Urine albumin excretion and urine concentration capacity are better markers for disease severity in autosomal dominant polycystic kidney disease than glomerular filtration rate

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Abstract: Autosomal dominant polycystic kidney disease (ADPKD) is the most prevalent hereditary renal disease, characterized by cyst formation in the kidneys leading to end stage kidney failure. **Methods**: Included were 15 prevalent ADPKD patients (Ravine criteria). ADPKD patients were compared with 32 age- and gender-matched healthy controls, none of them had proteinuria, hypertension or evidence of hyperfiltration. Measured were blood pressure by ambulatory blood pressure monitoring, total renal volume (TRV) by magnetic resonance imaging, GFR by 99Tc DTPA. Twenty-four-hour urine was collected for volume and albumin excretion (UAE). Then all patients and control subjects underwent a standard prolonged water deprivation test. Urine and plasma osmolality were measured. The effect of a synthetic vasopressin analog (Desmopressin, Nasal Spray Solution, 0.01%) inhaled at the moment of maximal urine concentrating capacity was also studied. Data are given as mean [standard deviation]. Student's t-test (for normally distributed data) and Mann-Whitney test are used for statistical analysis. **Results**: Mean age was 30.5 [5.3] years in the ADPKD group, not significantly different from the controls with an average age of 28.8 [6.6] years (P=0.92). Mean serum creatinine was 1.1 [0.3] mg/dl for the ADPKD group and 1.0 [0.2] mg/dl for controls, P=0.19. The mean GFR was 128.2 [22.5] ml/min/1.73 m^2 in the ADPKD group, significantly higher than the controls with 102.5 [11.4] ml/min/1,73 m2, P=0.0001). Of the 15 patients, 9 patients had manifest hypertensive blood pressure measurements while 3 out of the rest had sporadic hypertension by ambulatory blood pressure monitoring. Moreover, ADPKD patients also had higher 24-hour urinary volumes, lower 24-hour urinary osmolarity, and higher urinary albumin excretion (UAE) than healthy controls. After 14 hours of water deprivation, ADPKD patients tended to have higher plasma osmolality (P=0.08) whereas urine osmolality was similar in ADPKD patients and controls (685 versus 669 mOsmol/kg; P=0.70). Maximal urine concentrating capacity was lower in ADPKD patients (735 versus 894 mOsmol/kg in controls; P,0.002). **Conclusions**: We can conclude that early ADPKD patients have marked renal abnormalities, including impaired maximal urine concentrating capacity brought out upon dehydration, increased UAE, despite modestly enlarged TRV and near-normal GFR. UAE and urine concentration function may thus be better markers for disease severity than GFR.
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Key Words: ADPKD, urinary albumin, urine concentration.

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most frequent hereditary kidney disease, affecting between 1 in 400 and 1 in 1000 individuals of the general population [1,2]. The growth of innumerable cysts in both kidneys causes progressive kidney dysfunction leading to end stage renal disease (ESRD) by the sixth decade in 50% of affected patients [3].

The disease is caused by mutations in the PKD1 (85% of cases) or the PKD2 gene (15% of cases). The disease course of ADPKD is characterized by high inter and intra-familial variability that hampers the prediction of disease progression [4].

Affected individuals may retain adequate renal function until their 9th decade, whereas others progress to ESRD by their 3rd decade. Genetic modifiers as well as environmental factors are likely to influence the disease course, although information on these factors is sparse and the currently known factors only account for a small proportion of the predictive power for prognosis [5-7].

In particular, glomerular filtration rate (GFR) remains stable for many decades in the early disease stages, when predicting disease progression would be most valuable for counseling ADPKD patients [8].

The diagnosis of ADPKD is usually based on the observation of kidney cysts by ultrasound in patients with positive family history for ADPKD [9]. However, ultrasound imaging has limited sensitivity in children and young adults, particularly those with PKD2 mutations, and thus ADPKD cannot be reliably excluded by ultrasound before the age of 30 years [9]. Furthermore molecular diagnosis by genetic testing has been hampered by the genetic complexity of ADPKD, and only 65% of ADPKD

patients exhibit definitive pathogenic (i.e. truncating) mutations [10].

Among most patients, renal function remains intact until the fourth decade of life. Once the glomerular filtration rate starts to decline, the average reduction is 4.4 to 5.9 mL/min per year [11].

