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Novel non-cystic features of polycystic kidney disease: having new eyes or seeking new landscapes

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ABSTRACT

Abstract. For decades, researchers have been trying to decipher the complex pathophysiology of autosomal dominant polycystic kidney disease (ADPKD). So far these efforts have led to clinical trials with different candidate treatments, with tolvaptan being the only molecule that has gained approval for this indication. As end-stage kidney disease due to ADPKD has a substantial impact on health expenditures worldwide, it is likely that new drugs targeting kidney function will be developed. On the other hand, recent clinical observations and experimental data, including PKD knockout models in various cell types, have revealed unexpected involvement of many other organs and cell systems of variable severity. These novel non-cystic features, some of which, such as lymphopenia and an increased risk to develop infections, should be validated or further explored and might open new avenues for better risk stratification and a more tailored approach. New insights into the aberrant pathways involved with abnormal expression of PKD gene products polycystin-1 and -2 could, for instance, lead to a more directed approach towards early-onset endothelial dysfunction and subsequent cardiovascular disease. Furthermore, a better understanding of cellular pathways in PKD that can explain the propensity to develop certain types of cancer can guide post-transplant immunosuppressive and prophylactic strategies. In the following review article we will systematically discuss recently discovered non-cystic features of PKD and not well-established characteristics. Overall, this knowledge could enable us to improve the outcome of PKD patients apart from ongoing efforts to slow down cyst growth and attenuate kidney function decline.

Keywords: bronchiectasis, cancer, cardiovascular, endothelial, infections, inflammation, lymphopenia, polycystic kidney, polycystin

INTRODUCTION

Polycystic kidney disease (PKD) was already known for a long time to include extrarenal features, which traditionally have not received much attention as compared with renal cyst formation [1]. Over the last decade, topical findings of previously unrecognized clinical traits and explanatory insights into the pathophysiology of PKD have been reported, revealing clinically relevant extrarenal and non-cystic manifestations of PKD. Therefore we aimed to summarize the recent literature in this field with a focus on novel traits beyond the complex phenotype of PKD. In this review we will cover haematological abnormalities such as lymphopenia and thrombopenia and an increased risk of infections and cancer, bronchiectasis, vascular including lymphatic abnormalities, abnormalities in glucose metabolism and neurocognitive involvement. Functional abnormalities of polycystin-1 and/or -2 are mostly crucial in their development. We will outline why lymphopenia is a possible mediator of an enhanced infection and malignancy risk (Figure 1). We will not discuss well-recognized characteristics such as the propensity to develop cerebral aneurysms, colonic diverticulosis and

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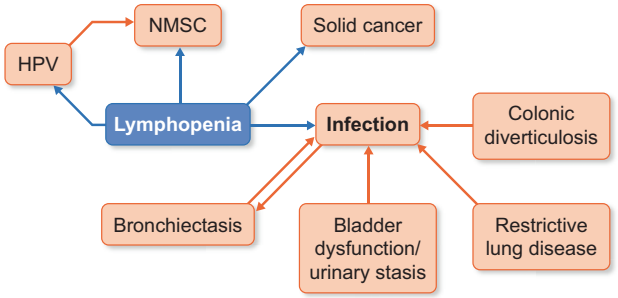

FIGURE 1: A potential role of lymphopenia in ADPKD.

Lymphopenia in patients with ADPKD can contribute to the development of an increased infection or malignancy risk both directly and indirectly [for instance, by an increased risk of human papilloma virus (HPV) infection]. NMSC, non-melanoma skin cancer.

inguinal or incisional hernia. We believe that recognition of the aforementioned novel features should enable clinicians to optimize risk stratification and scrutinize preventive strategies. Although some findings certainly warrant further exploration and validation, we will make some careful and preliminary suggestions towards an adapted treatment approach for subjects with PKD.

Infection risk

Based on a limited number of epidemiological studies, people with PKD have increased odds for infection, for example, diverticulitis [2]. About 30–70% of all patients with PKD contract urinary tract infections (UTIs) during their lifetime, which considerably exceeds the general population risk [3]. In addition, many of these UTIs are complicated by pyelonephritis, which is far more common in persons with end-stage kidney disease (ESKD) with PKD as compared with those with another aetiology (16 versus 2%) [3–7]. Apart from anatomical issues such as urinary stasis with increased risk of pyelonephritis, urodynamic analysis recently revealed bladder dysfunction, including reduced maximal urinary flow and increased voiding time, in subjects with PKD as compared with control chronic kidney disease (CKD) patients [8]. Recurrent UTI occurs more frequently in PKD patients with larger kidneys as compared with age- and gender-matched controls [9].

