under evaluation, with first-generation disease-modifying drugs and other interventions to slow disease progression likely to become available in the near future. It may also become feasible to accurately predict an individual's future risk of renal failure using sophisticated genetic tests and biomarkers. This could potentially guide the use of new interventions in early adulthood before irreversible destruction of the kidney has occurred. MT

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COMPETING INTERESTS: Dr Rangan is a Principal Investigator in clinical trials of tolvaptan (manufactured by Otsuka) in patients with ADPKD. Dr Nankivell: None.