Autosomal dominant polycystic kidney disease
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Tubular secretion of creatinine in Autosomal Dominant Polycystic Kidney Disease: Consequences for cross-sectional and longitudinal performance of kidney function estimating equations

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ABSTRACT

Background
Autosomal dominant polycystic kidney disease (ADPKD) is characterized by renal tubular cell proliferation and dedifferentiation, which may influence tubular secretion of creatinine (CCr(TS)).

Study Design
Diagnostic test study.

Setting & Participants
We therefore investigated CCr(TS) in patients with ADPKD and controls and studied consequences for the performance of glomerular filtration rate (GFR) estimating equations.

Index & Reference Tests
In patients with ADPKD and healthy controls, we measured GFR as $^{125}$I-iothalamate clearance while simultaneously determining creatinine clearance.

Other Measurements
24-hour urinary albumin excretion.

Results
In 121 patients with ADPKD (56% men; mean age, 40 ± 11 [SD] years) and 215 controls (48% men; mean age, 53 ± 10 years), measured GFR (mGFR) was 78 ± 30 and 98 ± 17 mL/min/1.73 m², respectively, and CCr(TS) was 15.9 ± 10.8 and 10.9 ± 10.6 mL/min/1.73 m², respectively (P < 0.001). The higher CCr(TS) in patients with ADPKD remained significant after adjustment for covariates and appeared to be dependent on mGFR. Correlation and accuracy between mGFR and CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) estimated GFR (eGFR) were 0.95 and 99%, respectively; between mGFR and MDRD (Modification of Diet in Renal Disease) Study eGFR, they were 0.93 and 97%, respectively. Values for bias, precision, and accuracy were similar or slightly better than in controls. In addition, change in mGFR during 3 years of follow-up in 45 patients with ADPKD correlated well with change in eGFR.

Limitations
Cross-sectional, single center.

Conclusions
CCr(TS) in patients with ADPKD is higher than that in controls, but this effect is limited and observed at only high-normal mGFR. Consequently, the CKD-EPI and MDRD Study equations perform relatively well in estimating GFR and change in GFR in patients with ADPKD.
INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease and has a prevalence of approximately 1 in every 1,000 individuals.¹ It is characterized by progressive cyst formation in both kidneys and loss of kidney function.¹,²

In ADPKD, cysts are formed through epithelial cell proliferation in renal tubules. These proliferated cells are less well differentiated,³,⁴ which may alter tubular functioning. It has been suggested that at earlier stages of ADPKD, cysts are seen mainly in the proximal tubules and loops of Henle, and that during later stages, these cysts diminish and cysts in the collecting ducts dominate.⁴ Normal tubular function includes degradation of proteins, reabsorption of water, secretion of waste products, and regulation of homeostatic function. Creatinine is secreted as waste product by proximal tubular cells. In healthy individuals, tubular secretion of creatinine (CCr(TS)) accounts for 10% - 15% of total renal creatinine clearance (CCr).⁵,⁶ In patients with ADPKD, proliferation and dedifferentiation of proximal tubular cells may result in aberrant tubular creatinine secretion.

To our knowledge, analysis of CCr(TS) in patients with ADPKD has not been performed yet. Therefore, we investigated CCr(TS) in patients with ADPKD and compared this with the situation in healthy controls. If CCr(TS) is affected in ADPKD, it may be expected that glomerular filtration rate (GFR) estimating equations perform less well in patients with ADPKD. We therefore also investigated the performance of GFR estimating equations in this patient group cross-sectionally and longitudinally.