Kidney transplant recipients (KTRs) with PKD also more often develop pneumonia necessitating hospitalization and have higher mortality attributable to pneumonia [10, 11]. According to Danish registry data, KTRs with PKD have a higher risk of *Pneumocystis jirovecii* pneumonia (PJP), with an incidence rate ratio of 4.25 (95% confidence interval 1.55–11.7) as compared with KTRs without PKD [12]. Also, bronchiectasis with mostly mild lower lobar involvement is fairly common in PKD patients with CKD (19–37%), with a three times higher risk as compared with controls with CKD, and this risk is aggravated in smokers [13, 14]. About one-third of KTRs with bronchiectasis had PKD and 37% had recurrent respiratory infections according to data from the French SPIESSER group [15]. The often very short interval (months) between diagnosis and time after transplantation suggests pre-existing disease.

The exact mechanism remains uncertain, but deficient expression of polycystin-1 and -2 encoded by *Pkd1* and *Pkd2*, respectively, on motile cilia of non-autosomal dominant polycystic kidney disease (ADPKD) airway epithelium cells and airway smooth muscle cells suggests a causative role for dysfunctional airway cilia [14, 16]. In these abnormal cilia, flow sensing is interrupted, leading to impaired mucociliary clearance, bronchial remodelling and finally bronchiectasis [17]. Reminiscent of this, an animal ciliary knockout model of PKD demonstrated bronchial remodelling [18]. In another smooth muscle–specific *Pkd2* knockout mice model, not only functional respiratory but also structural abnormalities compatible with bronchiectasis were observed, such as increased bronchial thickness [19]. The propensity to develop bronchiectasis in PKD patients could have therapeutic implications and may suggest the avoidance of exposure to high doses of mycophenolate mofetil, which has been associated with the development of bronchiectasis [20, 21]. As cigarette smoking impairs mucociliary clearance, it is conceivable that smoking acts synergistically in subjects with ciliary dysfunction, including PKD [13]. This should urge patients to strive for early smoking cessation upon diagnosis of PKD (Table 2).

On top of bronchiectasis and anatomical factors such as enlarged cystic kidneys or liver contributing to a restrictive pulmonary function deficit, lymphopenia, which is more common in PKD patients [22, 23], could increase the risk of urinary and respiratory tract infections. In a prospective Danish study in a general population sample, lymphopenia (lymphocytes $<1.1 \times 10^9$/L or the 2.5th percentile of the general population) was independently associated with a 40% higher risk of infection, whereas the risk of infection-related death increased by 70% [24]. In a sensitivity analysis excluding subjects with autoimmune and/or haematological disease, this association remained robust [24]. In specific study populations such as people with autoimmune disease orhuman immunodeficiency virus, residents of long-term care facilities and patients admitted to the intensive care unit, lymphopenia is also a risk factor for infection [24, 25]. In the latter analysis, lymphocyte counts at admission between 1.0 and 1.5×10^9/L were associated with a 60% higher risk of nosocomial infection as compared with those with higher lymphocyte counts [25].

