

Metabolic abnormalities in autosomal dominant polycystic kidney disease

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ABSTRACT

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disorder and is known to affect all ethnic groups with a prevalence of 1:400–1:1000 live births. The kidney in ADPKD is characterized by the formation of numerous cysts which progressively expand and eventually destroy normal kidney structure and function. Cysts occur in other organs outside the kidney, most commonly in the liver, pancreas and spleen. Important non-cystic features include intracranial aneurysms and cardiac valve defects. Less well recognized are a range of metabolic abnormalities, which could be involved in cystic disease progression or be associated with other disease complications. In this review, we summarize the literature suggesting that metabolic abnormalities could be important under-recognised and under-treated features in ADPKD.

Keywords: ADPKD, calculi, lipids, NODAT, uric acid

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disorder and is known to affect all ethnic groups with a prevalence of 1:400–1:1000 live births [1]. It is characterized primarily by structural changes, i.e. the formation of fluid-filled cysts which arise from normal glomeruli and tubules that progressively expand to destroy normal kidney structure and function. By the age of 60 years, 50% of ADPKD patients will have developed end-stage renal disease (ESRD). Genetically, ADPKD is caused by mutations in one of two genes, *PKD1* (chromosome region 16p13.3; ~85% of cases) and *PKD2* (4q21; ~15% of cases) [2–4]. At the cellular level, abnormalities in cell proliferation, apoptosis, polarity, basement membrane morphology and fluid secretion have been

reported as underlying abnormalities resulting from defects in the ADPKD proteins, polycystin-1 and polycystin-2 [5].

Despite its name, ADPKD can be regarded as a systemic disease since there is an increased prevalence of cystic and non-cystic abnormalities in other organs. These include hepatic, pancreatic and splenic cysts, intracranial aneurysms and cardiac valve defects. Less well recognized are reports of metabolic changes in this disease indicating that the function of the polycystins might extend beyond the preservation of normal structure to the regulation of specific aspects of nephron function. We review the evidence for metabolic changes in ADPKD and consider how they might lead to under-recognised complications and contribute to cardiovascular mortality and disease progression [6].

GLUCOSE METABOLISM IN ADPKD

Several groups have reported that ADPKD patients could have an increased incidence of post-transplant diabetes mellitus (PTDM) or new-onset diabetes after transplantation (NODAT)—summarized in Table 1. In a retrospective case control study, Ducloux *et al.* compared 26 French ADPKD patients who had undergone kidney transplantation with 26 controls matched for age, gender, immunosuppressive therapy and transplant year [7]. They found that PTDM occurred in 10 ADPKD patients and four controls (34.6 versus 15.3%; $P < 0.005$). In a larger study, de Mattos *et al.* [8] reported on a cohort of 135 US patients with ADPKD who had received a primary kidney transplant who were compared with a control group matched for patient number, body mass index (BMI), per cent increase in BMI, episodes of acute rejection, prednisone dose, use of diuretics or beta-blockers, delayed graft function and serum creatinine levels. Once again, the incidence of PTDM was significantly higher in the ADPKD group (17

Table 1. Studies on relationship between ADPKD and NODAT/PTDM after kidney transplantation