METHODS

Patient Population

For this study, all consecutive patients with ADPKD visiting our outpatient clinic from January 2007 until August 2011 were asked to participate (N = 136). Diagnosis of APDKD was made based on the revised Ravine criteria.⁷ Individuals were considered ineligible to participate if they received renal replacement therapy (including kidney transplantation), had undergone renal surgery, were unable to undergo magnetic resonance (MR) imaging (as having distorting foreign bodies or aneurysmal clips), had other systemic diseases potentially affecting kidney function (such as diabetes mellitus), or had other specific medical conditions, such as pregnancy or lactation or were less than 6 months postpartum. After screening, individuals underwent an
extensive medical history. Thirteen patients refused to participate and 2 patients were not eligible to participate, leaving 121 patients for analysis. Participants were scheduled for a 1-day outpatient clinical evaluation. For 45 of these patients, data were available at 3 years' follow-up. For this study, all potential kidney donors who underwent kidney function measurement in our department from March 2006 to March 2009 were used as controls (N = 247). Potential kidney donors were invited for kidney function measurement only if they had no history of cardiovascular or kidney disease and a routine investigation of blood hematology, chemistry, and urinalysis showing no abnormalities. For 32 potential kidney donors, there were insufficient data to calculate CCr(TS), CCr, or measured GFR (mGFR), leaving 215 for analysis. These 2 groups did not differ in baseline characteristics listed in Table 1. Only a slight difference in use of antihypertensive medication was observed (13.3% and 20.6%; \( P < 0.001 \)). None of the study participants used medication that could interact with CCr(TS), such as trimethoprim-sulfamethoxazole or cimetidine. This study was performed in adherence to the Declaration of Helsinki. All participants gave written informed consent.

**Measurements and Calculations**

All participants collected a 24-hour urine sample the day preceding the kidney function measurement. Urinary albumin concentration was determined in these samples by nephelometry (BNII; Dade Behring Diagnostics). At the day of kidney function measurement, blood pressure was assessed at rest in a supine position with an automatic device (Dinamap; GE Medical Systems) for 15 minutes during kidney function measurement, and weight and height were determined. Body mass index (BMI) was calculated as weight in kilograms divided by height in square meters. Body surface area was calculated according to the DuBois formula. Baseline blood samples were drawn for determination of creatinine. Creatinine was measured with an enzymatic assay (isotope-dilution mass spectrometry traceable; Modular, Roche Diagnostics). GFR was estimated using the 4-variable MDRD (Modification of Diet in Renal Disease) Study equation and 2009 CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) creatinine equation (generating estimated GFR \( [\text{eGFR}_{\text{MDRD}}] \) and \( [\text{eGFR}_{\text{CKD-EPI}}] \)). In patients with ADPKD, MR imaging was performed immediately after kidney function measurement, using a standardized abdominal MR imaging protocol without the use of intravenous contrast. Scanning was performed with a 1.5-Tesla MR scanner (Magnetom Avento; Siemens), and in 12 patients, with a 3.0-Tesla MR scanner (Intera; Philips). Total kidney volume was assessed using these MR images with Analyze Direct 8.0 software (AnalyzeDirect Inc).
Kidney Function Measurement

Kidney function measurement was performed using a constant infusion method with \(^{125}\)I-iothalamate to determine mGFR and simultaneous infusion of \(^{131}\)I-hippuran to measure effective renal plasma flow and correct for voiding errors.\(^{13,14}\) Patients were not asked to fast and were allowed to drink ad libitum. Antihypertensive medication was not withheld. At 8:00 AM, a priming solution of 0.04 mL/kg body weight was administered, containing 0.04 MBq of \(^{125}\)I-iothalamate and 0.03 MBq of \(^{131}\)I-hippuran per 1 mL of saline solution plus an extra 0.6 MBq of \(^{125}\)I-iothalamate, followed by a constant infusion of these tracers at a rate depending on eGFR for
5.5 hours. After a stabilization period of 1.5 hour, two 2-hour clearance periods followed, in which mGFR and CCr were assessed simultaneously. CCr and mGFR were calculated per clearance period as (urine volume * urinary concentration of creatinine or $^{125}$I-iothalamate)/ plasma concentration of creatinine or $^{125}$I-iothalamate, respectively. Because urinary clearance of $^{131}$I-hippuran equals plasma clearance in case of perfect urine collection, we routinely use the ratio of plasma to urinary clearance of $^{131}$I-hippuran to correct urinary clearance of $^{125}$I-iothalamate as a measure of GFR for voiding errors. This procedure has been described in detail previously.\textsuperscript{14} For calculating CCr, a similar procedure was followed. Urine was collected by spontaneous voiding. CCr and mGFR are given as the average of both 2-hour clearance periods and normalized for body surface area. Day-to-day variability in mGFR using this method is 2.5%.\textsuperscript{13} CCr(TS) was defined as CCr minus mGFR. Urinary creatinine excretion, glomerular filtered load of creatinine, and CCr(TS) were calculated as described previously.\textsuperscript{15}

