J Nephrol (2016) 29:755–763
DOI 10.1007/s40620-016-0349-7

REVIEW

ADPKD: clinical issues before and after renal transplantation

Piergiorgio Messa[1,2] · **Carlo Maria Alfieri**[1,2] · **Emanuele Montanari**[1,3] · **Mariano Ferraresso**[1,4] · **Roberta Cerutti**[1,2]

Received: 13 July 2016 / Accepted: 29 August 2016 / Published online: 20 October 2016

Abstract Autosomal dominant polycystic kidney disease (ADPKD) is the first genetic cause of end-stage renal disease (ESRD) and the number of these patients who are listed for or receive a kidney transplant (KTx) is continuously increasing over time. Hence, nephrologists are involved not only in the handling of ADPKD patients during the long course of the disease, but also in programming and performing a renal transplant. The handling of all these processes implies the complete awareness of a number of critical points related to the decisions to be taken both before and after the transplant intervention. In the present review, we will briefly deal with the main critical points related to the clinical handling of the patients both before and after KTx.

Introduction

Worldwide recent epidemiological data confirm that autosomal dominant polycystic kidney disease (ADPKD) is the fourth general and the first genetic cause of end-stage renal disease (ESRD), with 7–10% of ESRD patients suffering from this inherited condition [1–4]. The two recognized causative genes of ADPKD are PKD1 and PKD2, which code for polycystin-1 (PC1) and polycystin-2 (PC2) respectively. Of the total number of pathogenic mutations found in ADPKD patients, PKD1 mutations make up about 85% of the genetically defined cases, with the remaining 15% due to mutations in PKD2, though in 5–15% of patients no pathogenic mutation is found in either of the two genes [5, 6]. The phenotypic expression of the disease and the rate of disease progression are highly variable among subjects, depending largely on the genetic background (PKD1 being worse than PKD2, and truncating mutations worse than non-truncating), but also on other potential acquired conditions (life-style, drugs, additional comorbidities, etc.). In the last decade much effort has been made to reduce the progression of ADPKD [7–11]. However, none of the present therapeutic tools has been clearly demonstrated to substantially change the long-term outcome of the disease [12] and most of these patients continue to reach ESRD within their lifetime.

Since ESRD patients with ADPKD are generally younger and burdened by a relatively lower number of comorbidities in comparison to renal patients affected by other kidney diseases [13], and given the very good results of kidney transplantation (KTx) in ADPKD patients [14, 15], the number of these patients who are listed for or receive a KTx is continuously increasing over time [3].

Hence, nephrologists are more and more involved in facing some key problems related to the handling of ADPKD patients during the long course of the disease, and specifically at the time of programming and after performing a renal transplant in these patients. Most of these issues have been addressed by a comprehensive recent review [16]. However, given the growing interest and

✉ Piergiorgio Messa
pmessa@policlinico.mi.it; piergiorgio.messa@unimi.it

1 Fondazione Ca' Granda IRCCS Ospedale Maggiore Policlinico di Milano, Università agli studi di Milano, Area Omogenea Nefro-Urologica e Trapianto di Rene, Milan, Italy

2 Unità di Nefrologia e Dialisi, Università agli studi di Milano, Milan, Italy

3 Unità di Urologia, Università agli studi di Milano, Milan, Italy

4 Unità Chirurgia del Trapianto di Rene, Università agli studi di Milano, Milan, Italy

the increasing number of published studies on this topic, we think it is worthwhile updating our own knowledge, focusing mainly on the most recently published studies on the subject.

Evaluating the progression rate in the ADPKD patient

When planning renal replacement therapy (RRT) in patients with ADPKD, nephrologists need to know as precisely as possible the timing of disease progression, since some specific procedures need to be performed long before starting any replacement therapy and in particular before performing KTx (see below).

The reduction of glomerular filtration rate (GFR), evaluated in clinical practice using standardized formulas [17, 18], is considered the most reliable marker of the progression of any kidney disease. However, the reliability of estimated GFR (eGFR) has been questioned in ADPKD [19, 20]. Furthermore, it is common experience that the rate of eGFR changes is quite variable not only among ADPKD patients, but also in the same patient during the course of the disease. So the need to find more precise predictors of the time when ADPKD patients will achieve ESRD still remains unsatisfied.

A number of factors encompassing genetic, physical and clinical parameters, have been indicated as possible individual predictors of progression (Table 1) [2, 21–25].

Recently, the group of CRISP investigators proposed a method for predicting progression in the typical forms of ADPKD, based on the measurement of the height-adjusted total kidney volume (ht-TKV) and the patient's age. Assuming a starting ht-TKV of 150 ml, they measured its percentage annual increase and stratified patients into five subclasses based on the yearly percent increase: 1.5% (subclass 1A), 1.5–3% (1B), 3–4.5% (1C), 4.5–6% (1D), or.6% (1E). The striking result was that the incidence of ESRD after 10 years was 2.4 and 66.9% in the 1A and 1E subclasses, respectively [26]. More recently, a French group proposed a prognostic model derived from a multivariate analysis which identified four variables (genetic and clinical) which were highly related to the age of onset of ESRD. The authors built a scoring system (0 → 9) giving the following weight to the chosen variables: male gender (one point); hypertension before 35 years of age (two points); urologic events before 35 years of age (two points); PKD2 mutation (zero points); non truncating PKD1 mutation (two points); truncating PKD1 mutation (four points). Having a score ≤3 was associated with an incidence of ESRD before 60 years of age lower than 10%, while a score >6 was associated with >80% incidence of ESRD before 60 years in ADPKD patients [27].