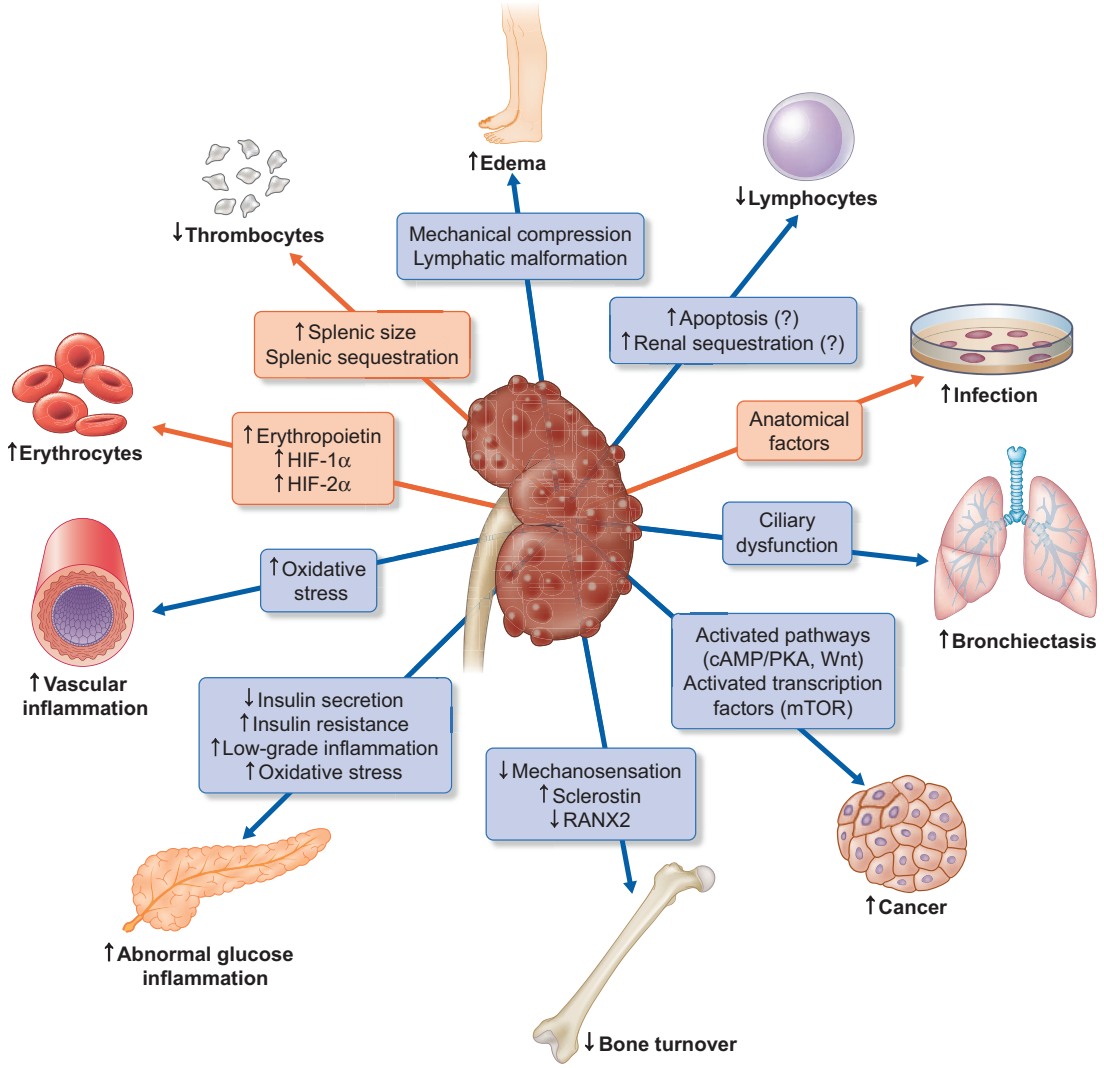

FIGURE 2: Extrarenal features of ADPKD.

Arrows in blue depict clinical traits where aberrant polycystin glycoproteins play a role in the development of the abnormality, while this has not been demonstrated for features depicted with an orange arrow. HIF, hypoxia-inducible factor.

We reported lower counts of monocytes, thrombocytes and especially lymphocytes as features of PKD patients across all stages of kidney dysfunction including ESKD [22] (Figure 2). Lymphocyte counts, adjusted for age and C-reactive protein were ~300/μL lower in subjects with PKD as compared with CKD controls [22]. While in our overall analysis in patients with ESKD ($n = 700$), 18% had PKD, this proportion was significantly higher (29%) when analysing the lowest quintile of lymphocytes ($<1.04 \times 10^9$/L) [22]. In the general population, the multivariable-adjusted hazard ratio for any infection sharply increased for lymphocyte counts $>1.4 \times 10^9$/L, which was close to the median of our cohort of ESKD patients with PKD (1.33×10^9/L) [22, 24]. Also, haemodialysis patients with PKD had a significantly higher prevalence of lymphopenia and lower numbers of circulating monocytes [23].