**Statistical Analysis**

Analyses were performed with SPSS, version 18.0 (SPSS Inc). Normality was assessed by Q-Q plot. Normal distributed variables are expressed as mean ± standard deviation (SD), whereas non-normally distributed variables are given as median (interquartile range [IQR]). A 2-sided $P < 0.05$ was considered to indicate statistical significance.

Differences in baseline characteristics between patients with ADPKD and controls were tested using 2-sample t-test when normally distributed or Mann-Whitney test when not normally distributed. Follow-up data for patients with ADPKD were tested using paired-samples t test.

To investigate whether CCr(TS) differed between patients with ADPKD and controls, multivariate linear regression analysis was performed, adjusting for covariates that potentially may be confounders (mGFR, sex, BMI, urinary albumin excretion, and total kidney volume). Albuminuria and total kidney volume were natural log transformed to fulfil the requirement of normal distribution of residuals. Two models were built. First, a possible difference in CCr(TS) between patients with ADPKD and controls was assessed adjusting for mGFR only (model 1). Second, additional adjustment was performed for sex, BMI, serum albumin level, albuminuria, and filtration fraction (model 2). Effective renal plasma flow was not added to model 2 because mGFR and effective renal plasma flow show high collinearity (variance inflation factors of 40 and 44). These characteristics are known from the literature to
potentially influence CCr(TS).\textsuperscript{5,16} To test whether these patient characteristics may influence any difference between patients with ADPKD and controls in CCr(TS), interaction terms were entered in this multivariate model. In addition, regression analysis was performed per study group separately (patients with ADPKD and controls, respectively). To visualize potential differences between patients with ADPKDK and controls, CCr(TS) was plotted for both study groups stratified according to chronic kidney disease (CKD) stages. Differences in CCr(TS) were analyzed with a 2-sample \( t \) test.

To investigate whether mGFR correlated with eGFR, Pearson correlation coefficient was calculated. Agreements between mGFR and eGFR values were evaluated by Bland-Altman analysis, with calculation of agreement limits (bias ± 2 SD). Bias was defined as the difference between mGFR and eGFR. Precision was measured as 1 SD of the bias. Accuracy was calculated as the percentage of estimates within 10% and 30% (of mGFR \( P_{10} \) and \( P_{30} \), respectively). \( P \) values for differences in dichotomous accuracy values between patients with ADPKD and controls were calculated with \( \chi^2 \) test.

**RESULTS**

**Study Participants**

Patient characteristics are listed in Table 1. A total of 121 patients with ADPKD and 215 healthy controls participated in this study, of which 56.2% and 48.4% were men, respectively. Patients with ADPKD were relatively young, with a mean age of 40.4 ± 10.8 years, but already had clear disease characteristics. Most patients with ADPKD used antihypertensive medication (77%) and their mean plasma creatinine concentration was increased (1.30 ± 0.74 mg/dL), as were urinary albumin excretion (median, 38 [IQR, 15-120] mg/24 h) and total kidney volume (median, 1.47 [IQR, 0.96-2.33] L). In patients with ADPKD, mGFR ranged from 15-139 mL/min/1.73m\(^2\), whereas in controls, mGFR ranged from 57 - 144 mL/min/1.73m\(^2\). In comparison, controls were older, with a mean age of 53.1 ± 10.3 years. As expected, controls had a low cardiovascular and renal risk-factor profile with well-preserved kidney function (mGFR, 97.7 ± 17.0 mL/min/1.73m\(^2\)) and low urinary albumin excretion (median, 4 [IQR, 3-7] mg/24 h). Baseline characteristics of patients with ADPKD and controls stratified for mGFR are given in Supplementary Table 1.

