Vasopressin, Copeptin, and Renal Concentrating Capacity in Patients with Autosomal Dominant Polycystic Kidney Disease without Renal Impairment

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Summary

Background and objectives 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. It is clinically acknowledged that ADPKD patients have impaired urine concentrating capacity, but the mechanism behind this observation is unknown.

Design, setting, participants, & measurements Fifteen ADPKD patients (estimated GFR ≥60 ml/min per 1.73 m²) and 15 age- and sex-matched healthy controls underwent a standard prolonged water deprivation test in which urine and plasma osmolality, vasopressin, and copeptin were measured. The effect of a synthetic vasopressin analog (desmopressin) injected at the moment of maximal urine concentrating capacity was also studied.

Results After 14 hours of water deprivation, ADPKD patients tended to have higher plasma osmolality (P=0.07) and significantly higher vasopressin and copeptin levels (both P<0.05), whereas urine osmolality was similar in ADPKD patients and controls (710 versus 742 mOsmol/kg; P=0.61). Maximal urine concentrating capacity was lower in ADPKD patients (758 versus 915 mOsmol/kg in controls; P<0.001). At maximal urine concentrating capacity, plasma osmolality, vasopressin, and copeptin levels were significantly higher in ADPKD patients. The median increase in urine osmolality after desmopressin administration in ADPKD patients was less than in healthy controls.

Conclusions Already early in their disease, ADPKD patients have impaired maximal urine concentrating capacity brought out upon dehydration, with no evidence of impaired hypothalamic response. To maintain fluid balance, vasopressin concentration increases, which is hypothesized to play a role in ADPKD disease progression.

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease, with an estimated prevalence of approximately 1 in 1000. ADPKD is characterized by progressive bilateral cyst formation in the kidneys, leading to pain, hematuria, and end stage kidney failure that usually occurs in the fourth to sixth decade of life (1).

The pathogenetic mechanisms responsible for cyst formation in ADPKD are complex (1). 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 (2–4). cAMP is an important player in cyst formation, causing proliferation of tubular cells and chloride-driven fluid secretion into cysts (5).

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 (6). In line with these assumptions are experimental studies showing that a vasopressin V2 receptor antagonist decreases the rate of cyst formation (7–9). Clinical trials are ongoing to examine the effect of vasopressin V2 receptor antagonists in ADPKD patients (10).

Despite this alleged pivotal role of AVP in ADPKD, surprisingly little is known about AVP levels in ADPKD patients. It is, however, clinically well acknowledged that ADPKD patients cannot concentrate their urine well (11). This effect can be observed at a young age (12–14). 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 (15) or to insensitivity to AVP (e.g., due to a receptor defect) (4,16). Theoretically, a lower renal concentrating capacity
could also have a central cause (i.e., impaired AVP release by the pituitary gland).

Given this background, we 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 as well as plasma concentrations of AVP and copeptin (part of the precursor hormone of AVP). In addition, we studied the effect of an injection of a synthetic AVP analog, desmopressin (DDAVP), at the moment of maximal urine concentrating capacity to determine whether an impaired hypothalamic response is involved.

Materials and Methods

Study Population

ADPKD patients with a diagnosis based on the criteria of Ravine et al. (17) and healthy controls aged between 18 and 65 years were eligible for this study. An additional inclusion criterion for both groups was an estimated GFR (eGFR) ≥60 ml/min per 1.73 m² to exclude a renal urine concentrating defect that can be observed in participants with a low GFR (18). Exclusion criteria were as follows: 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 smoking, menstruation, urinary tract infection, pregnancy, and consumption of ≥4 alcohol beverages per day; and active cardiovascular disease, which is a contraindication for DDAVP administration. Healthy controls were matched for age (within 5 years) and sex with ADPKD patients. A healthy individual was defined according to the aforementioned criteria and had no evidence of CKD (eGFR ≥60 ml/min per 1.73 m², albuminuria <30 mg/d, and no plasma electrolyte abnormalities). This study was approved by our institutional review board and was performed in adherence to the Declaration of Helsinki. All participants gave written informed consent.