Though the predictive power of the latter method seems to be higher than the former one, it has the disadvantage of needing genetic analysis which is as yet limited to only a few centers and still expensive. It is also worth mentioning that efforts directed to looking for reliable marker(s) of ADPKD progression also include proteomic analysis [28]; however, these proposals have not yet been proven superior to the clinical and radiological markers and, more importantly, are costly and as yet performable only in a few specialized laboratories.

From a practical point of view, for an indirect prediction of rapid progression one could also rely on the criteria recently proposed to define the group of ADPKD patients who could have access to new proposed therapies [29].

Table 1 Proposed individual predictors of progression in ADPKD

Genetic predictors
PKD1
Truncating mutations
Associated mutations in other genes
General and clinical predictors
Young age at diagnosis
Male gender
Early reduced GFR
High kidney volume
Early onset of hypertension
Macrohematuria
Nephrolithiasis
Cyst infections
Life-style related predictors
Low water intake
High caloric and protein intake
Smoking
High caffeine intake
Laboratory predictors
Proteinuria
High copeptin
High urinary osmolality

Notes: *ADPKD* autosomal dominant polycystic kidney disease, *GFR* glomerular filtration rate

Clinical issues preceding renal transplant

KTx is by far the best therapy for any ESRD patient and in particular for patients with ADPKD, who are directed to the kidney transplant program more frequently than any other ESRD patients [3, 30]. This, despite the many problems that need to be confronted before listing an ADPKD patient for a KTx. In the following paragraphs, we address the most common problems that nephrologists have to deal with, in the light of the most recent literature and our own experience.

Programming the transplant from a living donor

The transplant community has long been aware that the KTx from a living donor (LD) has a graft outcome much better than that from a deceased donor (DD) [31, 32]. A further advantage of a KTX from a LD is the possibility to perform it before starting dialysis (pre-emptive KTx).

However, in the case of a living related donor exclusion of the presence of the disease in the potential donor is mandatory. The basic diagnostic criteria for ADPKD are based on the radiologic assessment (ultrasonography, US) of the number of renal cysts present in both kidneys, depending on the age of the subject and her/his family history (Table 2) [33, 34]. However, in many borderline cases, in particular in young subjects, the sensitivity of US is relatively limited. Though the diagnostic sensitivity could be improved by the use of computed tomography (CT) or magnetic resonance imaging (MRI) using different cut-offs for the number of cysts, in the case of dubious results it is recommended to perform a genetic diagnosis before proceeding to KTx in an ADPKD patient from a related living donor [25, 35–37]. It should, however, be borne in mind that also genetic analysis has some limitations. In addition to being a labor-intensive and costly procedure, the search for mutations in PKD1 and PKD2 can prove fruitless in up to 15 % of cases [5, 6, 25]. The reason for such a high number of undefined mutations is in great part due to the technical difficulties related to the presence of 6 pseudogenes homolog of the PKD1 gene, to the frequent presence of mosaicism and to the difficult interpretation of the meaning of inframe insertion/deletion mutations of unknown significance, etc. However, it cannot also be excluded that mutations in other not yet recognized genes may contribute to this percentage of genetically undefined cases. Anyway, more advanced tools of genetic analysis, such as next generation sequencing (NGS), could increase the diagnostic power of genetic analysis [38, 39].

Table 2 Radiological criteria for the diagnosis of ADPKD

Age (years)	Number of cysts
Diagnostic criteria for an at-risk individual with positive family history	
15–39	At least 3 (unilateral or bilateral)
40–49	At least 2 in each kidney
≥60	At least 4 in each kidney
Exclusion criteria for an at-risk individual with positive family history	
<40	No recommendation
≥40	<2 in each kidney

Note: *ADPKD* autosomal dominant polycystic kidney disease

In our daily practice, in each proposed living donor genetically related to an ADPKD patient, we perform a precise preliminary radiological study, adding the genetic analysis when the donor age is lower than 40 or at any age if there is some interpretative diagnostic doubt regarding radiological diagnosis. In any case, even if both radiological and genetic tests are negative, in the case of ADPKD patients, we are usually unwilling to accept a living donation from a related donor younger than 25 years unless they have shown themselves to be very motivated and determined, even after in-depth information on the potential risks that the donor could develop a cystic disease later on during his/her life.

Combined liver-kidney transplant

Polycystic liver disease (PLD) is the most common extra-renal complication associated to ADPKD, occurring in over 80 % of patients [40, 41]. Though the number and volume of hepatic cysts usually grow progressively over time, particularly in women who undergo pregnancy or make use of estrogen [42–44], a clinically relevant impairment of liver function is observed only in a very limited number of cases, in contrast to the behavior of the renal function. So, the need for considering a combined liver and renal transplant due to the contemporary failure of both organs is very unusual and mostly limited to the presence of other genetic causes of liver disease (such as Caroli's syndrome), which are more frequently associated with the recessive than the dominant form of PKD [45–47].

On the other hand, it can occasionally occur that the increase in the mass of liver cysts causes clinically relevant symptoms, due to the interference of the hugely increased liver volume with the function of other organs (Table 3). When the impact of the symptoms is so significant that it largely affects the well-being of the patient and his/her quality of life, it is worth considering a combined liver and kidney transplant, independently of the presence or not of a liver function impairment [48, 49]. As already mentioned, this circumstance is encountered more commonly in women than in men, due to the effects of estrogens in promoting liver cyst growth.