**Tubular Secretion of Creatinine**

CCr(TS) was higher in patients with ADPKD than in controls (15.9 ± 10.8 vs 10.9
± 10.6 mL/min/1.73m²; difference $P < 0.001$). Table 2 shows 2 multiple regression models. Model 1 shows that CCr(TS) was higher in patients with ADPKD than controls when adjusted for mGFR. Model 2 shows that this difference remained significant when adjusted for covariates that are known from the literature to also potentially be associated with CCr(TS): age, sex, BMI, filtration fraction, serum albumin level, and albuminuria. In our model, higher BMI was associated significantly with increased CCr(TS). In contrast, albuminuria and filtration fraction showed no association with CCr(TS). The difference between patients with ADPKD and controls in CCr(TS) was found to be dependent on mGFR level because the interaction term with mGFR was found to be statistically significant ($P = 0.003$). In a sensitivity analysis, use of antihypertensive medication and different classes of antihypertensive medications were added to the multivariate model. Neither was associated with CCr(TS) (data not shown).

Table 2. Multivariate linear regression analyses investigating differences between ADPKD patients and controls in tubular secretion of creatinine (mL/min/1.73m²), adjusting for covariates potentially associated with tubular creatinine secretion

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β</strong></td>
<td>95%CI</td>
<td>p-value</td>
</tr>
<tr>
<td>ADPKD vs control (1 or 0)</td>
<td>+6.30</td>
<td>3.7 - 8.9</td>
</tr>
<tr>
<td>Baseline mGFR (mL/min/1.73m²)</td>
<td>+0.07</td>
<td>0.01 - 0.12</td>
</tr>
<tr>
<td>Female vs male (1 or 0)</td>
<td>-1.88</td>
<td>-4.43 - 0.68</td>
</tr>
<tr>
<td>Age (year)</td>
<td>-0.10</td>
<td>-0.24 - 0.04</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>+0.76</td>
<td>0.44 - 1.08</td>
</tr>
<tr>
<td>Serum albumin (mg/mL)</td>
<td>+0.34</td>
<td>-0.18 - 0.86</td>
</tr>
<tr>
<td>LnAlbuminuria (mg/24h)</td>
<td>+0.29</td>
<td>-0.84 - 1.4</td>
</tr>
<tr>
<td>Filtration fraction</td>
<td>-4.44</td>
<td>-35.0 - 26.2</td>
</tr>
<tr>
<td>Interaction term (mGFR*ADPKD status)</td>
<td>+0.18</td>
<td>0.06 - 0.30</td>
</tr>
</tbody>
</table>

Dependent variable is CCr(TS). A positive sign indicates that there is a positive association between the variable under investigation and CCr(TS). Abbreviations are: mGFR, measured glomerular filtration rate; 95%CI, 95% Confidence Interval for β.

Figure 1 shows this interaction. CCr(TS) was plotted separately for patients with ADPKD and controls, both groups stratified according to CKD stage. This figure shows that CCr(TS) is significantly higher in patients with ADPKD only at high-normal mGFRs. It also shows that in patients with ADPKD, but not controls, mGFR is correlated with CCr(TS). Differences in CCr between patients with ADPKD and controls at mGFRs of 60-90, 90-105, and 105-120 mL/min/1.73m² were 2%, 4%, and 8%, respectively.
Given the fact that the association between mGFR and CCr(TS) was different between ADPKD patients and control subjects, we also investigated which factors may be associated with CCr(TS) in ADPKD and controls separately. In ADPKD patients, CCr(TS) was not associated with ln total kidney volume (β 0.3 CI -3.8;4.3, p=0.9), female sex (β -2.7 CI -7.1;1.7 p=0.2), filtration fraction (β -50.2, CI -115;14.6 p=0.1), serum albumin (β 0.1, CI -0.7;0.9 p=0.8) or ln albuminuria (β 0.01, CI -1.8;1.9 p=0.9). However, BMI (β 0.8 CI 0.3;1.2 p=0.003) and baseline mGFR (β 0.1, CI 0.01; 0.2 p=0.03) were significantly associated with CCr(TS), whereas age (β -0.7 CI -7.1; 1.7 p=0.07) showed a trend towards such an association. In controls, essentially similar findings were observed, with body mass index also being associated with CCr(TS) (β 0.9, CI 0.4;1.4 p<0.001). The only difference being that in healthy controls, in contrast to the situation in ADPKD patients, baseline mGFR was not associated with CCr(TS).

