Increase in Serum Creatinine in a Patient on Continuous Peritoneal Dialysis: Potential Mechanisms and Management

A large elevation in serum creatinine (SCr) on an unchanged peritoneal dialysis (PD) schedule is usually caused by a decrease in total creatinine clearance (CCr), but may also reflect an increase in creatinine (Cr) production. A meticulously compliant 43-year-old man with lupus nephritis on automated nocturnal PD plus an additional daytime exchange developed a rise in SCr to 16.73 mg/dL from 8.06 mg/dL after starting fenofibrate, while total CCr decreased only to 61.5 L/1.73 m² from 77.4 m² weekly. Creatinine excretion was 16.4 mg/(kg·24 h) pre-fenofibrate. It increased to a high of 26.2 mg/(kg·24 h) during the period of fenofibrate intake and returned to 21.9 mg/(kg·24 h) 2 months after discontinuation of that drug. The patient’s age, weight, height, body mass index, 24-h drain and urine volumes, total Kt/V urea, serum urea nitrogen, urea nitrogen excretion, and (for the pre-fenofibrate period) SCr, Cr excretion, estimated Cr production, and measured-to-predicted Cr excretion (using a formula developed in PD patients) were within the 95% confidence intervals (CIs) obtained in a control group of 24 other men on similar PD schedules. The patient’s Cr excretion and production were above the 95% CIs of the control group while he was on fenofibrate, and they returned toward or within the 95% CIs after cessation of the drug. The patient’s serum creatine phosphokinase was not elevated while he was taking fenofibrate.

A thorough investigation of the potential mechanisms of a rise in SCr during the course of PD is warranted to determine if the rise is disproportional to any fall in total CCr. In the latter case, Cr excretion and production should be evaluated, and if elevated, conditions potentially causing the rise in Cr production (fenofibrate in this patient) should be sought, and appropriate therapeutic interventions should be implemented.

Key words
Serum creatinine, creatinine excretion, creatinine production, fenofibrate

Introduction
Creatinine clearance (CCr) is the major determinant of serum creatinine (SCr) in patients on peritoneal dialysis (PD) (1). Large increases in SCr during the course of PD are usually caused by decreases in total (peritoneal + renal) CCr. However, other mechanisms in addition to changes in CCr may also cause increases of SCr in PD patients. We present a patient who illustrates the differential diagnosis of a rise in SCr during PD.

Methods

Case report
A 43-year-old man with lupus nephritis commenced PD in January 2011. A peritoneal equilibration test (2) indicated a low-average transport type. His PD schedule consisted of nighttime automated PD (APD) using 4 exchanges, a fill volume initially 2.5 L and 3 L after March 2011, and 1 daytime exchange (2.5 L). The patient was meticulously compliant with all aspects of his treatment throughout all the years of follow-up in our hospital.

In 2007, this man developed diffuse muscular pains without an elevation in serum creatine phosphokinase (CPK) after starting gemfibrozil. Gemfibrozil
was stopped, and the muscle symptoms disappeared. In April 2011, he was started on fenofibrate (45 mg fenofibric acid daily). A large elevation in $S_{Cr}$ was noted in September 2011 (Table I). At the same time, the patient experienced muscle and joint pains. Serum CPK at that time was 76 U/L (normal range: 55 – 170 U/L). Fenofibrate was discontinued, and because of low total Kt/V urea, the duration of his nighttime APD was increased by 2 hours without any change in the 24-h fill volume. The patient reported no muscle symptoms on the 2 subsequent follow-up visits.

**Estimates**

Changes in creatinine (Cr) excretion and production were evaluated along with those in $S_{Cr}$ (3). The Cr and urea nitrogen excretion were calculated by adding the amounts excreted in urine to those determined in dialysate during clearance studies. The Cr excretion was also expressed as the measured-to-predicted Cr fraction. The estimate of the predicted Cr excretion (in milligrams over 24 hours) was obtained using the formula

$$\text{Predicted Cr excretion} = 302.150 - 4.380 \cdot A + 171.234 \cdot G - 39.041 \cdot D + 11.730 \cdot W$$  \[\text{equation 1}\]

which was derived from data obtained in a large number of North American patients on PD (4), and in which $A$ is the patient’s age in years, $G$ is the patient’s sex (male = 1, female = 0), $D$ is the patient’s diabetes status (yes = 1, no = 0), and $W$ is the patient’s weight in kilograms. The Cr production was estimated as the sum of the measured Cr excretion plus an estimate for “metabolic” Cr elimination (through the gastrointestinal tract), which, assuming a metabolic $C_{Cr}$ of 0.036 L/(kg·24 h) (5,6) is calculated as

$$\text{Metabolic Cr elimination} = 0.036 \cdot W \cdot S_{Cr} \cdot 10,$$  \[\text{equation 2}\]

where $S_{Cr}$ is expressed in milligrams per deciliter.