KTRs with PKD had 25 and 31% fewer circulating $CD8^+$ T lymphocytes and B lymphocytes, respectively, as compared with those without PKD (both $P < 0.001$) [22]. KTRs with fewer B lymphocytes at baseline developed sinopulmonary infections more frequently [26]. In this prospective study, 30% of KTRs with B cells <98 cells/μL (the fifth percentile of controls) had sinopulmonary infections as compared with 9% in those with more circulating B cells ($P = 0.001$) [22, 26]. In KTRs, $CD4^+$ lymphocytopenia at admission, defined as <200 $CD4^+$ cells/μL, is associated with increased mortality from PJP [27].

The underlying mechanisms behind lymphopenia in PKD remain elusive. Renal sequestration of lymphocytes and/or mononuclear cells is conceivable considering the local recruitment of $CD4^+$ T cells and especially activated $CD8^+$ T cells in the renal parenchyma of patients with PKD [23, 28]. Data on absolute intrarenal leucocyte counts and on a possible increase in circulating lymphocytes after nephrectomy would support this further. Increased apoptosis or decreased proliferation of lymphocytes and monocytes or their precursors is another possible explanation [22]. Subjects with PKD had a low proliferation rate of immortalized B lymphoblastoid cells in line with decreased intracellular calcium concentrations, suggesting a role of the polycystin complex in lymphocyte physiology [29]. In contrast, subjects with PKD had increased neutrophil chemotaxis and proliferation of T lymphocytes as compared with

Table 1. Aberrant polycystin expression and organ involvement

Cell type	Pathways involved	Clinical effect
T Lymphocytes	mTOR (↑) NF-κB (↑) ERK (↑) MIF (↑)	Increased proliferation with sequestration in kidneys (lymphopenia)?
Osteoblasts	Akt/β-catenin signalling (↓) RunX2 (↓)	Decreased bone turnover
Endothelial cells	STAT-1 (↓)	Endothelial dysfunction Abnormal lymphatic development/oedema
VSMC	MEK/ERK/myc (↑)	Aortic dissection
Cardiac (myo)fibroblasts	TGF-β (↓) SMAD-3 (↓)	Decreased cardiac recovery after myocardial infarction
Neurons	mTOR (↑)	Alzheimer's disease?
Cancer cells	mTOR (variable) Wnt (variable) JAK (variable)	Cancer-dependent proliferation

MIF, migration-inhibitory factor; STAT-1, signal transducer and activator of transcription 1; VSMC, vascular smooth muscle cell; JAK, Janus kinase; TGF, transforming growth factor; Wnt, wingless-related integration site.

controls [30]. This occurred in line with abnormal activation of extracellular signal-regulated kinase (ERK) and mammalian target of rapamycin (mTOR) kinases and nuclear factor κB (NF-κB) [30] (Table 1).

Not all observational studies that evaluate infection risk in KTRs and integrate PKD as a covariate consistently demonstrate an increased risk of infection in this subgroup. Lower odds were observed for post-transplant fungal infections and BK polyoma viremia in KTRs with PKD as compared with patients with other aetiologies of kidney failure [31, 32]. Most studies report the infection risk in subpopulations as a *post hoc* finding in small study populations with inherent risk of type 2 error. Certainly the role of lymphopenia in the development of fungal infections such as PJP in KTRs is well-established [27, 33]. The relationship between lymphopenia and incident BK polyoma infections remains less certain. Prospective verification not only of the association between PKD and lymphopenia, but also of the increased infection risk, certainly is warranted in populations of adequate size. Alternatively, lymphopenia could predispose subjects with PKD solely to specific infections. In the general population, however, lymphopenia not only significantly increased the risk of UTI and pneumonia, but also sepsis, diarrheal disease, endocarditis and other infections [24], rendering this hypothesis less plausible.

In light of the current pandemic of coronavirus disease 2019 (COVID-19), the increased risk of lymphopenia and impaired mucociliary clearance in PKD patients might predispose them to a more severe course of disease. Lymphopenia is a cardinal feature and prognostic marker of severe COVID infections in the general population but also in KTRs [34, 35]. Impaired mucociliary clearance as observed in ageing subjects is believed to facilitate the spread of severe acute respiratory syndrome coronavirus 2 into the lungs [36]. According to a systematic review, bronchiectasis is detected in 5% of all patients with COVID-19 infection [37]. Registry data will possibly shed light on the attributable risk of PKD in severe COVID-19 infections.