Performance of GFR Estimating Equations in ADPKD Patients
The correlation between mGFR and eGFR in patients with ADPKD using the CKD-EPI and MDRD Study equations, respectively, is shown in Figure 2. A high correlation between mGFR and eGFR\textsubscript{CKD-EPI} and eGFR\textsubscript{MDRD} was observed (R = 0.95 [P < 0.001] and R = 0.93 [P < 0.001], respectively). Figure 3 shows Bland-Altman plots of mGFR versus the difference between mGFR and eGFR. eGFR\textsubscript{CKD-EPI} and
eGFR_{MDRD} showed clear homogeneity of bias at any mGFR, albeit that the MDRD Study equation tended to underestimate mGFR.

Performance of the CKD-EPI and MDRD Study equations to estimate GFR in patients with ADPKD and controls is listed in Table 3. In controls and patients with ADPKD, the CKD-EPI equation performs slightly better than the MDRD Study equation to estimate GFR with numerically less bias and better precision and accuracy. In patients with ADPKD, both eGFR equations underestimated true GFR slightly. The precision and accuracy of both GFR estimating equations hardly differed between patients with ADPKD and controls, with bias, precision, and accuracy even slightly better in patients with ADPKD.

**Performance of GFR Estimating Equations to Measure Change in GFR**

Follow-up data for mGFR were available for 45 of 121 patients with ADPKD. Three years after the baseline measurement, GFR had decreased in these participants from 82.1 ± 22.9 to 73.6 ± 29.1 mL/min/1.73m² (P < 0.001), and CCr(TS), from 15.9 ± 9.0 to 13.4 ± 7.8 mL/min/1.73m² (P = 0.04). The mean annual change in kidney function measured as $^{125}$I-iothalamate clearance was -2.8 ± 3.4 mL/min/1.73m²; by eGFR_{CKD-EPI}, -3.2 ± 3.3 mL/min/1.73m²; and by eGFR_{MDRD}, -2.9 ± 3.2 mL/min/1.73m². Figure 4 shows the change in mGFR compared with change in eGFR. A high correlation between change in mGFR and change in eGFR_{CKD-EPI} and eGFR_{MDRD} was observed (r = 0.73 [P < 0.001] and r = 0.71 [P < 0.001], respectively). Figure 5 shows Bland-Altman plots of the change in mGFR versus the difference between change in mGFR and eGFR. There was homogeneity in the differences between changes in mGFR and eGFR for both GFR estimating equations.
Figure 2. Correlation between measured GFR and estimated GFR in ADPKD patients. GFR estimated with the CKD-EPI (left panel) and MDRD (right panel) equations. The dotted line represents the line of identity and the straight line the actual Pearson’s regression line describing the correlation between measured and estimated GFR.

Figure 3. Bland-Altman plots showing mGFR versus difference between mGFR and eGFR in ADPKD patients. GFR estimated with the CKD-EPI (left panel) and MDRD (right panel) equations. Dotted lines represent mean bias ± 2SD.
Table 3. Performance of CKD-EPI and MDRD equations to estimate absolute GFR at baseline.