It is also worth mentioning that some transplant centers suggest a surgical intervention of partial hepatectomy and/or cyst fenestration as the alternative to the combined transplant [36, 50]. However, more knowledge and experience about this approach and on the long-term efficacy of such alternative surgical interventions are needed.

So, the final decision in these critical cases should be taken by a multidisciplinary team (liver and kidney transplant surgeons, nephrologists, hepatologists, anesthetists), taking into account the local expertise in the different surgical approaches.

Table 3 Possible clinically relevant effects of increased liver cyst volume

Gastro-intestinal tract
Pain
Sense of early satiety
Reduced appetite
Nausea, vomiting
Pancreatitis
Biliary tract obstruction
Malnutrition
Lungs
Dyspnea
Pleural effusion
Respiratory failure
Obstruction of venous vessels
Inferior vena cava
Hepatic venous system
Portal system
Musculoskeletal system
Abdominal wall herniations
Spine deformation
Back pain

Intracranial aneurisms (ICAs)

ICAs are a frequent and potentially life threatening complication in ADPKD. Their prevalence is reported to be at least seven times higher in ADPKD patients than the general population, though the reported values are quite different from one center to another (4–41 %), with this variability probably depending on the different indication criteria for screening ADPKD patients [51–53]. The potential rupture of an ICA in an ADPKD patient is often a catastrophic event and it usually occurs at a relatively younger age than in the general population [54]. The main risk factor for an ICA rupture is considered to be a positive family history of intracranial bleeding and the presence of persistent headaches, which are considered to be also the clearest indications to screen an ADPKD patient for an ICA. However, the presence of hypertension, a smoking habit, some occupational conditions (airplane pilots or subway drivers) might be an indication to perform a screening. There is no widespread agreement on the criteria for performing the screening for ICA when an ADPKD patient is put on the waiting list for a KTx, but all centers agree that angiographic nuclear MR (NMR) is the method of first choice to search for ICAs [25, 35, 36]. In our clinical practice, we perform screening for ICAs in all ADPKD patients waitlisted for KTx.

A second point is: which of the found ICAs need to be treated? Most guidelines agree that the need to treat ICAs is dependent on their rupture risk: there is agreement that, in addition to the above mentioned factors which are indications for the screening, the dimension of the lesion (>6–7 mm), the location (posterior at higher risk than anterior), and shape (saccular) can be considered factors to assist the decision-making for intervention or not [25, 36, 55].

Finally, the decision of which type of intervention should be preferred for unruptured ICAs is still not completely clear. In fact, although surgical clipping exposes the patient to a relatively higher operative risk, endovascular procedures (coil embolization) require the use of radiological contrast media, which sometimes can be critical for a patient still not on dialysis. However, taking into account that sometimes the number of ICAs to be closed are multiple, recent studies, though underlining an overall increased operative risk for all these procedures in ADPKD compared to the general population, underscore that coil embolization is the safest procedure [56, 57].

Again, each transplant center should decide the criteria for the screening, the indications and the type of intervention for ICA correction in the ADPKD patient on the KTx waiting-list, according to the local expertise in the field, possibly deciding to refer the patient to another transplant center when appropriate.

Programming nephrectomy

One of the most critical and debated issues in the ADPKD patient who has to be waitlisted for a KTx regards the indications, the timing and the type of a native kidney nephrectomy (Nx). There is general agreement that the removal of one or both polycystic kidneys in ADPKD patients is indicated and should be performed before KTx in the case of relapsing cyst infections, recurrent symptomatic hemorrhagic events, complicated nephrolithiasis and when there is the suspicion of a renal cancer: in all these conditions the choice of removing one or both kidneys will depend on the possibility to precisely define if the causative complication is monolateral or bilateral [25, 58–60]. Recent data suggest also that both unilateral and bilateral native Nx are associated with a better control of hypertension in ADPKD after KTx [61]. Much more complex and subjective is the decision to perform a pre-KTx Nx, when it is judged that there is not sufficient room for the allograft [62]. The decision is particularly critical in the case when a bilateral Nx is planned in a pre-emptive KTx, since this decision will make a temporary dialysis treatment necessary. Moreover, the decision of a Nx before KTx should also take into account the possibility of a regression of the native kidney volume after KTx as described [63, 64].

To maximize the use of native kidney renal function, many transplant centers prefer to perform Nx at the time of KTx, with the choice of removing one or both native kidneys, depending on the native kidney volume and the operative conditions evaluated at the time of the intervention.

Though most of the studies sharing this surgical policy agree that the Nx performed simultaneously to KTx is characterized by longer intervention duration, increased need for transfusions and longer hospital stay, they also report at least equivalent long-term results related to the patient and graft outcomes, as compared with either mono or bilateral Nx performed before KTx [65–68].

Which technique is to be preferred for performing the Nx (laparoscopic vs. open surgery) is a further debated issue. A recent systematic review and meta-analysis identified seven studies which included 195 cases, of whom 118 were submitted to a laparoscopic Nx (LN) and 77 to open surgery Nx (ON). Though LN was associated with longer operative time, it was also characterized by a lower need of transfusions, less complications and a shorter hospital stay [69]. As an alternative to native kidney Nx, some centers propose the intravascular embolization of kidney(s) as a valid and effective method even in the long term [70].

In our opinion, the technique to be carried out should be the one which the local surgical team is more expert in and more used to performing.