| No. | Author and year of publication | Nature of study | Definition of NODAT/PTDM | Patient numbers | Single or multi-centre | Ethnicity | Overall prevalence of NODAT/PTDM (ADPKD versus non-ADPKD) | Other covariates (age, BMI immunosuppressive regime, time of dialysis, gender) |
|----------|--|--|--|---|-----------------------------------|--|--|--|
| POSITIVE | | | | | | | | |
| 1 | Ducloux <i>et al.</i> (1999) [7] | Retrospective cohort study | Fasting glycaemia >7.8 mmol/L and need for insulin or oral antidiabetic therapy | 26 ADPKD versus 26 controls | Single centre (France) | NA | 34.6 versus 15.3% matched cohort (P < 0.005) | No difference between ADPKD and matched cohort |
| 2 | de Mattos <i>et al.</i> (2005) [8] | Retrospective cohort study | Persistent hyperglycaemia (random blood glucose levels >11.1 mmol/L on two consecutive measurements at least 1 day apart) at least 30 days from an acute rejection episode | 135 ADPKD versus 135 matched controls versus 162 non-matched cohort | Single centre (USA) | 95% Caucasians 1.5% Hispanics 1.5% Asians 0.7% African American 1.5% Pacific Islanders | 17 versus 7.4% matched cohort (P = 0.016) versus 8% non-matched cohort (P = 0.02) | No differences between ADPKD and matched cohort |
| 3 | Hamer <i>et al.</i> (2007) [9] | Retrospective cohort study | Random blood glucose \geq 11.1 mmol/L on two separate days >6 weeks post-transplantation | 429 Patients analysed (including 67 with ADPKD) | Single centre (UK) | 96.7% White 3.3% Non-white | 13.4 versus 5.2% (P = 0.01) | ADPKD patients older than non-ADPKD (P = 0.01). No differences for other covariates |
| 4 | Caillard <i>et al.</i> (2011) [10] | Prospective study | A fasting glucose level \geq 7.0 mmol/L on at least two occasions; a non-fasting glucose level >11.1 mmol/L; a 2-h glucose level of a standard OGTT > 11.1 mmol/L; the need for antidiabetic medication. | 18 ADPKD versus 112 non-ADPKD | Single centre (France) | 95% White 4.2% Black 0.8% Asian | 55.6 versus 28% | Univariate analysis identified ADPKD as risk factor for NODAT (P = 0.002) |
| 5 | Gentil <i>et al.</i> (2002) [11] | Retrospective study | the requirement for continuous use of insulin \geq 1 month | 42 ADPKD versus 312 non-ADPKD | Six centres (Spain) | NA | 23.8 versus 5.8% | All patients were Hepatitis C positive. ADPKD patients older, shorter time on dialysis and a tendency towards a higher BMI at transplant compared with non-ADPKD |
| NEGATIVE | | | | | | | | |
| 1 | Pietrzak-Nowacka <i>et al.</i> (2008) [12] | Retrospective study, matched-pair design the control group received graft from the same donors as ADPKD patients | two fasting plasma glucose >7.0 mmol/L or two random glucose >11.1 mmol/L, 3 days after transplantation | 98 ADPKD patients versus 98 non-ADPKD | Four centres (NW Poland) | All Caucasian | 19.4 versus 18.4% (P = 1.0) | ADPKD patients were older with higher BMI and body mass, higher percentage of haemodialysis than non-ADPKD. Azathioprine and sirolimus more frequently used and mycophenolate mofetil less frequently used in ADPKD. |
| 2 | Bayer <i>et al.</i> (2010) [13] | Prospective | Two measurements of fasting plasma glucose \geq 7.0 mmol/L, a single plasma glucose >11.1 mmol/L, or the use of insulin or an oral hypoglycaemic agent between 30 days and 1 year post-transplantation | 640 patients recruited including 84 PKD | Three centres (Philadelphia, USA) | 63.1% White, 31.6% African American, 5.3% Other | 31.4% of all recipients by the end of first year post-transplantation (NA for PKD patients) Multivariable analysis showed PKD was not an independent predictor of NODAT | 15.8% of metabolic syndrome pre-transplant patients were PKD versus 9.5% in non-metabolic syndrome. |

| | | | | | | | | |
|---|---|-------------------------------|--|---|------------------------------|---|--------------------------------------|--|
| 3 | Ruderman <i>et al.</i> (2012) [14] | Retrospective cohort study | Any blood glucose estimates ≥11.1 mmol/L on two separate days; two fasting blood glucose estimations of ≥7.0 mmol/L at least 60 days post- transplantation; two or more estimations of HbA1C of ≥6.5%; use of hypoglycaemic medication or insulin | 79 ADPKD patients and 423 non-ADPKD controls | Single centre (Australia) | 98.7% Caucasian for ADPKD patients versus 88.5% Caucasian for non-ADPKD | 16.5 versus 17.1% ($P = 0.883$) | ADPKD patients were heavier, older than non-ADPKD and the percentage of males and proportion of patients having prednisolone as primary rejection treatment lower in ADPKD than non-ADPKD; other covariates similar. |
| 4 | Hjeltnessaeth <i>et al.</i> (1999) [15] | Prospective study | NA | 29 ADPKD versus 144 non- ADPKD | Single centre (Norway) | NA | 23 versus 18% | NA |

ADPKD, autosomal dominant polycystic kidney disease; NODAT, new-onset diabetes after transplantation; PTDM, post-transplant diabetes mellitus; NA, not available.

versus 7.4%, $P = 0.016$). In a multivariate analysis, ADPKD remained a significant risk factor with an OR of 2.87 ($P = 0.014$) for developing PTDM. A third retrospective study from the UK confirmed this association [9]. In this study, a total of 429 patients were reviewed, including 67 with ADPKD. The overall incidence of NODAT was 6.5% but was notably higher in patients with ADPKD (13.4%) than non-ADPKD patients (5.2%; $P < 0.01$). Although ADPKD patients were older, ADPKD remained a significant risk factor following multivariate analysis (OR 2.4). A fourth retrospective study from Spain albeit in Hepatitis C positive patients confirmed this association [11].