<table>
<thead>
<tr>
<th></th>
<th>ADPKD</th>
<th>Controls</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>121</td>
<td>215</td>
<td></td>
</tr>
<tr>
<td>mGFR (mL/min/1.73m²)</td>
<td>77.7 ± 30.1</td>
<td>97.7 ± 17.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR CKD-EPI (mL/min/1.73m²)</td>
<td>75.1 ± 29.9</td>
<td>89.7 ± 13.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bias (mL/min/1.73m²)</td>
<td>2.7</td>
<td>8.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Precision</td>
<td>9.6</td>
<td>13.4</td>
<td></td>
</tr>
<tr>
<td>Accuracy P₁₀</td>
<td>54.5%</td>
<td>50.7%</td>
<td>0.5</td>
</tr>
<tr>
<td>Accuracy P₃₀</td>
<td>99.2%</td>
<td>96.7%</td>
<td>0.2</td>
</tr>
<tr>
<td>eGFR MDRD (mL/min/1.73m²)</td>
<td>71.5 ± 28.3</td>
<td>88.5 ± 15.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bias (mL/min/1.72m²)</td>
<td>6.2</td>
<td>9.3</td>
<td>0.03</td>
</tr>
<tr>
<td>Precision</td>
<td>10.8</td>
<td>14.4</td>
<td></td>
</tr>
<tr>
<td>Accuracy P₁₀</td>
<td>50.4%</td>
<td>45.1%</td>
<td>0.4</td>
</tr>
<tr>
<td>Accuracy P₃₀</td>
<td>96.7%</td>
<td>96.7%</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Bias is defined as mean difference between mGFR and eGFR. Precision is defined as one SD of the bias. Accuracy is defined as the percentage of eGFR values within 10% (P₁₀) and 30% (P₃₀) of their corresponding mGFR value. P-values are calculated by Student’s t-test when normally distributed and $X^2$ when non-normally distributed.
Figure 4. Correlation association between change in measured GFR and change in estimated GFR in 45 ADPKD patients who had follow-up data available. GFR estimated with the CKD-EPI (left panel) and MDRD (right panel) equations. The dotted line represents the line of identity and the straight line the actual Pearson’s regression line describing the correlation between change in measured and change in estimated GFR.

Figure 5. Bland-Altman plots showing change in mGFR versus difference between change in both mGFR and eGFR in ADPKD patients. GFR estimated with the CKD-EPI (left panel) and MDRD (right panel) equations. Dotted lines represent mean bias ± 2SD.
DISCUSSION

In this study, we investigated CCr(TS) in patients with ADPKD and controls and studied the consequences of a potential difference for the performance of GFR estimating equations. In patients with ADPKD with high-normal mGFR, we found higher CCr(TS) compared with healthy controls, whereas at low-normal mGFR, no significant difference was observed. Creatinine-based eGFR correlated well with mGFR in patients with ADPKD in cross-sectional and longitudinal analyses.

In line with the literature, our data show that in healthy participants, CCr(TS) accounts for 12% of total CCr.6 We found CCr(TS) to be elevated in patients with ADPKD with higher kidney function compared with healthy controls with similar kidney function. At lower kidney function, this difference between patients with ADPKD and controls was no longer observed. What can be the reason for this higher CCr(TS) in patients with ADPKD with well-preserved kidney function? Based on the literature, 5 different explanations may be possible.

First, it has been observed that CCr(TS) is increased in patients with nephrotic-range proteinuria.16 It was suggested that in such individuals, albumin reabsorption in the proximal tubule stimulates CCr(TS).16 In the patients with ADPKD included in our study, albuminuria was only limited. Furthermore, no association was observed between albuminuria and CCr(TS) in controls or patients with ADPKD. Second, obese individuals have been found to have increased CCr(TS), the underlying mechanism has not been elucidated yet.5 Consistent with this, we found a significant association between BMI and CCr(TS) in controls and patients with ADPKD. Importantly, there was no difference in BMI between controls and patients with ADPKD. Third, protein intake may influence CCr(TS).17 However, no significant difference in 24-hour urea excretion was observed between controls and patients with ADPKD, indicating that protein intake was similar in both groups. Our observations therefore make differences in albuminuria, obesity, or protein intake between patients with ADPKD and controls unlikely as a cause for the increased CCr(TS) in patients with ADPKD. Fourth, glomerular hyperfiltration has been shown to be associated with increased proximal tubular activity in patients with diabetes,18,19 and consequently, proximal tubules may secrete more creatinine. In clinical practice, it is impossible to directly measure hyperfiltration. However, it is assumed that hyperfiltration is occurring in patients with ADPKD, even when kidney function is (near) normal and not different from that in age- and sex-matched controls.20-22 In our study, we found a significant difference in filtration fraction between patients with ADPKD and controls, but no association
between filtration fraction and CCr(TS) in either the overall group or patients with ADPKD or controls separately. These findings may suggest that hyperfiltration does not play a major role in causing the increased CCr(TS). However, our findings should be interpreted cautiously because high filtration fraction is only a surrogate for hyperfiltration. A fifth potential explanation for higher CCr(TS) in patients with ADPKD with well-preserved kidney function could be that the increased creatinine secretion is caused by increased surface of the proximal tubular cells as a result of sac-like protrusion of the tubular wall and/or dilated tubules in ADPKD.4,23,24 Our observational data unfortunately do not allow a firm conclusion on the mechanism of the increased creatinine secretion in patients with ADPKD with near-normal kidney function.