Clinical issues after renal transplant

Patient and graft outcomes

As already discussed, KTx is considered to be by far the best therapeutic option for the treatment of ESRD in ADPKD patients, since it is associated with optimal outcomes for both the patient and the transplanted organ, which are even better than those observed in all the other cohorts of ESRD who receive a KTx [3, 4, 14, 30, 71–73].

The reasons for this particularly positive post-KTx outcome are not completely clear. A lower age at the time of ESRD and a reduced number of comorbidities could play a role [14]. However, it should also be borne in mind that these patients often benefit from nephrological care long before the achievement of ESRD. This implies a more strict control of the most common comorbidities and explains why ADPKD patients receive a pre-emptive KTx, peritoneal dialysis treatment and an arterial-venous fistula more often than other renal patients. All these factors might contribute to the better outcomes before and after KTx. Incidentally, this should make the medical community reflect on the beneficial effect of early referral to the nephrologist concerning the clinical outcomes of patients affected by any renal disease.

Immunosuppressive (IS) therapy

Though a potential beneficial role of the inhibitors of mammalian target of rapamycin (mTOR) in reducing the cyst growth after KTx has been suggested, there is no clear evidence that such hypothesized effects are relevant [16, 74]. Moreover, since these IS drugs are not free of side effects, their use should be based on strict immunological and clinical indications. In conclusion, the prescription of IS therapy in the transplanted ADPKD patient should follow the rationale used for any other KTx patient.

Renal complications after KTx

Although it has been reported that cyst volume could spontaneously regress after KTx [64], it is common experience that problems related to the increased cyst mass can sometimes heavily affect patient well-being. There is some anecdotal suggestion that somatostatin analogues can induce a regression or at least slow the growth of both kidney and liver cysts [75, 76]. However these drugs, in addition to the fact of not being as yet registered for that use, need to be administered by parenteral route and would be added to the already high burden of drugs which KTx patients take. So, at the present time, there is no strong evidence to support the use of such compounds in ADPKD patients after KTx.

Transplanted patients are more prone to infective complications due to the need of maintaining an immune-suppressed status, so there would be no wonder if cyst infections occur after KTx more frequently in ADPKD than in other groups of renal patients. However, in a survey on a relatively large group of KTx patients, the incidence of the overall number of urinary tract infections, including pyelonephritis, was not higher in ADPK than in the other patients [71]. Anyway, cyst infections when they happen after KTx are often a challenging diagnostic and therapeutic problem. It has been suggested that 18F-fluorodeoxyglucose positron emission tomography–CT (18-FDG PET–CT) can consistently improve the sensitivity and specificity in the diagnosis of cyst infections in ADPKD as compared to CT and MRI [77, 78].

Though some scanty data report on an increased risk for native kidney cancer in ADPKD after KTx [79], most of the available data suggest that the risk for kidney cancer is not different, if not lower, than that observed in all other KTx patients [69, 80]. This could be explained by a more strict diagnostic approach to the native kidneys and a more frequent use of Nx before KTx in ADPKD patients. However, it should be emphasized that the diagnosis of an asymptomatic and small renal cancer can be a challenging problem in a polycystic kidney with the US diagnostic approach, which is the tool most commonly utilized in the clinical practice.

Extra-renal complications after KTx

The main medical complications of KTx recipients fall into the following four categories: cardiovascular (CV) diseases, infections, cancer, and metabolic disease. So, it is worth

knowing whether ADPKD patients have a comparable risk for each of these pathologies after KTx.

It is common knowledge, that ADPKD patients have a high number of CV risk factors, including a higher prevalence of hypertension, dyslipidemia, and post-transplant diabetes mellitus [21, 71]. However, CV events have not been found to be higher in ADPKD patients after KTx and their overall mortality has been reported to be even lower than that of other cohorts of KTx patients [14, 15, 71, 81, 82]. Nevertheless, it would be wise that ADPKD patients have a strict control of their blood pressure levels, be strongly encouraged to stop smoking, to increase their physical activity and to consume a low caloric diet.

As mentioned before, ADPKD patients have a number of clinical conditions which could be at risk of infections, such as renal and liver cyst, intestinal diverticulosis, heart valve diseases, etc. Though former reports indicated an increased occurrence of gastrointestinal infections [83], more recent data do not confirm such increased infection risks [71]. However, we should always be aware that some kinds of infection, such as liver cyst infections, when they happen, portray a serious complication in ADPKD. Checking for the changes in carbohydrate antigen 19-9 (CA 19-9), which is secreted by the biliary epithelium lining the cysts, may help in an early diagnosis of a liver cyst infection [84]. In the suspicion of an infectious complication in a transplanted ADPKD patient, a fast and complete diagnostic protocol should quickly be started to locate the origin of the process, starting antibiotic therapy as soon as possible.

We have already dealt with native kidney cancer risk in ADPKD. As far as the risk of other types of cancer is concerned, ADPKD patients not only seem not to have a higher, but an even reduced risk of cancer [71, 80], except for non-melanoma skin cancer which has been reported to be more frequent in ADPKD patients after KTx [85, 86]. So, a reduced and protected exposure to sunlight should be highly recommended to these patients.