Risk factors that have been identified for progressive renal disease in ADPKD include [7,12-20]:

- Genetic factors (PKD1 versus PKD2)
- Hypertension
- Early onset of symptoms including proteinuria and hematuria
- Male gender
- Increased kidney size and rate of kidney growth
- Increased left ventricular mass index
- Dipstick detectable proteinuria

Methods:

Included were 15 prevalent ADPKD patients (Ravine criteria). Patients were compared with 32 age- and gender-matched healthy controls, none of them had proteinuria, hypertension or evidence of hyperfiltration. An additional inclusion criterion for both groups was an estimated GFR (eGFR) ≥60 ml/min per 1.73 m^2 to exclude a renal urine concentrating defect that can be observed in participants with a low GFR.

Exclusion criteria were the use of medication that influences renal concentration capacity, such as diuretics and postmenopausal hormone therapy; history of diseases influencing renal concentration capacity, such as diabetes mellitus, diabetes insipidus, adrenal or thyroid deficiencies, or kidney diseases other than ADPKD; other factors that can influence renal concentration capacity such as menstruation, urinary tract infection, pregnancy, and active cardiovascular disease, which is a contraindication for DDAVP administration. A healthy individual was defined according the aforementioned criteria and had no evidence of CKD (eGFR ≥60 ml/min per 1.73 m^2, albuminuria <30 mg/d, and no plasma electrolyte abnormalities). This study was approved by our institutional review board. All participants gave written informed consent.

Study Protocol:

Measured were blood pressure by ambulatory blood pressure monitoring, total renal volume (TRV) by magnetic resonance imaging, GFR by 99Tc DTPA. Twenty-four-hour urine was collected for volume and albumin excretion (UAE). Then all patients and control subjects underwent a standard prolonged water deprivation test, based on the protocol originally described by Miller *et al.*[21]

The day before the water deprivation test, participants were not allowed to smoke or consume caffeine-containing products. Participants received a standard meal and were not allowed to eat or drink after 8 p.m. During an in-hospital visit the next day, urine specimens were collected every hour and blood samples were taken every 2 hours from 10 a.m. onward until urine osmolality became constant, defined as an increase in urine osmolality between two consecutive urine collections <30 mOsml/kg. Plasma osmolality was also measured.

The effect of a synthetic vasopressin analog (Desmopressin, Nasal Spray Solution, 0.01%) inhaled at the moment of maximal urine concentrating capacity was then studied (i.e. after reaching plateau of urine osmolality). Two hours after, blood and urine samples were again collected. Thereafter, participants were allowed to drink and eat *ad libitum*. The stopping criteria during the water deprivation test to ensure patient safety were as follows: reaching a body weight reduction >3% compared with body weight measured at 8 p.m. the day before, or a plasma sodium >150 mmol/L any time during the study.

Interpretation of a Water Deprivation Test [22]

According to the standard criteria, a water deprivation test is considered normal when urine osmolality is >800 mOsm/kg at plateau. Complete central nephrogenic diabetes insipidus can be expected in patients with urine osmolality <300 mOsm/kg at plateau and a >50% increase in urine osmolality after AVP administration. Partial central diabetes insipidus is expected in participants with a maximum urine osmolality between 300 and 800 mOsm/kg and a 9%–50% increase in urine osmolality after AVP administration. Complete renal diabetes insipidus is expected in participants with urine osmolality <300 mOsm/kg at plateau and a <9% increase in urine osmolality after AVP administration, whereas partial renal diabetes insipidus is suspected in participants with a maximum urine osmolality between 300 and 800 mOsm/kg and a <9% increase in urine osmolality after AVP administration.

Measurements

Standard biochemical evaluation was performed in fresh urine and plasma samples, using an autoanalyser. GFR was estimated with the Chronic Kidney Disease Epidemiology Collaboration equation [23]. Plasma and urine osmolality were measured directly using an Osmometer (Fresenius medical care, Germany).

Statistical Analyses

Parametric variables are expressed as mean ± SD. Values for differences between ADPKD patients and healthy controls were tested using a chi-squared

test for categorical data as well as a *t* test for parametrical and a Mann–Whitney *U*test for nonparametric continuous data. All analyses were performed using the SPSS statistical package (version 18.0; SPSS Inc, Chicago, IL). A two-sided *P* value <0.05 was considered statistically significant.