It is possible that the higher incidence of NODAT reported reflects the stress that an increased diabetogenic state places on top of a basal abnormality due to ADPKD itself. A prospective study to identify patients at risk of developing NODAT using a pre-transplant screening oral glucose tolerance test (OGTT) found that ADPKD was a significant risk factor for developing NODAT (RR 3) following multivariate analysis [10]. In this context, it is worth noting that increased insulin resistance in ADPKD patients with normal renal function compared with normal subjects had been reported in a small prospective study of 15 patients [16]. Conversely, a second study reported impaired insulin secretion in ADPKD patients with normal kidney function after an oral glucose load compared with healthy controls [17]. These findings suggest the possibility of insulin secretion or action being abnormal in ADPKD. Insulin resistance has been associated with an increase in membrane fluidity and abnormalities in erythrocyte Na/Li counter-transport [13, 18, 19]. How this links to polycystin function is unclear. On the other hand, the polycystin proteins have been shown to be expressed in pancreatic islet beta cells [20]. It is possible that they could regulate insulin secretion.

The relationship between glucose metabolism and ADPKD remains controversial (see Table 1). A recent study which investigated the association between pre-transplant metabolic syndrome and NODAT in 640 incident renal transplant recipients found significantly more ADPKD patients with metabolic syndrome but did not identify ADPKD as an independent risk factor in multivariate analysis; of interest, only pre-transplant high-density lipoprotein (HDL) was an independent predictor of NODAT in this cohort [13]. Other groups have also failed to confirm the association between PKD and PTDM/NODAT [12, 14, 15]. An early study by Fliser *et al.* [21] examined 29 patients with IgA glomerulonephritis, 29 patients with ADPKD at different stages of renal failure and matched healthy subjects. They reported that insulin resistance and concomitant hyperinsulinemia were present early in disease, irrespective of the aetiology of the primary renal disease. A recent cross-sectional study comparing 144 ADPKD patients with different degrees of blood pressure and renal function and 50 healthy controls failed to detect a significant difference in insulin resistance (HOMA index) between controls and subjects with ADPKD [22].

LIPID METABOLISM IN ADPKD

A link between abnormal lipid metabolism and PKD progression was first suggested from rodent models. In Han:

SPRD rats, a non-orthologous model of ADPKD, a high fat diet led to larger kidneys, higher renal fluid and cyst scores [23]. There is also evidence of abnormal lipid metabolism in *Pkd1* and *Pkd2* deficient mice. Notably, genes regulating apolipoprotein synthesis and transport (*ApoA1*, *ApoAIV* and *ApoB*) were upregulated in placental tissue and cystic kidneys resulting in increased apolipoprotein levels; these changes were correlated to alterations in activity of the nuclear hormone receptor, hepatocyte nuclear factor-4 [24]. In contrast, *apoA1*, a major component of the high-density lipoprotein complex, was shown to be significantly decreased in the polycystic kidneys of *Mxi-1* deficient mice [25]. Clinically, an inverse correlation between serum HDL-cholesterol levels and both the rate of kidney growth (as estimated by magnetic resonance total kidney volumes) and decline in glomerular filtration rate (GFR) (univariate analysis) was observed over a 6-year follow-up period in the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) cohort study [26]. The mechanism by which higher HDL levels are protective is unclear. HDL has potent anti-atherogenic effects mediated through its role in reverse-cholesterol transport. It may also exert anti-inflammatory actions through its known interactions with the sphingosine-1-phosphate receptor family and the Class B Type 1 scavenger receptor [26]. Whatever the precise mechanism, HDL represents a potentially modifiable factor in retarding kidney growth and renal function decline [27].

Oxidative modification of low-density lipoprotein (LDL) is an early event in atherosclerosis and is thought to play an important role in renal and vascular damage in chronic kidney disease (CKD) [28, 29]. Several experimental and clinical studies have shown that there is significant oxidative stress in early stage ADPKD prior to deterioration in renal function and development of hypertension [22, 30–32]. This increase in oxidative stress could contribute to kidney damage, dysregulation of lipid metabolism and endothelial dysfunction. Conceivably, the diseased kidney could directly to systemic vascular damage through oxidative modification of LDL.