Study Protocol

Before the water deprivation test, urine was collected for 24 hours and blood was drawn for measurement of albuminuria, creatinine clearance, AVP, and copeptin. Eligible ADPKD patients and healthy controls underwent a standard prolonged water deprivation test, based on the protocol originally described by Miller et al. (19). 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 6 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 8 a.m. onward until urine osmolality became constant, defined as an increase in urine osmolality between two consecutive urine collections <30 mOsm/l/kg. After reaching this plateau, participants received an intramuscular injection of 2 µg of DDAVP. Two hours after injection, 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 6 a.m. the day before, or a plasma sodium >150 mmol/L any time during the study.

Interpretation of a Water Deprivation Test

According to the standard criteria, a water deprivation test (19,20) 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 DDAVP 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 DDAVP 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 DDAVP 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 DDAVP administration.

Measurements

Standard biochemical evaluation was performed in fresh urine and plasma samples, using a Roche Modular Autoanalyser (Hitachi, Tokyo, Japan). GFR was estimated with the Chronic Kidney Disease Epidemiology Collaboration equation (21). Plasma and urine osmolality were measured directly via determination of freezing point depression using an Osmometer (Arkray, Kyoto, Japan), with a variation coefficient <1.0%.

Blood for plasma AVP measurement was taken into a chilled syringe, placed in a chilled lithium heparin container, and immediately centrifuged at 4°C and stored at −80°C until assay. AVP was measured by RIA after an extraction using ODS-silica (DiaSorin, Stillwater, MN) in the General Clinical Laboratory of the IJsselland Hospital (Capelle aan de IJssel, The Netherlands). The assay range was between 0.2 and 4.7 pg/ml, with a sensitivity of 0.2 pg/ml with 2.5 ml of plasma. The average duplo coefficients of variation were 4.3% for the low range (0.2-0.4 pg/ml), 4.7% for the intermediate range (0.4-1.0 pg/ml), and 3.5% for the high range (1.0-8.1 pg/ml), respectively.

Plasma samples for copeptin measurement were taken into EDTA tubes, and the peptide was measured using a sandwich immunoassay (B.R.A.H.M.S. AG, Hennigsdorf/Berlin, Germany). The lower limit of detection was 0.4 pmol/L and the functional assay sensitivity (interassay coefficient of variation <20%) was <1 pmol.

Statistical Analyses

A power analysis was performed to determine how many participants were to be included in this study. The literature provides no data on AVP levels in ADPKD patients at an early stage of their disease, the primary parameter of interest. We therefore powered this study based on maximal urine concentrating capacity of 812±144 mOsmol/kg in healthy
individuals and 680±186 mOsmol/kg in ADPKD patients (15). These data, adopting a 5% two-sided α and 80% power, indicated that at least 15 healthy participants and 15 ADPKD patients were needed to show a significant difference in urine concentrating capacity between ADPKD patients and healthy participants.

Parametric variables are expressed as mean ± SD, whereas nonparametric variables are given as median (interquartile range). P 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 nonparametrical continuous data. To test correlations between AVP and copeptin, both variables were log-normalized and Pearson’s regression analysis was used. 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.

Results

Characteristics of the participating patients and healthy controls are presented in Table 1. Fifteen ADPKD patients and 15 age- and sex-matched healthy controls were studied. Importantly, ADPKD patients and healthy controls had similar kidney function, but albuminuria was higher in ADPKD patients. ADPKD patients had similar BP compared with healthy controls, but used antihypertensive medications more often. Per protocol, none of the participating participants used diuretics. Lastly, AVP and copeptin levels were higher in ADPKD patients compared with healthy controls but not significantly.

Table 2 shows the results of the prolonged water deprivation test. All subjects completed the water deprivation test without any complications (i.e., none of the stopping criteria were met).