Table 1: Characteristics of ADPKD patients and healthy controls

Characteristics	ADPKD N = 15	Control N= 32	P<
Age (yr), mean ± SD	30.5 ± 5.3	28.8 ± 6.6	0.92
Men, n (%)	11 (73)	23(72)	0.90
Body mass index (Kg/m2)	24± 4	26 ±5	0.31
Hypertension, n (%) Office hypertension Ambulatory blood pressure monitoring Normotension	 9 (60) 3 (20) 3 (20)	 0 (0) 5 (15) 27 (85)	 0.0001
Smoker, n (%)	7 (46)	14 (43)	0.84
Serum creatinine, mg/dl, mean ±SD	1.1 ± 0.3	1.0 ± 0.2	0.19
Urinary albumin excretion (mg/day), range	29 (12-143)	8 (3-18)	0.001
Urine volume (llitre/24h), mean ± SD	2.3 ±0.72	1.6 ±0.60	0.05
Urine osmolality (mOsm/kg per 24h), mean ±SD	424 ±156	543 ±176	0.01
Total Renal Volume (cm3) Males Females	 487.5 ± 205 375 ± 167	 207 ± 41 161 ± 38	 0.001 0.001
Glomerular filtration rate (ml/min per 1.73 m2)	128.2 ± 22.5	102.5 ± 11.4	0.0001

Results:

Table 1 shows characteristics of ADPKD patients and healthy controls. Mean age was 30.5 ±5.3 years in the ADPKD group, not significantly different from the controls with an average age of 28.8 [6.6] years (P=0.92). Mean serum creatinine was 1.1 [0.3] mg/dl for the ADPKD group and 1.0 [0.2] mg/dl for controls, P=0.19. The mean GFR was 128.2 [22.5] ml/min/1.73 m^2 in the ADPKD group, significantly higher than the controls with 102.5 [11.4] ml/min/1,73 m^2, P=0.0001). Of the 15 patients, 9 patients had manifest hypertensive blood pressure measurements while 3 out of the rest had sporadic hypertension by ambulatory blood pressure monitoring. On the other hand, ADPKD patients had higher 24-hour urinary volumes, lower 24-hour urinary osmolarity, and higher urinary albumin excretion (UAE) than healthy controls.

Water deprivation test

Data are shown in table 2. After 14 hours of water deprivation, ADPKD patients tended to have higher plasma osmolality (P=0.08) whereas urine osmolality was similar in ADPKD patients and controls (685 versus 669 m Osmol/kg; P=0.70). Maximal urine concentrating capacity was lower in ADPKD patients (735 versus 894 m Osmol/kg in controls; P <0.002).

Table 2: 14 hour water deprivation test in both ADPKD and healthy controls

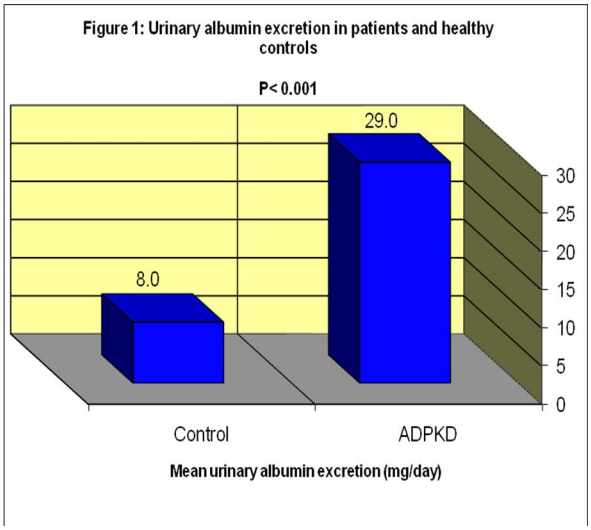
Characteristic	ADPKD	Control	P<
Plasma osmolality mOsmol/kg, mean ± SD	286 ± 5.5	281 ± 3.3	0.08
Urine osmolality mOsmol/kg, mean ±SD	685 ± 100	669 ± 71	0.70
Maximal urine concentrating capacity mOsmol/kg, mean ±SD	735 ± 90	894 ± 105	0.001

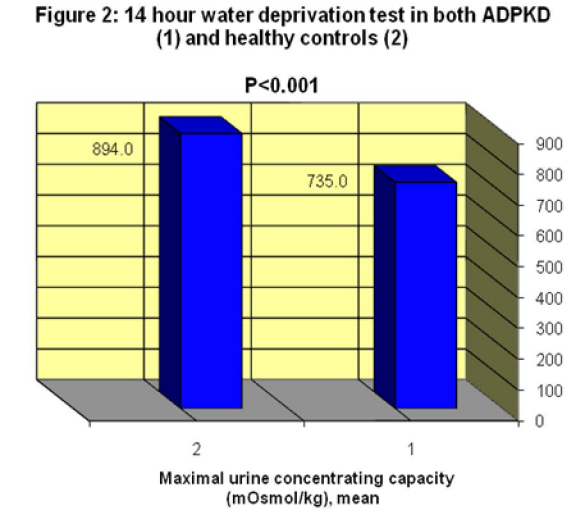
Discussion:

Autosomal dominant polycystic kidney disease (ADPKD) is the most prevalent inherited renal disease with an estimated prevalence of approximately 1 in 1000. The disease is characterized by pain, hematuria, and most importantly by progressive cyst formation in both kidneys, often leading to ESRD that usually occurs in the fourth to sixth decade of life [8].