Despite the finding of abnormal lipid metabolism in ADPKD models, a beneficial effect of statins on renal function in ADPKD patients remains unproven. In a short-term double-blind crossover study, 10 ADPKD patients with normal serum cholesterol levels were treated with 40 mg simvastatin or placebo daily in random order for 4 weeks with a 4-week washout period in between treatment phases [33]. Simvastatin treatment was associated with an increase in GFR (124 ± 4 – 132 ± 6 mL/min) and effective renal plasma flow (ERPF) (494 ± 30 – 619 ± 67 mL/min). A similar effect of lovastatin on renal blood flow was reported in male Han:SPRD rats [34]. In a second open-label study, 49 ADPKD patients were randomized to receive 20 mg pravastatin or standard care for 2 years [35]. This trial, however, showed no beneficial effect of pravastatin on renal function or urinary protein excretion at 2 years despite a significant fall in total serum cholesterol in pravastatin-treated patients. The effects of pravastatin on changes in renal volume and left ventricular mass index are being further investigated in a double-blind randomized placebo-controlled trial involving 107 children and young adults (age 8–22 years) over a 3-year study period (NCT00456365) [36].

Recently, glucosylceramide (GlcCer) levels were found to be elevated in ADPKD kidney tissues and inhibition of GlcCer synthesis showed surprising beneficial effects in inhibiting cystogenesis in three PKD mouse models (*PKD1*, *jck* and *pcy*) [37]. This could be a promising therapeutic strategy though it is unclear whether these changes are primary to polycystin mutation or secondary to cystic change.

RENAL CALCULI FORMATION IN ADPKD

Nephrolithiasis has been reported in up to 20% of patients with ADPKD [38]. The chemical composition of stones is most frequently that of uric acid and/or calcium oxalate. Apart from the distorted renal structure, metabolic factors are likely to play an important role in the pathogenesis of kidney stones.

URINARY CITRATE EXCRETION

Hypocitraturia has been noted to be a common metabolic derangement in patients with ADPKD and kidney stones with a reported incidence of 67% [38]. Grampsas [39] confirmed the high incidence of hypocitraturia in ADPKD especially in those with kidney stones (60%) and even in those without stones (49%). In a third study involving 125 ADPKD patients, the incidence of hypocitraturia and hypomagnesuria was increased in patients with or without kidney stones [40]. In the CRISP study, urinary citrate in ADPKD patients declined over time from baseline to Year 2 with no change in serum bicarbonate [26]. Conversely, urinary citrate excretion was significantly increased in heterozygous non-cystic male Han:SPRD rats compared to their wild-type littermates [41].

Citrate supplementation would therefore be a logical treatment to prevent stone formation in ADPKD. There could be additional benefits. For instance, administration of potassium citrate plus citric acid to Han:SPRD rats reduced the decline in GFR [42]. This could be related to abnormal renal handling of citrate and ammonia in this model [43]. How these findings relate to ADPKD has not been tested.

URINARY ACID EXCRETION

The majority of ADPKD patients have a urinary pH of <5.5 [38, 40, 44–46]. The molecular basis for this observation is unclear but could represent a compensation for the defect in urinary ammonia excretion secondary to a lower urine concentrating capacity. Of interest, an increase in apical Na^+/H^+ exchanger activity in principal cells derived from cortical collecting duct of the *orpk* mouse has been shown [47]. However, there is no consistent evidence that ADPKD patients suffer with metabolic alkalosis at different stages of disease [48].

URATE METABOLISM

A high incidence of gout in ADPKD patients has been noted implying that uric acid metabolism could be altered [49, 50].

To clarify the relationship between hyperuricaemia and gout in ADPKD, Mejias *et al.* [51] studied ADPKD patients, patients with proven gout and CKD, patients with gout and normal renal function, and patients with CKD without gout. They found that mean serum uric acid concentrations were higher in ADPKD patients than in controls and clinical gout was identified in 24% of ADPKD patients. Fractional excretion of uric acid and activity of hypoxanthine guanine phosphoribosyl transferase were, however, not different among the groups. A second study confirmed a higher incidence of hyperuricaemia and gouty arthritis in ADPKD compared with other kidney diseases but concluded that this was due to a greater reduction in urate excretion relative to the decline in renal function [52]. Uric acid renal excretion depends on the balance between glomerular filtration, tubular reabsorption and tubular secretion. In the CRISP cohort, ADPKD patients with larger kidneys had reduced renal blood flow despite normal GFR values; the increase in filtration fraction could impair uric acid secretion and increase uric acid reabsorption [53, 54]. Since urinary pH tends to be lower in PKD patients, the acid urine is likely to reduce urate clearance further by stimulating more active reabsorption [55].