At 8:00 a.m. (after 14 hours of water deprivation), ADPKD patients tended to have higher plasma osmolality (P=0.07) and significantly higher plasma AVP and copeptin levels compared with healthy controls (P=0.03 and P=0.04, respectively), whereas urine osmolality was not different between the two study groups at this time point (P=0.61). The higher plasma osmolality at 8:00 a.m. in ADPKD patients was primarily due to higher plasma urea levels (P=0.002), with plasma sodium levels being comparable between both study groups (P=1.00).

Maximal urine concentrating capacity was reached after a median of 16 hours in ADPKD patients and 17 hours in healthy controls (P=0.02). Maximal urine concentrating capacity was significantly lower in ADPKD patients compared with healthy controls (P<0.001) (Table 2, Figure 1). The difference in maximal urine osmolality between ADPKD patients and healthy controls was related to a difference in urine urea concentration, whereas urine sodium concentration was not different between both study groups (P=0.25).

Nine of 15 ADPKD patients did not reach a urine osmolality >800 mOsmol/kg, whereas this was the case in only 2 of 15 healthy controls (60% versus 13%; P=0.03). A significant difference was found in maximal urinary concentrating capacity between ADPKD patients taking antihypertensive drugs (697±96 mOsmol/kg) and normotensive ADPKD patients (826±60 mOsmol/kg; P=0.009). Maximal urinary concentrating capacity was significantly lower in normotensive ADPKD patients (826±60 mOsmol/kg) compared with healthy controls (915±91 mOsmol/kg; difference P=0.03). At the time point of maximal urine concentrating capacity, ADPKD patients had significantly higher plasma osmolality as well as higher plasma AVP and copeptin levels (P=0.02, P=0.004, and P=0.01, respectively) (Figure 2).

After DDAVP injection, median urine osmolality increased slightly in ADPKD patients (3.2%; interquartile range, 1.2%–7.7%; P=0.009) as well as healthy controls (12.0%; interquartile range, 5.8%–17%; P=0.002), but significantly less in ADPKD patients (difference P<0.02). Only two of the nine ADPKD patients that had a maximal urine concentrating capacity <800 mOsmol/kg showed a >9% increase in urine osmolality after DDAVP injection, whereas such a rise was observed in both healthy controls that had not reached a urine osmolality >800 mOsmol/kg on thirsting. Plasma osmolality and copeptin concentration

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ADPKD Patients (n=15)</th>
<th>Healthy Controls (n=15)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>36±15</td>
<td>35±12</td>
<td>0.93</td>
</tr>
<tr>
<td>Male (%)</td>
<td>47</td>
<td>47</td>
<td>1.00</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27±5</td>
<td>25±4</td>
<td>0.33</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>100±7</td>
<td>96±21</td>
<td>0.59</td>
</tr>
<tr>
<td>Using antihypertensives (%)</td>
<td>53</td>
<td>0</td>
<td>0.001</td>
</tr>
<tr>
<td>Estimated GFR (ml/min per 1.73 m²)</td>
<td>100±23</td>
<td>104±12</td>
<td>0.62</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min per 1.73 m²)</td>
<td>116±35</td>
<td>117±19</td>
<td>0.97</td>
</tr>
<tr>
<td>Urine volume (L/24 h)</td>
<td>2.00±0.65</td>
<td>2.20±0.99</td>
<td>0.63</td>
</tr>
<tr>
<td>Urine albumin (mg/24 h)</td>
<td>30.0 (16.0–124.0)</td>
<td>3.0 (2.0–5.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urine osmolality (mOsmol/kg per 24 h)</td>
<td>548±149</td>
<td>495±209</td>
<td>0.45</td>
</tr>
<tr>
<td>Plasma arginine vasopressin (pg/ml)</td>
<td>1.34 (0.25–3.07)</td>
<td>0.87 (0.28–2.38)</td>
<td>0.19</td>
</tr>
<tr>
<td>Plasma copeptin (pmol/L)</td>
<td>8.92 (0.66–21.86)</td>
<td>6.08 (0.92–10.79)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