The pathogenetic mechanisms responsible for cyst formation in ADPKD are complex [8]. Due to a genetic defect in the polycystin complex of the primary cilium, intracellular calcium concentration is reduced in cells of the collecting tube, which results in increased levels of intracellular cAMP [24]. cAMP is an important player in cyst formation, causing proliferation of tubular cells and chloride-driven fluid secretion into cysts [25].

Arginine vasopressin (AVP) is assumed to have a detrimental role in the pathogenesis of ADPKD. Production of cAMP by adenylyl cyclase is enhanced when AVP is bound to the vasopressin V2 receptor at the basolateral side of collecting tube cells, causing cyst enlargement via the aforementioned mechanisms [26].





Current treatment cannot prevent renal failure [27]. However, a better understanding of the pathophysiology of the disease and the availability of animal models identified promising candidate drugs for renal preservation [28]. When efficacy of these agents has been established, a pivotal question will be when to initiate such treatment. Given that ADPKD is a progressive condition, it seems most appropriate to initiate intervention as early in life as possible to delay or prevent long-term consequences, including renal failure and cardiac complications. On the other hand, ESRD occurs in approximately 50% of affected subjects [29], and it is not appropriate to expose those subjects that will not reach ESRD to excessive medical treatment to such an extent as to cause adverse events, especially because all candidate drugs have considerable side effects. GFR is believed to be stable for a long period, despite progression of renal anatomical abnormalities, because of compensatory hyperfiltration. GFR is therefore assumed not to be representative of disease severity [30].

Total renal volume (TRV) has been proposed as a surrogate marker for disease progression [30]. However, despite a significant overall association, there are subjects with a high TRV but normal renal function [31].

Because of these reasons, it will be important to discover markers that identify ADPKD patients who will develop rapid disease progression. In such patients, therapy could be instituted in an early phase.

In the study presented here, we were able to compare young adult ADPKD patients (mean age was 30.5 ±5.3 years) with age- and gender-matched healthy controls to identify early renal abnormalities in such patients.

Our findings clearly showed that hypertension was significantly more prevalent among ADPKD patients compared to normal healthy subjects (80 % vs 15% respectively, P=0.0001).

Similar results were found by Ecder and Schrier who reported that hypertension is a common early finding in ADPKD, occurring in 50 to 70 % of cases before any significant reduction in glomerular filtration rate within an average age onset of 30 years of age [32].

Increased activity of the renin-angiotensin system and extracellular volume expansion are often present early in ADPKD (ie, prior to elevation in the serum creatinine) and may play an important role in the rise in blood pressure [33].

It has been suggested that cyst expansion, leading to focal areas of renal ischemia and enhanced renin release, is largely responsible for at least the initial rise in blood pressure [34].

In addition, GFR was found to be higher among ADPKD patients compared to normal healthy subjects (128.2 ± 22.5 vs 102.5 ± 11.4 ml/min per 1.73 m^2 respectively, P=0.0001).

These results are supported by Franz and Reubi [35] who demonstrated that the phenomenon of compensatory hyperfiltration occurs in ADPKD patients and can explain why GFR stays stable for several years and then rapidly declines.

Neurohumoral activation has been described to occur early in ADPKD [36], and efferent renal vasoconstriction related to increased neurohumoral activation is characteristic of other hypertensive conditions [37].

It was hypothesized that this hemodynamic profile indicates hyperfiltration. The loss of nephrons due to the disease process results in a decreased effective renal plasma flow, whereas compensatory GFR goes up in the remnant nephrons [30].

Dimitrakov *et al.* [38] conducted a study on patients with ADPKD and they suggested hyperfiltration on the basis of measurement of creatinine clearance and serum B2-microglobulin levels. Another study described a high GFR in very young ADPKD patients (9.8 ± 5.9 years), as measured with a technetium 99m DTPA single-injection technique [39].

Moreover, we found that ADPKD patients had higher urinary albumin excretion than healthy controls. Chapman et al. [5] reported that dipstick-detectable proteinuria occurs in < 18% of ADPKD patients with most demonstrating < 1 g/24 h. They also reported that microalbuminuria is more common than proteinuria, occurring in 35% of ADPKD individuals. Also, albuminuria has been described to occur at early stages of the disease [40].