Post-transplant diabetes mellitus (PTDM) is one of the most common metabolic complications after KTx and negatively impacts on patient and graft outcomes [87]. There is controversy about whether ADPKD is associated with an increased risk for PTDM or not, with some studies reporting a higher incidence of these metabolic complications [88] and others denying it [71, 89]. A recent meta-analysis [90] included 12 cohort studies, comprising 1379 ADPKD patients out of a total number of 9849 patients who received a KTx. The authors found a relative risk (RR) of PTDM higher in ADPKD than in the other KTx patients, and this result was confirmed also when the analysis was limited to studies where the results were adjusted for the confounders [RR 1.98; 95% confidence interval (CI) 1.33–2.94]. On the other hand, the number of PTDM requiring insulin treatment was not significantly different between ADPKD and the other KTx patients. These results confirm that ADPKD patients are more prone to develop glucose metabolism derangements, but the clinical weight of these metabolic derangements is relatively mild.

Conclusive remarks

ADPKD is a complex disease characterized by both the involvement of the kidneys, which is the leading clinical problem, and the derangement of many other organs and tissues [91]. The progression of the renal disease is the most common event in these patients and many of them achieve ESRD during their life time. Despite the large number of potential complications, the outcome of KTx is optimal in these patients. So, it is mandatory to consider KTx every time we forecast the upcoming ESRD in these patients, possibly planning the transplant before starting dialysis. To obtain this result, it is important to program in a timely manner any operative decision and this can be done easily if these patients are referred to a nephrologist at an earlier stage during the course of their disease.

Compliance with ethical standards

Conflict of interest No conflict of interest related to the present manuscript.

References

1. United States Renal Data System. 2015 annual report: chapter 1: incidence, prevalence, patient characteristics, and treatment modalities. http://www.usrds.org/adr.aspx
2. Ong AC, Devuyst O, Knebelmann B, Walz G, ERA-EDTA Working Group for Inherited Kidney Diseases (2015) Autosomal dominant polycystic kidney disease: the changing face of clinical management. Lancet 385:1993–2002
3. Spithoven EM, Kramer A, Meijer E, ERA-EDTA Registry, Euro-CYST Consortium, WGIKD et al (2014) Renal replacement therapy for autosomal dominant polycystic kidney disease (ADPKD) in Europe: prevalence and survival—an analysis of data from the ERA-EDTA Registry. Nephrol Dial Transplant 29(Suppl 4):iv15–iv25
4. Pippias M, Jager KJ, Kramer A et al (2016) The changing trends and outcomes in renal replacement therapy: data from the ERA-EDTA Registry. Nephrol Dial Transplant 31(5):831–841
5. Harris PC, Torres VE (2014) Genetic mechanisms and signaling pathways in autosomal dominant polycystic kidney disease. J Clin Investig 124(6):2315–2324
6. Hwang YH, Conklin J, Chan W et al (2016) Refining genotype–phenotype correlation in autosomal dominant polycystic kidney disease. J Am Soc Nephrol 27(6):1861–1868
7. Serra AL, Poster D, Kistler AD et al (2010) Sirolimus and kidney growth in autosomal dominant polycystic kidney disease. N Engl J Med 363(9):820–829
8. Walz G, Budde K, Mannaa M et al (2010) Everolimus in patients with autosomal dominant polycystic kidney disease. N Engl J Med 363(9):830–840