ADPKD patients and healthy controls were age and sex matched. Data are given as mean ± SD for parametric data or median (interquartile range) for nonparametric data. Significance was tested using a chi-squared test, t test, or Mann–Whitney U test, when appropriate. ADPKD, autosomal dominant polycystic kidney disease.
Table 2. Characteristics of ADPKD patients and age- and sex-matched healthy controls at 8:00 a.m. (after 14-hour water deprivation), when reaching plateau (increase in urinary osmolality between two consecutive urine collections <30 mOsmol/kg), and after desmopressin administration during a standard prolonged water deprivation test

<table>
<thead>
<tr>
<th></th>
<th>ADPKD Patients (n=15)</th>
<th>Healthy Controls (n=15)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:00 a.m. (14-h water deprivation)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>plasma osmolality (mOsmol/kg)</td>
<td>285±5</td>
<td>282±3</td>
<td>0.07</td>
</tr>
<tr>
<td>plasma sodium (mmol/L)</td>
<td>141.2±1.6</td>
<td>141.2±1.0</td>
<td>1.00</td>
</tr>
<tr>
<td>plasma urea (mmol/L)</td>
<td>6.5±1.9</td>
<td>4.7±1.0</td>
<td>0.002</td>
</tr>
<tr>
<td>urine osmolality (mOsmol/kg)</td>
<td>710±103</td>
<td>742±216</td>
<td>0.61</td>
</tr>
<tr>
<td>urine sodium (mmol/L)</td>
<td>111.4±41.0</td>
<td>103.9±41.7</td>
<td>0.75</td>
</tr>
<tr>
<td>urine urea (mmol/L)</td>
<td>333±390</td>
<td>366±143</td>
<td>0.46</td>
</tr>
<tr>
<td>plasma arginine vasopressin (pg/ml)</td>
<td>1.08 (0.66–3.75)</td>
<td>0.43 (0.40–0.81)</td>
<td>0.03</td>
</tr>
<tr>
<td>plasma copeptin (pmol/L)</td>
<td>14.85 (4.92–18.68)</td>
<td>8.48 (2.90–9.37)</td>
<td>0.04</td>
</tr>
<tr>
<td>Plateau (maximal urinary concentrating capacity)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>plasma osmolality (mOsmol/kg)</td>
<td>285±4</td>
<td>282±3</td>
<td>0.02</td>
</tr>
<tr>
<td>plasma sodium (mmol/L)</td>
<td>141.5±1.8</td>
<td>141.0±1.5</td>
<td>0.39</td>
</tr>
<tr>
<td>plasma urea (mmol/L)</td>
<td>6.5±1.9</td>
<td>4.6±0.9</td>
<td>0.002</td>
</tr>
<tr>
<td>urine osmolality (mOsmol/kg)</td>
<td>758±103</td>
<td>915±91</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>urine sodium (mmol/L)</td>
<td>138.7±46.7</td>
<td>119.4±36.5</td>
<td>0.25</td>
</tr>
<tr>
<td>urine urea (mmol/L)</td>
<td>312±87</td>
<td>400±102</td>
<td>0.02</td>
</tr>
<tr>
<td>plasma arginine vasopressin (pg/ml)</td>
<td>1.26 (0.94–2.58)</td>
<td>0.47 (0.36–1.06)</td>
<td>0.004</td>
</tr>
<tr>
<td>plasma copeptin (pmol/L)</td>
<td>14.74 (7.47–18.96)</td>
<td>4.62 (3.42–7.84)</td>
<td>0.01</td>
</tr>
<tr>
<td>2 h after desmopressin admin.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>plasma osmolality (mOsmol/kg)</td>
<td>285±4</td>
<td>282±3</td>
<td>0.03</td>
</tr>
<tr>
<td>plasma sodium (mmol/L)</td>
<td>141.5±1.6</td>
<td>141.9±1.9</td>
<td>0.54</td>
</tr>
<tr>
<td>plasma urea (mmol/L)</td>
<td>6.6±1.8</td>
<td>4.8±0.9</td>
<td>0.002</td>
</tr>
<tr>
<td>urine osmolality (mOsmol/kg)</td>
<td>790±99</td>
<td>1015±114</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>urine sodium (mmol/L)</td>
<td>141.1±47.5</td>
<td>120.1±45.1</td>
<td>0.76</td>
</tr>
<tr>
<td>urine urea (mmol/L)</td>
<td>280±56</td>
<td>405±110</td>
<td>0.001</td>
</tr>
<tr>
<td>plasma arginine vasopressin (pg/ml)</td>
<td>1.7 (1.13–2.41)</td>
<td>0.92 (0.72–2.15)</td>
<td>0.07</td>
</tr>
<tr>
<td>plasma copeptin (pmol/L)</td>
<td>17.01 (7.94–17.78)</td>
<td>7.75 (3.81–8.80)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Data are given as mean ± SD for parametric data or as median (interquartile range) for nonparametric data. Significance was tested using a t test or Mann–Whitney U test, when appropriate. ADPKD, autosomal dominant polycystic kidney disease.