Proteinuria has been identified as a key factor for the prognosis of renal disorders[41], and the occurrence of proteinuria has also been evaluated in ADPKD patients, where it seems to be associated with a more aggressive course of the disease [42].

Massive alterations of the tubulointerstitium occur during cyst development, and it is therefore important to address the role of impaired tubular function in the development of proteinuria and albuminuria. Net urinary excretion of filtered proteins critically depends on the structural integrity of the proximal tubule, where most of the proteins are reabsorbed by endocytosis [43].

In patients of ADPKD; nephrotic range proteinuria, with or without an accompanying decline in renal function, is unusual and needs to be investigated further to exclude coexisting glomerular disease. Moreover, proteinuria hastens the progression of ADPKD to ESRD if it is untreated [44].

The reason of proteinuria in ADPKD is still unclear; however possible explanation would be damage to capillary endothelium and glomerulosclerosis due to hypertension [45].

ADPKD patients with microalbuminuria may be at increased risk for cardiovascular morbidity and mortality-the most common cause of death in ADPKD patients [46].

Given that hypertension in ADPKD is mediated by the activation of the renin-angiotensin-aldosterone axis [47], angiotensin- converting enzyme inhibition therapy may provide benefits in reducing the rate of progression of renal disease and reducing the level of proteinuria independent of the level of systemic blood pressure. If the reabsorption of urinary protein itself contributes to tubular interstitial disease [41], then the reduction of proteinuria may provide renal protection.

In our ADPKD patients, 24-hour urinary volume was higher and 24-hour urinary osmolarity was lower compared with normal controls. These findings are consistent with the decreased concentrating capacity that has been described in these patients [48].

It is clinically well acknowledged that ADPKD patients cannot concentrate their urine well [49]. This effect can be observed at a young age [50-52]. The mechanism behind this decreased urine concentrating capacity is not known, but it is suggested to have a renal origin. The impaired ability to reabsorb water could be secondary to cyst induced abnormality in renal architecture, leading to an impaired medullary osmotic gradient [48] or to insensitivity to AVP (e.g., due to a receptor defect) [24,53]. Theoretically, a lower renal concentrating capacity could also have a central cause (i.e., impaired AVP release by the pituitary gland).

Given this background, it was hypothesized that ADPKD patients have an impaired renal concentrating capacity, leading to an increase in plasma AVP levels as a compensatory response. To test this hypothesis, we performed a water deprivation test in ADPKD patients early in their disease, and in age- and sex-matched healthy controls, in which we measured urine and plasma osmolality. In addition, we studied the effect of an injection of a syntheticAVP analog, desmopressin (DDAVP), at the moment of maximal urine concentrating capacity to determine whether an impaired hypothalamic response is involved.

Our findings of an impaired concentrating mechanism, brought out upon dehydration in ADPKD patients may help shed light on a pathophysiologic mechanism causing disease progression in ADPKD. It was previously hypothesized [54] that cysts are formed due to a genetic defect, leading to disturbance of medullary architecture and consequently to an impaired urine concentrating capacity early in the disease when kidney function is still normal. As compensatory mechanism AVP levels increase to maintain fluid balance, AVP in turn causes increased levels of cAMP in collecting tube cells [55], leading to proliferation of tubular cells and chloride- driven fluid secretion into cysts [25,56].

Thus, a vicious circle may arise leading to further cyst formation, cyst growth and kidney function decline. This hypothesis is supported by the fact that AVP was found to be increased at normal

kidney function in our study and that copeptin, a surrogate for AVP, was shown to predict kidney function decline in another study.

Strengths of our study are that we included ADPKD patients and age- and sex-matched healthy controls with similar kidney function. This allowed us to conclude whether differences between ADPKD patients and healthy controls were due to the disease process itself, and not due to differences in age, sex distribution, or kidney function. These latter factors have been shown to influence maximal urine concentrating capacity [57-61].

Second, we measured maximal endogenous urine concentrating capacity, as well as the reaction to DDAVP administration. By administering DDAVP, a central component contributing to decreased maximal urine concentrating capacity could be made unlikely.

We acknowledge that this study has limitations. First, a relatively small number of ADPKD patients and healthy controls were included. Second, we didn't measure AVP and copeptin concentrations. Finally, we think that it would be better to follow up these patients to see whether albuminuria and impaired maximal urine concentration capacity correlate with disease progression.

In conclusion, already at young adult age, ADPKD patients have marked renal abnormalities including impaired maximal urine concentrating capacity brought out upon dehydration, increased UAE, despite only modestly enlarged kidneys and a near-normal GFR. UAE and urine concentration function may thus be better markers for disease severity than GFR.

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