9. Torres VE, Chapman AB, Devuyst O, TEMPO 3:4 Trial Investigators et al (2012) Tolvaptan in patients with autosomal dominant polycystic kidney disease. N Engl J Med 367(25):2407–2418
10. Torres VE, Higashihara E, Devuyst O, TEMPO 3:4 Trial Investigators et al (2016) Effect of tolvaptan in autosomal dominant polycystic kidney disease by CKD stage: results from the TEMPO 3:4 Trial. Clin J Am Soc Nephrol 11(5):803–811
11. Caroli A, Perico N, Perna A, ALADIN Study Group et al (2013) Effect of longacting somatostatin analogue on kidney and cyst growth in autosomal dominant polycystic kidney disease (ALADIN): a randomised, placebo-controlled, multicentre trial. Lancet 382(9903):1485–1495
12. Bolignano D, Palmer SC, Ruospo M, Zoccali C, Craig JC, Strippoli GF (2015) Interventions for preventing the progression of autosomal dominant polycystic kidney disease. Cochrane Database Syst Rev 7:CD010294
13. Brunelli SM, Blanchette CM, Claxton AJ, Roy D, Rossetti S, Gutierrez B (2015) End-stage renal disease in autosomal dominant polycystic kidney disease: a comparison of dialysis-related utilization and costs with other chronic kidney diseases. ClinicoEcon Outcomes Res 7:65–72
14. Haynes R, Kheradmand F, Winearls CG (2012) Survival after starting renal replacement treatment in patients with autosomal dominant polycystic kidney disease: a single-centre 40-year study. Nephron Clin Pract 120(1):c42–c47
15. Pippias M, Stel VS, Aresté-Fosalba N et al (2016) Long-term kidney transplant outcomes in primary glomerulonephritis: analysis from the ERA-EDTA Registry. Transplantation 100(9):1955–1962
16. Kanaan N, Devuyst O, Pirson Y (2014) Renal transplantation in autosomal dominant polycystic kidney disease. Nat Rev Nephrol 10(8):455–465
17. Levey AS, Stevens LA, Schmid CH et al (2009) A new equation to estimate glomerular filtration rate. Ann Intern Med 150(9):604–612
18. Levey AS, Inker LA (2016) GFR as the "gold standard": estimated, measured, and true. Am J Kidney Dis 67(1):9–12
19. Rule AD, Torres VE, Chapman AB, CRISP Consortium et al (2006) Comparison of methods for determining renal function decline in early autosomal dominant polycystic kidney disease: the consortium of radiologic imaging studies of polycystic kidney disease cohort. J Am Soc Nephrol 17(3):854–862
20. Ruggenenti P, Gaspari F, Cannata A, GFR-ADPKD Study Group et al (2012) Measuring and estimating GFR and treatment effect in ADPKD patients: results and implications of a longitudinal cohort study. PLoS One 7(2):e32533
21. Helal I, Reed B, Schrier RW (2012) Emergent early markers of renal progression in autosomal-dominant polycystic kidney disease patients: implications for prevention and treatment. Am J Nephrol 36(2):162–167
22. Cornec-Le Gall E, Audrézet MP, Rousseau A et al (2013) Type of PKD1 mutation influences renal outcome in ADPKD. J Am Soc Nephrol 24(6):1006–1013
23. Schrier RW, Brosnahan G, Cadnapaphornchai MA, Chonchol M, Friend K, Gitomer B, Rossetti S (2014) Predictors of autosomal dominant polycystic kidney disease progression. J Am Soc Nephrol 25(11):2399–2418
24. Chapman AB, Devuyst O, Eckardt KU et al (2015) Autosomal-dominant polycystic kidney disease (ADPKD): executive summary from a kidney disease: improving global outcomes (KDIGO) controversies conference. Kidney Int 88(1):17–27
25. Irazabal MV, Rangel LJ, Bergstralh EJ, CRISP Investigators et al (2015) Imaging classification of autosomal dominant polycystic kidney disease: a simple model for selecting patients for clinical trials. J Am Soc Nephrol 26(1):160–172
26. Cornec-Le Gall E, Audrézet MP, Rousseau A et al (2016) The PROPKD score: a new algorithm to predict renal survival in autosomal dominant polycystic kidney disease. J Am Soc Nephrol 27(3):942–951
27. Pejchinovski M, Siwy J, Metzger J et al (2016) Urine peptidome analysis predicts risk of end-stage renal disease and reveals proteolytic pathways involved in autosomal dominant polycystic kidney disease progression. Nephrol Dial Transplant. doi:10.1093/ndt/gfw243
28. Gansevoort RT, Arici M, Benzing T et al (2016) Recommendations for the use of tolvaptan in autosomal dominant polycystic kidney disease: a position statement on behalf of the ERA-EDTA Working Groups on inherited kidney disorders and European renal best practice. Nephrol Dial Transplant 31(3):337–348
29. Reule S, Sexton DJ, Solid CA, Chen SC, Collins AJ, Foley RN (2014) ESRD from autosomal dominant polycystic kidney disease in the United States, 2001–2010. Am J Kidney Dis 64(4):592–599
30. Hariharan S, Johnson CP, Bresnahan BA, Taranto SE, McIntosh MJ, Stablein D (2000) Improved graft survival after renal transplantation in the United States, 1988–1996. N Engl J Med 342:605–612
31. Legendre C, Canaud G, Martinez F (2014) Factors influencing long-term outcome after Kidney transplantation. Transpl Int 27:19–27
32. Ravine D, Gibson RN, Walker RG, Sheffield LJ, Kincaid-Smith P, Danks DM (1994) Evaluation of ultrasonographic diagnostic criteria for autosomal dominant polycystic kidney disease 1. Lancet 343(8901):824–7
33. Pei Y, Obaji J, Dupuis A et al (2009) Unified criteria for ultrasonographic diagnosis of ADPKD. J Am Soc Nephrol 20(1):205–212
34. Rangan GK, Alexander SI, Campbell KL et al (2016) KHA-CARI guideline recommendations for the diagnosis and management of autosomal dominant polycystic kidney disease. Nephrology 21(8):705–716
35. Ars E, Bernis C, Fraga G, Spanish Working Group on Inherited Kidney Disease et al (2014) Spanish guidelines for the management of autosomal dominant polycystic kidney disease. Nephrol Dial Transplant 29(Suppl 4):iv95–iv105
36. Simms RJ, Travis DL, Durkie M, Wilson G, Dalton A, Ong AC (2015) Genetic testing in the assessment of living related kidney donors at risk of autosomal dominant polycystic kidney disease. Transplantation 99(5):1023–1029
37. Qi XP, Du ZF, Ma JM et al (2013) Genetic diagnosis of autosomal dominant polycystic kidney disease by targeted capture and next-generation sequencing: utility and limitations. Gene 516(1):93–100
38. Eisenberger T, Decker C, Hiersche M et al (2015) An efficient and comprehensive strategy for genetic diagnostics of polycystic kidney disease. PLoS One 10(2):e0116680
39. Bae KT, Zhu F, Chapman AB et al (2006) Magnetic resonance imaging evaluation of hepatic cysts in early autosomal-dominant polycystic kidney disease: the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) cohort. Clin J Am Soc Nephrol 1:64–69
40. Hogan MC, Abebe K, Torres VE et al (2015) Liver involvement in early autosomal-dominant polycystic kidney disease. Clin Gastroenterol Hepatol 13:155–164
41. Franchitto A, Onori P, Renzi A, Carpino G, Mancinelli R, Alvaro D, Gaudio E (2013) Recent advances on the mechanisms regulating cholangiocyte proliferation and the significance of the neuroendocrine regulation of cholangiocyte pathophysiology. Ann Transl Med 1(3):27
42. Kesby GJ (1998) Pregnancy complicated by symptomatic adult polycystic liver disease. Am J Obstet Gynecol 179(1):266–267
43. Chapman AB (2003) Cystic disease in women: clinical characteristics and medical management. Adv Ren Replace Ther 10(1):24–30