were significantly higher in ADPKD patients after DDAVP injection compared with healthy controls (P=0.03 and P=0.04, respectively) and AVP tended to be higher in ADPKD (P=0.07). Individual responses to the water deprivation test are shown in Supplemental Figure 1.

Measurements of AVP and copeptin yielded similar results during the entire water deprivation test (Table 2). Moreover, significant associations were found between plasma AVP and copeptin levels at 8:00 a.m. (R²=0.58, P<0.001), plateau (R²=0.58, P<0.001), and 2 hours after DDAVP administration (R²=0.40, P<0.001). Plots showing the associations between AVP and copeptin are given in Figure 3.

Total kidney volume (TKV) of 10 patients based on magnetic resonance imaging was available, with a median of 936 ml (interquartile range, 849–1614). Associations (R²) of TKV with AVP and copeptin in these 10 patients were 0.47 (P=0.03) and 0.22 (P=0.17), respectively.

Discussion

In this study, we performed a standard prolonged water deprivation test in 15 ADPKD patients and 15 age- and sex-matched healthy controls and measured AVP and copeptin levels. Our findings of an impaired concentrating mechanism, brought out upon dehydration, in ADPKD patients are in agreement with the literature (12–15,22,23). It was also emphasized that this impaired concentrating capacity was already present early in the disease course (12–14). Gabow et al. observed that cyst number and size, and remaining volume of normal parenchyma were associated with greater impairment of urine concentrating capacity (15); thus, the impaired urine concentrating capacity is thought to be caused by an impaired medullary osmotic gradient due to distorted renal architecture by cyst formation. There are important differences between this study and the previously performed studies. All previous studies measured urine osmolality at a fixed time period after water deprivation (and concurrent DDAVP administration in most of them), whereas we measured urine osmolality in consecutively collected urine samples and studied the effect of DDAVP administration when participants had reached maximal endogenous concentrating capacity. This procedure allows us to study whether a central component is involved when impaired renal concentrating capacity is found. Furthermore, unlike the previous studies, we measured AVP and copeptin concentrations under the standardized circumstances of dehydration to test the consequences of the impaired concentrating mechanism in view of the suggested unfavorable long-term effects of increased AVP concentration.
After 14 hours of water deprivation, plasma osmolality was significantly higher in ADPKD patients compared with healthy controls with similar age, sex distribution, and kidney function. Plasma AVP was also increased at that time point, whereas urine osmolality in these patients was still similar to urine osmolality in healthy controls. AVP seemed to increase to maintain fluid balance. Maximal urine concentrating capacity was impaired in the ADPKD patients, with 9 of the 15 patients not reaching a urine osmolality >800 mOsmol/kg. At the time point of maximal urine concentrating capacity, ADPKD patients again had higher plasma osmolality and higher AVP. DDAVP administration increased urine osmolality slightly in ADPKD patients, with only two of the nine patients showing a >9% increase in urine osmolality after DDAVP injection. Importantly, the median increase in urine osmolality after DDAVP administration in ADPKD patients was less than in healthy controls. These data should be interpreted as an impaired renal concentrating capacity with no evidence for a central component (i.e., impaired AVP release by the pituitary gland).