Haematological abnormalities

For decades we have known that people with PKD are less prone to develop anaemia as compared with subjects with comparable estimated glomerular filtration rates (eGFRs) due to CKD of other aetiologies [38]. This finding parallels the lower consumption of erythropoietin-stimulating agents and the higher incidence of post-transplant erythrocytosis in persons with PKD [39–41]. There is a correlation between the degree of erythropoietin production and the renal cyst size, although this also holds true for acquired renal cysts [38, 42–44]. In patients with von Hippel–Lindau disease, erythropoietin and its receptors are co-expressed both in malignant lesions and in benign renal cysts, while the coexistence of polycythemia and renal cell carcinoma (RCC) is well recognized [45, 46]. Regional hypoxia in the epithelial cells lining the cyst wall can upregulate hypoxia-inducible factor (HIF) and HIF-2α, promoting both cyst growth and erythrocytosis in PKD [47, 48].

Of interest, in a magnetic resonance imaging–based case–control study, patients with PKD had a 28% higher splenic volume irrespective of the presence of splenic cysts as compared with controls [49] (Figure 2). Moreover, height-adjusted total spleen volume correlated with kidney volume, reflecting a more severe disease phenotype [49]. Spleen volume inversely correlated with thrombocyte ($P < 0.001$) but not leucocyte counts [49]. This observation aligns with previous findings from the HALT Progression of Polycystic Kidney Disease Study A, where thrombocytes were lower with increasing splenic and liver volume [50]. Possibly thrombocytes are sequestrated in the enlarged spleen in PKD [49]. We also observed that subjects with PKD and ESKD had significantly lower thrombocyte numbers as compared with patients with another aetiology of ESKD ($P < 0.001$) [22]. This was also observed in haemodialysis patients with PKD and in normotensive subjects with PKD and preserved kidney function [51, 52]. The clinical relevance of mild thrombocytopenia that has been associated with increased platelet volume remains doubtful [52].

Cancer risk

KTRs with PKD are 1.5 times more likely to develop non-melanoma skin cancer (NMSC) and earlier after transplantation [53–56]. Based on this, dermatological follow-up of KTRs with PKD should be emphasized and lifelong sun avoidance pursued after diagnosing PKD. Considering the higher prevalence of lymphopenia in subjects with PKD, immunological factors might

contribute to the development of skin cancer [22, 23, 57]. $CD4^+$ lymphopenia was previously recognized as a risk factor for the development of skin cancer in KTRs [58]. Lymphopenia is a predisposing factor to develop recurrent human papilloma virus (HPV) infection [59], and evidence is accumulating that viruses, and especially HPV strains, are involved in the oncogenesis of NMSC [60]. The aforementioned factors certainly add to the already enhanced background risk to develop NMSC in people exposed to immunosuppressive drugs, such as KTRs.

For more than a decade, patients with PKD have been considered to have an increased risk of developing RCC lesions, and this is supported by nephrectomy data [61]. According to observational data, 5–12% of nephrectomy specimens of subjects with PKD contained RCC, although the variable case mix and absence of controls with comparable kidney function hampered the validity of this and other studies [62–64]. Apart from this, PKD was traditionally not considered a risk factor for solid cancer [56, 65]. This has been challenged by a large cohort study in the general Korean population, in which patients with PKD not only had an increased risk of RCC, but also of colonic and hepatic cancer in the primary and competing risk analysis and after stratification for CKD [66]. Also, a strikingly higher incidence of cancer in children with PKD was observed as compared with general population registry data, which suggests inherent genetic rather than environmental factors [67]. Other observational data also disclosed PKD as a risk factor for solid cancer in KTRs [68].