Because CCr(TS) is increased in patients with ADPKD with (near) normal kidney function, this may influence the performance of GFR estimating equations. Upcoming therapeutic interventions in this patient group need to be investigated for efficacy with respect to kidney function preservation in large patient groups.25-27 For this purpose, adequate GFR estimating equations are needed. We therefore investigated the association between mGFR and eGFR. In a cross-sectional analysis, we found that eGFR\textsubscript{CKD-EPI} and eGFR\textsubscript{MDRD} correlated well with mGFR. The values for bias, precision and accuracy that we found in our controls are consistent with values obtained in the validation cohort of the study in which the CKD-EPI equation was developed.11 Although patients with ADPKD at high-normal mGFR had increased CCr(TS), this apparently did not result in high bias or low precision or accuracy of the equations that use creatinine to estimate GFR. In patients with ADPKD, values for bias, precision, and accuracy were numerically even slightly better than in controls, although differences did not always reach statistical significance.

To date, only 2 other studies investigated the performance of GFR estimating equations in patients with ADPKD.28,29 We found slightly higher accuracy than Orskov et al 29 (P\textsubscript{30} for eGFR\textsubscript{CKD-EPI} of 90% vs. 99% in the current study) and Ruggenenti et al 28 (P\textsubscript{10} for eGFR\textsubscript{CKD-EPI} of 51.4% vs. 54.5% in the current study). In our longitudinal analysis, we also found a high correlation in change in mGFR and change in eGFR during 3 years of follow-up. Rule et al 30 similarly showed in the CRISP (Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease) cohort a significant, albeit weaker, correlation between change in mGFR and change in eGFR\textsubscript{MDRD} after 3 years of follow-up (r = 0.30; P < 0.001). In contrast, Ruggenenti et al28 did not find a significant correlation between 1-year change in mGFR and eGFR. Differences between these studies may be explained by differences in patient characteristics, methods of creatinine measurement (modified Jaffé method 28 or enzymatic assay
gold-standard GFR measurement technique (plasma iohexol disappearance, plasma $^{51}$Cr-EDTA disappearance, or urinary $^{125}$I-iothalamate clearance), or duration of follow-up. Studies with prolonged follow-up in general show more change in GFRs. Consequently, their results will be influenced less by random measurement variation, and true associations will become more apparent. Of note, the study by Rule et al., as well as our study, had 3 years of follow-up. In both studies, a significant correlation was found between change in mGFR and change in eGFR. In contrast, the study that suggested that changes in GFR cannot be assessed using GFR estimating equations had only 1 year of follow-up.