AVP is assumed to have a specific detrimental role in the pathogenesis of ADPKD. Despite this alleged pivotal role of AVP, surprisingly little is known about AVP levels in ADPKD patients. Data have shown AVP levels to be increased in participants with impaired kidney function due to non-ADPKD kidney disease (24). To our knowledge, only two studies have measured AVP levels in ADPKD patients and both showed increased AVP levels compared with healthy controls (25,26). To note, both studies included ADPKD patients with impaired kidney function. We therefore corroborate these findings, but extend the present knowledge on AVP levels in ADPKD by showing that AVP levels are already elevated in the early stages of the disease, because ADPKD patients and healthy controls had similar kidney function in our study.

The increase in AVP levels should be interpreted as a compensatory mechanism to maintain fluid balance. The fact that there are only limited data on AVP in ADPKD may be because AVP is difficult to measure due to its small size, binding to platelets, and very short ex vivo t1/2 (27,28). An assay was recently developed to measure copeptin (29). Copeptin is a part of the precursor of AVP, preprovasopressin, and has been suggested to be a relatively easy to measure, more stable (ex vivo), and reliable marker of AVP secretion (30). We therefore also measured copeptin in this study. Results with respect to copeptin during the water deprivation test closely mimic the results with respect to AVP. Moreover, significant associations were found between copeptin and AVP concentrations during all three time points on which these variables were measured. Copeptin seems therefore a reliable substitute for AVP in participants with ADPKD. Interestingly, copeptin has recently been investigated in several epidemiologic studies, among others in ADPKD patients (20,31–33) (W.E. Boertien et al., unpublished observations). In a cross-sectional
Study in 102 ADPKD patients, we found that copeptin levels were associated with various markers of disease severity, among which albuminuria, GFR, renal blood flow, and total renal volume (33). In a prospective study in 79 ADPKD patients, we subsequently showed that baseline copeptin levels were associated with faster kidney function decline when assessed as the change in either iothalamate clearance during short-term follow-up or eGFR during long-term follow-up (W.E. Boertien et al., unpublished observations). From these studies, it was not clear whether copeptin levels are higher in ADPKD patients compared with healthy controls, nor whether a rise in copeptin precedes disease progression or is merely a marker of impaired kidney function. This study, in which copeptin levels were measured under standardized circumstances, provides this information and shows that copeptin levels are already elevated in ADPKD patients with normal kidney function.

Our findings may help shed light on a pathophysiologic mechanism causing disease progression in ADPKD. We previously hypothesized (33) 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 influences maximal urinary concentrating capacity. Per protocol TKV in this study. An association of TKV with AVP and copeptin levels could therefore only be assessed in 10 patients. TKVs used in our association were measured approximately 3 years before this study. However, in a previous study (33), we showed that a higher AVP was independently associated with higher copeptin levels. Last, we observed a significant difference in urinary concentrating capacity between ADPKD patients taking antihypertensive drugs and normotensive ADPKD patients. An extensive literature search did not provide any evidence that antihypertensive medication (besides diuretics) can influence maximal urinary concentrating capacity. Per protocol, the use of diuretics was not allowed. We interpret this difference therefore as being the result of the fact that ADPKD patients that are hypertensive have more severe disease, and consequently also have more impaired urinary concentrating capacity. To note, we also observed a significant difference in urinary concentrating capacity between normotensive ADPKD patients and healthy controls. This strengthens our findings that patients still early in their disease have an impaired urinary concentrating capacity.

In conclusion, ADPKD patients already have impaired urine concentrating capacity, brought out upon dehydration, in the early stage of their disease. This study shows that a central component in this abnormality is unlikely. Furthermore, we found that AVP and copeptin levels are
already elevated after 14 hours of dehydration in this early disease stage, and thus precede kidney function decline in ADPKD patients. In cases in which AVP is indeed causally linked to cyst formation, cyst growth, and kidney function decline, these data provide support for a pathophysiological concept that may help explain disease progression in ADPKD.

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Disclosures

None.

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