There is a biological rational to support these epidemiological data. Recent findings in murine PKD models demonstrated that protein kinase Akt and mTOR complex 1 (mTORC1) hyperactivation in PKD leads to DNA damage accumulation [69]. Considering the crucial role of signalling pathways such as the cyclic adenosine monophosphate/protein kinase A pathway that is activated both in cancer and in PKD, this might herald a mechanistic framework explaining the epidemiological data [70, 71]. Both cancer and PKD share an upregulation of proto-oncogene activation, increased apoptosis and proliferation and epidermal growth factor receptor activation next to metabolic reprogramming, which includes a shift towards enhanced aerobic glycolysis, the so-called Warburg effect [72, 73]. The presence of an altered metabolism depends upon the type of tumour. Human RCC cells have high levels of oxidative glycolysis, while tumours in the brain and lungs do not [74]. Evidence is accruing that polycystin-1 plays a major role in cancer biology and it affects mTOR, wingless-related integration site (Wnt) and Janus kinase signalling pathways differently depending on which cancer cell lines were studied [75]. This could explain why the incidence of tumours is inconsistently increased among various epidemiological studies [65, 70, 76]. Both polycystin-1 and -2 regulate the downstream signalling Wnt pathway, which is implicated in colorectal cancer development and progression, and increased expression of both glycoproteins was observed in human colorectal tumour samples [76]. Finally, another possible contributory factor is the aberrant subset of lymphocytes in subjects with PKD [22, 23]. Lower circulating $CD4^+$ T and B cells predicted a higher incidence of solid cancer in KTRs [77]. The clinical relevance of the association between PKD, and especially skin cancer, could support the use of mTOR inhibitors at least in KTRs with PKD, considering the absence of nephroprotection in CKD [78, 79]. An immunosuppressive regimen encompassing low-dose tacrolimus and everolimus from the time of transplantation seems defendable in subjects with PKD and a low risk of rejection [80]. The possible causal relationship between mycophenolate mofetil exposure and bronchiectasis could further support this [20, 21].

Bone disease

ADPKD is characterized by a particular bone phenotype that is attributable to the role of polycystin in osteocyte physiology (Figure 2). Selective murine knockout models of osteoblastic *Pkd1* demonstrated low bone turnover by loss of mechanosensation and impairment of the increase in intra-osteoblastic calcium concentration with ensuing activation of downstream Akt/β-catenin signalling [81, 82]. Also, osteoblastic differentiation is decreased by reduced activity of the Runt-related transcription factor 2 (RunX2), with the transcriptional co-activator with PDZ-binding motif (TAZ) mediating the interaction between polycystin-1 and RunX2 [83]. Overall these data indicate that polycystin-1 is a regulator of osteoblast proliferation and health. This translates into bone abnormalities in subjects with PKD reflected by higher circulating sclerostin and lower bone-specific alkaline phosphatase (BALP) values [83]. Sclerostin is an inhibitor of the Wnt/β-catenin signalling pathway and is upregulated by mechanical unloading or attenuated mechanosensation [84]. In a case–control study, ESKD patients with PKD had signs of decreased bone turnover, reflected by compatible bone histomorphometric parameters, an increased plasma sclerostin concentration and a lower BALP as compared with subjects without PKD [85]. Bone mineral density (BMD) was preserved in skeletal sites rich in cortical bone in patients with PKD [84]. This could align with PKD mitigating hyperparathyroidism-related BMD loss by suppressed bone turnover [86]. Considering this particular bone phenotype, one should be cautious to prescribe prophylactic bisphosphonates to subjects with PKD [86] (Table 2).

Early-onset vascular inflammation

Cardiovascular disease already develops early in subjects with PKD. Young people with PKD and preserved kidney function have stiffer large elastic arteries, reflected by higher carotid–femoral pulse wave velocity and an increased augmentation index [87, 88], while they have more endothelial dysfunction and lower aerobic exercise capacity than healthy controls [89, 90]. Intima-media thickness is increased in normotensive subjects with PKD and preserved kidney function [91]. Of note, despite the absence of numerically different blood pressures in some of these case–control studies, both central and peripheral hypertension and nocturnal non-dipping are often overrepresented in the PKD group and already at a very young age [87, 92, 93]. Oxidative stress markers are increased early in the course of PKD and even before renal impairment in some but not all analyses [88, 94]. Moreover, infusion of the antioxidant ascorbic acid improved endothelial function in subjects with PKD and preserved kidney function, but not of healthy controls, suggesting early-onset vascular inflammation and oxidative stress [88]. This is reflected by higher endothelial expression of transcription factor NF-κB [88]. These vascular changes possibly predate the development of hypertension. Of interest, polycystin-1 contributes to activation of the calcium-dependent transcription factor signal transducer and activator of transcription 1 by modulating endothelial mechanosensitivity to shear stress and subsequent release of nitric oxide [95, 96]. This fuels the hypothesis that polycystin-1 and -2, both of which are present in the cilia of endothelial cells, contribute to vascular health. Of note, haemodialysis patients with PKD have more long-term arteriovenous