44. Gunay-Aygun M (2009) Liver and kidney disease in ciliopathies. Am J Med Genet C Semin Med Genet 151C(4):296–306
45. Shedda S, Robertson A (2007) Caroli's syndrome and adult polycystic kidney disease. ANZ J Surg 77(4):292–294
46. Wen JW, Furth SL, Ruebner RL (2014) Kidney and liver transplantation in children with fibrocystic liver-kidney disease: data from the US Scientific Registry of Transplant Recipients: 1990–2010. Pediatr Transplant 18(7):726–732
47. Newman KD, Torres VE, Rakela J, Nagorney DM (1990) Treatment of highly symptomatic polycystic liver disease. Preliminary experience with a combined hepatic resection-fenestration procedure. Ann Surg 212(1):30–37
48. He XS, Huang JF, Chen GH, Zheng KL, Ye XM (1999) A successful case of combined liver and kidney transplantation for autosomal dominant polycystic liver and kidney disease. World J Gastroenterol 5(1):79–80
49. Chebib FT, Harmon A, Irazabal Mira MV et al (2016) Outcomes and durability of hepatic reduction after combined partial hepatectomy and cyst fenestration for massive polycystic liver disease. J Am Coll Surg 223(1):118–126
50. Brisman JL, Song JK, Newell DW (2006) Cerebral aneurysms. N Engl J Med 355:928–939
51. Xu HW, Yu SQ, Mei CL, Li MH (2011) Screening for intracranial aneurysm in 355 patients with autosomal-dominant polycystic kidney disease. Stroke 42(1):204–206
52. Vlak MH, Algra A, Brandenburg R, Rinkel GJ (2011) Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis. Lancet Neurol 10(7):626–636
53. Pirson Y, Chauveau D, Torres V (2002) Management of cerebral aneurysms in autosomal dominant polycystic kidney disease. J Am Soc Nephrol 13(1):269–276
54. Rozenfeld MN, Ansari SA, Shaibani A, Russell EJ, Mohan P, Hurley MC (2014) Should patients with autosomal dominant polycystic kidney disease be screened for cerebral aneurysms? AJNR Am J Neuroradiol 35(1):3–9
55. Rozenfeld MN, Ansari SA, Mohan P, Shaibani A, Russell EJ, Hurley MC (2016) Autosomal dominant polycystic kidney disease and intracranial aneurysms: is there an increased risk of treatment? AJNR Am J Neuroradiol 37(2):290–293
56. Jung SC, Kim CH, Ahn JH, Cho YD, Kang HS, Cho WS, Kim JE, Ahn C, Han MH (2016) Endovascular treatment of intracranial aneurysms in patients with autosomal dominant polycystic kidney disease. Neurosurgery 78(3):429–435; **discussion 435**
57. Spithoven EM, Casteleijn NF, Berger P, Goldschmeding R (2014) Nephrectomy in autosomal dominant polycystic kidney disease: a patient with exceptionally large, still functioning kidneys. Case Rep Nephrol Urol 4(2):109–112
58. Cristea O, Yanko D, Felbel S, House A, Sener A, Luke PP (2014) Maximal kidney length predicts need for native nephrectomy in ADPKD patients undergoing renal transplantation. Can Urol Assoc J 8(7–8):278–282
59. Patel P, Horsfield C, Compton F, Taylor J, Koffman G, Olsburgh J (2011) Native nephrectomy in transplant patients with autosomal dominant polycystic kidney disease. Ann R Coll Surg Engl 93(5):391–395
60. Casteleijn NF, Gansevoort RT, Leliveld AM (2016) Nephrectomy in patients with autosomal dominant polycystic kidney disease, does size matter? World J Urol 34(7):907–908
61. Shumate AM, Bahler CD, Goggins WC, Sharfuddin AA, Sundaram CP (2016) Native nephrectomy with renal transplantation is associated with a decrease in hypertension medication requirements for autosomal dominant polycystic kidney disease. J Urol 195 (1):141–146
62. Lipke MC, Bargman V, Milgrom M, Sundaram CP (2007) Limitations of laparoscopy for bilateral nephrectomy for autosomal dominant polycystic kidney disease. J Urol 177(2):627–631
63. Jung Y, Irazabal MV, Chebib FT et al (2016) Volume regression of native polycystic kidneys after renal transplantation. Nephrol Dial Transplant 31(1):73–79
64. Yamamoto T, Watarai Y, Kobayashi T et al (2012) Kidney volume changes in patients with autosomal dominant polycystic kidney disease after renal transplantation. Transplantation 93(8):794–798
65. Song WL, Zheng JM, Mo CB, Wang ZP, Fu YX, Feng G, Shen ZY (2011) Kidney transplant for autosomal dominant polycystic kidney disease: the superiority of concurrent bilateral nephrectomy. Urol Int 87(1):54–58
66. Skauby MH, Øyen O, Hartman A, Leivestad T, Wadström J (2012) Kidney transplantation with and without simultaneous bilateral native nephrectomy in patients with polycystic kidney disease: a comparative retrospective study. Transplantation 94(4):383–388
67. Neeff HP, Pisarski P, Tittelbach-Helmrich D, Karajanev K, Neumann HP, Hopt UT, Drognitz O (2013) One hundred consecutive kidney transplantations with simultaneous ipsilateral nephrectomy in patients with autosomal dominant polycystic kidney disease. Nephrol Dial Transplant 28(2):466–471
68. Ahmad SB, Inouye B, Phelan MS et al (2016) Live donor renal transplant with simultaneous bilateral nephrectomy for autosomal dominant polycystic kidney disease is feasible and satisfactory at long-term follow-up. Transplantation 100(2):407–415
69. Guo P, Xu W, Li H, Ren T, Ni S, Ren M (2015) Laparoscopic nephrectomy versus open nephrectomy for patients with autosomal dominant polycystic kidney disease: a systematic review and meta-analysis. PLoS One 10(6):e0129317
70. Petitpierre F, Cornelis F, Couzi L et al (2015) Embolization of renal arteries before transplantation in patients with polycystic kidney disease: a single institution long-term experience. Eur Radiol 25(11):3263–3271
71. Jacquet A, Pallet N, Kessler M et al (2011) Outcomes of renal transplantation in patients with autosomal dominant polycystic kidney disease: a nationwide longitudinal study. Transpl Int 24(6):582–587
72. Martínez V, Comas J, Arcos E et al (2013) Renal replacement therapy in ADPKD patients: a 25-year survey based on the Catalan Registry. BMC Nephrol 14:186
73. Patel MS, Kandula P, Wojciechowski D, Markmann JF, Vagefi PA (2014) Trends in the management and outcomes of kidney transplantation for autosomal dominant polycystic kidney disease. J Transplant 2014:675697
74. Canaud G, Knebelmann B, Harris PC et al (2010) Therapeutic mTOR inhibition in autosomal dominant polycystic kidney disease: what is the appropriate serum level? Am J Transplant 10(7):1701–1706
75. Caroli A, Antiga L, Cafaro M, Fasolini G, Remuzzi A, Remuzzi G, Ruggenenti P (2010) Reducing polycystic liver volume in ADPKD: effects of somatostatin analogue octreotide. Clin J Am Soc Nephrol 5(5):783–789
76. van Keimpema L, Nevens F, Vanslembrouck R et al (2009) Lanreotide reduces the volume of polycystic liver: a randomized, double-blind, placebo-controlled trial. Gastroenterology 137(5):1661–1668.e1–2
77. Sallée M, Rafat C, Zahar JR, Paulmier B, Grünfeld JP, Knebelmann B, Fakhouri F (2009) Cyst infections in patients with autosomal dominant polycystic kidney disease. Clin J Am Soc Nephrol 4(7):1183–1189
78. Bobot M, Ghez C, Gondouin B et al (2016) Diagnostic performance of [(18)F]fluorodeoxyglucose positron emission tomography-computed tomography in cyst infection in patients with