In a retrospective analysis of 680 adult ADPKD patients followed up at a single centre, higher serum uric acid levels were associated with larger kidney volumes and increased ESRD hazard independent of gender, BMI and renal function suggesting that hyperuricaemia might itself play a role in ADPKD disease progression [56]. In contrast, serum uric acid was not associated with changes in total kidney volume or GFR decline in the CRISP study [26].

Other studies have reported normal urate handling and normal plasma urate levels in ADPKD patients with normal renal function [57, 58]. Intriguingly, a recent meta-analysis of 14 genome-wide association studies suggested that the genetic variability around the *PKD2* locus could contribute to serum uric acid concentrations at least in European populations [59]. However it is probable that these SNPs are functionally related to the urate transporter, ATP-binding cassette subfamily G, 2 (ABCG2) which is located next to *PKD2* in the same genomic region on chromosome 4 [60].

PHOSPHATE HANDLING

A study of patients with normal glomerular filtration rate found a high prevalence (38%) of hypophosphataemia in ADPKD [61]. Tubular phosphate reabsorption maximum and mean serum phosphate was lowest in ADPKD patients compared to non-ADPKD patients or healthy controls. Interestingly, the levels of fibroblast growth factor 23 (FGF23) were significantly higher (4-fold) in ADPKD whereas parathyroid hormone, 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels remained normal. In CKD, FGF23 secretion is thought to be triggered by phosphate retention as GFR decreases, serving as a counteracting mechanism to restore phosphate concentrations to the normal range [62]. However, this cannot explain the rise in FGF23 in ADPKD patients with normal GFR and suggests direct or indirect regulation by the polycystin

proteins on FGF23 secretion by osteocytes or its degradation. An alternative explanation for the phosphate leak in ADPKD is a functional defect in the Type II sodium/phosphate co-transporter (NaPi-2) [63]. In the Han:SPRD rat, rapid and progressive loss of NaPi-2 in kidney proximal tubules was noted leading to mild phosphaturia even with advancing renal failure in aged rats [64].

HAEMOGLOBIN AND ERYTHROPOIETIN

Several studies have reported higher levels of haemoglobin in ADPKD patients compared to patients with other forms of CKD. This is thought to be the consequence of increased erythropoietin production by cystic and interstitial cells [65, 66]. In transplanted patients, ADPKD was also independently associated with higher haemoglobin levels compared with other primary renal diagnoses; however, this association disappeared in patients who had undergone nephrectomy prior to transplantation [67]. The relative preservation of endogenous erythropoietin secretion in ADPKD might also explain differences in survival between ADPKD and other CKD patients. First an average ferritin of 100–800 ng/mL in ADPKD patients, has been shown to correlate with better survival whereas in non-ADPKD patients, the corresponding levels were 500–800 ng/mL [68]. Second, in PKD patients not receiving erythropoiesis stimulating agents (ESA), the association between haemoglobin and mortality was linear with a higher haemoglobin linked to better survival even when the haemoglobin concentration was >130 g/L. In contrast, a haemoglobin concentration >130 g/L was associated with a higher-risk of death in other CKD patients or ADPKD patients receiving ESA [69]. The increase in erythropoietin in ADPKD probably relates to chronic interstitial hypoxia since HIF-1 and HIF-2 expression in polycystin-1 deficient cells remain normally regulated by oxygen [70].

SUMMARY

In conclusion, a wide range of metabolic abnormalities have been reported as part of the clinical spectrum of ADPKD. However, there remains uncertainty as to the consistency of these findings in different populations and the precise underlying molecular mechanisms linking them to the genetic defects. We hope that this review will stimulate further clinical and scientific studies to answer these questions. An increased awareness of potential metabolic changes in these patients should improve their clinical management especially in reducing cardiovascular risk, the formation of renal calculi and the development of NODAT.

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CONFLICT OF INTEREST STATEMENT

None. The results presented in this paper have not been published previously in whole or part.

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