Table 2. Possible clinical implications of extrarenal features of ADPKD

Extra-renal feature	Possible clinical implications
Lymphopenia	Adapt dosage of anti-proliferative immunosuppressive drugs (for instance, mycophenolate mofetil and azathioprine) if necessary
Erythrocytosis	Consider early initiation of RAS inhibitors
Infection risk	Adequate preventive measures to contain UTI risk
	Consider urological evaluation after UTI including urodynamic testing
	Prolong duration of PJP prophylaxis in lymphopenic KTRs
Bronchiectasis	Avoid high doses of mycophenolate mofetil or replace mycophenolate mofetil by *de novo* mTOR inhibitors from the day of transplantation
	Insist on smoking cessation and avoidance strategies
	Participate in pulmonary rehabilitation programme and regular exercise
Solid cancer risk	Annual abdominal ultrasound screening post-transplantation; colorectal cancer screening following general population recommendations
	Insist on smoking cessation and encourage avoidance
Skin cancer risk	Avoidance of sun overexposure from the time of diagnosis
	Replace mycophenolate mofetil by mTOR inhibitors from the day of transplantation
Low bone turnover	Outweigh risk–benefit of bisphosphonates
Ventricular hypertrophy	Consider early initiation of RAS inhibitors
Early-onset endothelial dysfunction	Insist on smoking cessation and encourage avoidance
	Consider early initiation of statins
Oedema	Outweigh risk–benefit of calcium antagonists
Abnormal glucose metabolism	Combat obesity and encourage physical exercise. Consider corticosteroid withdrawal after transplantation

RAS, renin–angiotensin system; mTOR, mammalian target of rapamycin.

access dysfunction than controls with other aetiologies of kidney disease [96].

Bearing in mind that polycystin-1 and -2 are both present in lymphatic endothelial cells, it is not surprising that mutations in both *Pkd1* and *Pkd2* lead to abnormalities in lymphatic development in murine and zebrafish models [97, 98]. Mice with a deletion in either gene develop profound oedema without cardiac abnormalities and have reduced lymphatic vessel density and abnormal migration of lymphatic endothelial cell precursors [99]. In samples of primary lymphatic malformation in humans, polycystin-1 and -2 protein and gene expression were downregulated [100]. All these might translate into a higher prevalence of oedema in people with PKD. In a single-centre study in subjects with PKD and a mean GFR of 80 mL/min, a high prevalence of bilateral leg oedema was noted in 20% of all cases [101]. In patients with concomitant severe polycystic liver disease, the prevalence of oedema was 71%, possibly alluding to an additional mass effect [101]. Certainly we need more clinical data to verify this, but it seems plausible that especially KTRs with PKD face a higher risk to develop oedema while on mTOR inhibitors [80].

Endothelial damage is pivotal in the pathogenesis of aneurysm formation and inhibition of polycystin-1 reduces endothelial cell migration and increases permeability by disruption of cell–cell junctions [102]. Strikingly, PKD patients with aortic aneurysms and aortic dilatation were taller and had a more slender silhouette than controls, which suggests overlapping Marfan-like characteristics [103]. Also, the vascular smooth muscle cell (VSMC) phenotypic switch that occurs in various cardiovascular diseases such as aortic dissection is impaired in PKD [103]. Polycystin-1 is significantly downregulated in VSMCs of patients with aortic dissection and is involved in the crucial mitogen-activated protein kinase kinase/ERK/myc pathway [104]. In murine VSMC *Pkd1* knockout models, the aortic architecture changes with fragmentation of elastic fibres and increased matrix deposition [105].