autosomal dominant polycystic kidney disease. Clin Microbiol Infect 22(1):71–77
79. Frascà GM, Sandrini S, Cosmai L et al (2015) Renal cancer in kidney transplanted patients. J Nephrol 28(6):659–668
80. Wetmore JB, Calvet JP, Yu AS, Lynch CF, Wang CJ, Kasiske BL, Engels EA (2014) Polycystic kidney disease and cancer after renal transplantation. J Am Soc Nephrol 25(10):2335–2341
81. Helal I, Reed B, Mettler P, Mc Fann K, Tkachenko O, Yan XD, Schrier RW (2012) Prevalence of cardiovascular events in patients with autosomal dominant polycystic kidney disease. Am J Nephrol 36(4):362–370
82. Perrone RD, Ruthazer R, Terrin NC (2001) Survival after end-stage renal disease in autosomal dominant polycystic kidney disease: contribution of extrarenal complications to mortality. Am J Kidney Dis 38(4):777–784
83. Sarkio S, Halme L, Kyllönen L, Salmela K (2004) Severe gastrointestinal complications after 1,515 adult kidney transplantations. Transpl Int 17(9):505–510
84. Kanaan N, Goffin E, Pirson Y, Devuyst O, Hassoun Z (2010) Carbohydrate antigen 19-9 as a diagnostic marker for hepatic cyst infection in autosomal dominant polycystic kidney disease. Am J Kidney Dis 55(5):916–922
85. Kasiske BL, Snyder JJ, Gilbertson DT, Wang C (2004) Cancer after kidney transplantation in the United States. Am J Transplant 4(6):905–913
86. Jankowska M, Dębska-Ślizień A, Imko-Walczuk B, Piesiaków ML, Lizakowski S, Czarnacka K, Rutkowski B (2016) Skin cancer in kidney transplant recipients affected with autosomal dominant polycystic kidney disease. Clin Transplant 30(4):339–343
87. Cosio FG, Pesavento TE, Kim S et al (2002) Patient survival after renal transplantation: IV. Impact of post-transplant diabetes. Kidney Int 62:1440–1446
88. Hamer RA, Chow CL, Ong AC, McKane WS (2007) Polycystic kidney disease is a risk factor for new-onset diabetes after transplantation. Transplantation 83(1):36–40
89. Ruderman I, Masterson R, Yates C, Gorelik A, Cohney SJ, Walker RG (2012) New onset diabetes after kidney transplantation in autosomal dominant polycystic kidney disease: a retrospective cohort study. Nephrology (Carlton) 17(1):89–96
90. Cheungpasitporn W, Thongprayoon C, Vijayvargiya P, Anthanont P, Erickson SB (2016) The risk for new-onset diabetes mellitus after kidney transplantation in patients with autosomal dominant polycystic kidney disease: a systematic review and meta-analysis. Can J Diabetes. doi:10.1016/j.jcjd.2016.03.001
91. Grantham JJ (2008) Clinical practice. Autosomal dominant polycystic kidney disease. N Engl J Med 359(14):1477–1485