What might be the consequences of our study? From the literature, it is known that kidney function in patients with ADPKD, as measured by creatinine or creatinine-based GFR estimates, remains relatively stable during a prolonged period and deteriorates more rapidly from a certain time onward. Hyperfiltration of nephrons not affected by obstruction by (micro)cysts has been mentioned as a mechanism explaining this phenomenon. In the present study, we show that in patients with ADPKD, CCr(TS) is increased significantly at higher mGFRs, thus contributing to a lower plasma creatinine level, especially at the earlier stage of the disease. CCr(TS) therefore may be a second reason why kidney function, when assessed with creatinine-based techniques, remains relatively stable for a prolonged period. Of note, most of the macroscopic cysts are blind sacs, so any creatinine secreted by epithelial cells lining cysts will stay in these cysts. Increased CCr(TS) therefore is likely to be caused by intact nephrons. Important, the additional effect on CCr(TS) that we found in patients with ADPKD with high-normal mGFR accounts for only 8% of total CCr. For example, an extra decline in serum creatinine level of 8% from 0.80 to 0.74 mg/L represents only a minor change in eGFR$_{\text{CKD-EPI}}$ from 104 to 108 mL/min/1.73m$^2$ for a 50-year-old white man. Such limited changes appear to have no major negative effect on the performance of GFR estimating equations. However, in clinical practice, an increment in plasma creatinine level produced by drugs that interact with CCr(TS), such as cimetidine, might be expected to be greater in patients with ADPKD than average. Our results with respect to bias, precision, and accuracy of these GFR estimating equations in ADPKD patients are in line with or even better than the corresponding values obtained in the CKD-EPI equation validation cohort. These findings therefore suggest that in patients with ADPKD, these GFR estimating equations can be used as substitution for the more expensive, invasive, and time-consuming gold-standard GFR measurement techniques such as urinary $^{125}$I-iothalamate clearance.
A limitation of our study is that our results with respect to the correlation between mGFR and eGFR primarily hold true for a cross-sectional study design because follow-up data were available for only a limited number of participants. Furthermore, we did not include a non-ADPKD CKD control group. We observed higher creatinine secretion in patients with ADPKD compared with healthy controls in only the high mGFR range. Our healthy control group has a normal mGFR range and therefore is perfectly suited for our study. Such a high mGFR range probably will not be available in a non-ADPKD CKD cohort. Of note, in a previous study, CCr(TS) was found to be reduced in patients with ADPKD compared with other CKD groups.32 As result, it cannot be concluded that increased CCr(TS) is specific for ADPKD. Third, a minor difference in the use of antihypertensive medication was observed between missing controls and controls. However, sensitivity analysis with antihypertensive medication added to the multivariate model did not change our results. Strengths of our study are that we measured GFR by a gold-standard technique (i.e. $^{125}$I-iothalamate clearance) and simultaneously assessed CCr. This was done in a relatively large well-phenotyped cohort of 121 patients with ADPKD at various CKD stages, as well as in healthy controls.

In conclusion, our study shows that patients with ADPKD have higher CCr(TS), but only at high-normal GFR. At lower GFR, no difference is observed between patients with ADPKD and controls. This increased creatinine secretion has no major negative effect on GFR estimated with the CKD-EPI and MDRD Study equations. These GFR estimating equations perform relatively well and therefore can be used in this patient group.

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REFERENCES


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<td>Plasma creatinine (mg/dL)</td>
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<td>0.93±0.13</td>
<td>0.85±0.14</td>
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<td>CCR (mL/min/1.73m²)</td>
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<td>mGFR (mL/min/1.73m²)</td>
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<td>110.3±3.4</td>
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<td>CCr(TS) (mL/min/1.73m²)</td>
<td>13.6±5.5</td>
<td>7.2±1.3</td>
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<td>Ucr (mg/day/1.73m²)</td>
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<td>GFcr (mg/day/1.73m²)</td>
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<td>TSCr (mg/day/1.73m²)</td>
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<td>124±132</td>
<td>257±151</td>
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<td>ERPF (mL/min/1.73m²)</td>
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<td>0.29±0.05</td>
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**Abbreviations:** BP, blood pressure; AHT, antihypertensive therapy; mGFR, measured glomerular filtration rate; CCR, creatinine clearance; CCr(TS), tubular secretion of creatinine; U_{cr}, creatinine excretion; GF_{cr}, glomerular filtered load of creatinine; TS_{cr}, tubular secretion of creatinine; ERPF, estimated renal plasma flow; NA, not applicable. Parametric variables are expressed as mean ± SD, whereas non-parametric variables are given as median (interquartile range).
Tubular secretion of creatinine in ADPKD