Cardiac involvement

PKD is characterized by various cardiac abnormalities. In particular, ventricular hypertrophy is prevalent in PKD irrespective of blood pressure control and already at a very young age [93, 106, 107]. Also, more frequently reported in subjects with PKD as compared with other aetiologies of CKD are hypertrophic obstructive cardiomyopathy, idiopathic dilated cardiomyopathy (IDCM) and left ventricular non-compaction next to cardiac valve abnormalities such as mitral valve prolapse [108]. Also, emerging data point to a pathophysiological role of polycystin-1 and -2 dysfunction or ablation [109, 110]. Mutations in *Pkd1,* but especially *Pkd2,* have in registry data been associated with an increased prevalence of IDCM, even in normotensive subjects [111]. Also, biventricular diastolic dysfunction occurs frequently in subjects with PKD and irrespective of concomitant hypertension [107]. This aligns with experiments in *Pkd2* mutant zebra fish or mice that display impaired cardiac function and aberrant calcium signalling independent of kidney dysfunction [110]. Polycystin-2 is a ubiquitous stress–response protein with enhanced expression in heart, liver and brain cells in response to increased endoplasmic reticulum or oxidative stress [111]. Variable cellular expression of polycystin-2 modulates intracellular calcium signalling [111]. Murine *Pkd1* knockout (but not *Pkd2* knockout) cardiomyocytes demonstrated impaired myocyte repolarization by a reduction of action potential duration and contractility [111]. These data indicate a pivotal role of polycystin-1 in the inhibition of multiple voltage-dependent K^+ channels [112]. Both polycystin-1 and -2 affect mitochondrial morphology and dynamics and intersecting pathways control ciliary and mitochondrial function, which likely explains why

PKD is characterized by fragmented, dysfunctional mitochondria [113]. Mitochondrial dysfunction could further contribute to the development of cardiac abnormalities associated with PKD [114].

Recent data indicate a crucial role of polycystin-1 in cardiac remodelling after myocardial infarction [115]. This is conceivable as human fibroblasts and myofibroblasts harbor primary cilia and ciliated fibroblasts are enriched in areas of myocardial injury while depletion of cilia impairs local transforming growth factor-β signalling and SMAD-3 activation [115]. This might be clinically relevant for recovery after myocardial infarction. In a case–control study, people with PKD had more need of temporary pacemaker therapy (7.7 versus 1.0%) than age- and gender-matched controls with myocardial infarction but no PKD [116]. They also had a significantly higher mortality (13.5 versus 6.2%) after myocardial infarction [115].

Abnormal glucose metabolism

Subjects with PKD and normal kidney function have impaired beta-cell function with decreased insulin secretion and increased insulin resistance after dynamic assessment by oral glucose and insulin tolerance test, respectively [117, 118]. These observations can explain the 2- to 3-fold higher risk to develop diabetes after transplantation following a meta-analysis of observational studies [119, 120]. Polycystin glycoproteins have been detected in pancreatic islet beta cells and are possibly dysfunctional [121]. Alternatively, early-onset low-grade inflammation and oxidative stress, which has been observed in many experimental and clinical studies in PKD, could render beta cells vulnerable to a second hit, including immunosuppression. Of interest also, obesity is common in PKD and shared signalling pathways between both conditions indicate that PKD could drive obesity [122]. Strikingly, insulin resistance and diabetes negatively impact on the progression of kidney disease in PKD, which suggests a vicious circle [122].

Neurocognitive disease

Neurodegenerative diseases, such as Parkinson's but especially Alzheimer's disease, were associated with PKD in a propensity-based case–control study [123]. Dysfunction and/or activation of the mTORC1 signalling pathway as occurs in PKD leads to the accumulation of hyperphosphorylated tau and contributes to the development of Alzheimer's disease [104]. Polycystin-1 and -2 are critical for the balance between proliferation and differentiation of neuronal progenitor cells [124]. Primary neuron cilia play a role in the development of Alzheimer's disease [125]. Finally, subjects with PKD carry a high psychosocial burden and are at risk to develop depression or suffer from anxiety [126–128]. Nevertheless, this clinically very relevant domain so far has remained largely unexplored.

CONCLUSION

The spectrum of clinical characteristics attributed to the underlying ciliopathy in persons with ADPKD is rapidly expanding. Recent clinical observations and experimental data integrating PKD knockout models have expanded the list with numerous previously unrecognized traits of variable severity. Their recognition in PKD patients should improve risk stratification and has therapeutic implications. Considering the ubiquitous presence of polycystin-1 and -2 across many cell types, further dissection of their pathophysiological role in PKD seems indicated. This broader focus could improve the outcome of PKD patients apart from ongoing essential efforts to slow down cyst growth and delay the development of ESKD.

CONFLICT OF INTEREST STATEMENT

None declared. Results presented in this article have not been published previously in whole or part.

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