**Controls**

The control group consisted of 24 men on the same PD schedule (4 nocturnal APD exchanges plus 1 daytime exchange). The excretion of a second

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group</th>
<th>Study 1</th>
<th>Study 2</th>
<th>Study 3</th>
<th>Study 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59.7±13.4</td>
<td>43</td>
<td>43</td>
<td>43</td>
<td>43</td>
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<tr>
<td>Weight (kg)</td>
<td>94.7±22.3</td>
<td>88.9</td>
<td>83.6</td>
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<td>87.5</td>
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<tr>
<td>Height (cm)</td>
<td>174.8±6.2</td>
<td>172.7</td>
<td>172.7</td>
<td>172.7</td>
<td>172.7</td>
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<tr>
<td>Body mass index (kg/m²)</td>
<td>31.1±7.1</td>
<td>29.8</td>
<td>28.0</td>
<td>29.4</td>
<td>29.3</td>
</tr>
<tr>
<td>Body water (L)</td>
<td>47.3±8.5</td>
<td>46.8</td>
<td>45.0</td>
<td>46.4</td>
<td>46.3</td>
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<tr>
<td>Body surface area (m²)</td>
<td>2.08±0.23</td>
<td>2.03</td>
<td>1.97</td>
<td>2.01</td>
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<tr>
<td>Drain volume (L/24 h)</td>
<td>15.5±3.9</td>
<td>13.2</td>
<td>15.4</td>
<td>15.6</td>
<td>14.9</td>
</tr>
<tr>
<td>Urine volume (L/24 h)</td>
<td>0.8±0.7</td>
<td>0.3</td>
<td>0.8</td>
<td>0.3</td>
<td>0.7</td>
</tr>
<tr>
<td>Serum urea nitrogen (mg/dL)</td>
<td>42.2±14.4</td>
<td>42.0</td>
<td>31.0</td>
<td>56.0</td>
<td>31.0</td>
</tr>
<tr>
<td>Weekly total Kt/V urea</td>
<td>2.07±0.48</td>
<td>1.43</td>
<td>2.99</td>
<td>1.33</td>
<td>2.66</td>
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<tr>
<td>Urea N excretion (mg/kg·24 h)</td>
<td>63.4±26.8</td>
<td>45.5</td>
<td>72.3</td>
<td>59.1</td>
<td>65.2</td>
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<tr>
<td>Serum Cr (mg/dL)</td>
<td>7.24±2.41</td>
<td>8.06</td>
<td>4.57</td>
<td>16.73b</td>
<td>6.98</td>
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<td>Weekly total $C_{Cr}$ (L/1.73 m²)c</td>
<td>91.1±32.0</td>
<td>77.4</td>
<td>183.8b</td>
<td>61.5</td>
<td>81.9</td>
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<tr>
<td>Cr excretion (mg/(kg·24 h))</td>
<td>13.6±3.9</td>
<td>16.4</td>
<td>23.4b</td>
<td>26.2b</td>
<td>21.9b</td>
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<tr>
<td>Measured/predicted Cr excretion</td>
<td>0.985±0.270</td>
<td>1.091</td>
<td>1.549b</td>
<td>1.730b</td>
<td>1.464</td>
</tr>
</tbody>
</table>

*Estimated using the Watson formula.

*Exceeds the upper 95% confidence limit of the control group.

*Peritoneal plus renal.

$Cr =$ creatinine; $C_{Cr} =$ creatinine clearance.
azotemic substance, urea, was also evaluated as another control.

Statistics
In the control group, continuous variables are expressed as mean ± standard deviation. The values for the index patient were compared with the 95% confidence intervals (CIs) for the control group. The relation between Cr production and age was analyzed by linear regression. The estimates of Cr production for the index patient were compared with the 95% CIs from the regression for the control group.

Results
In the control group, 13 patients (54.2%) had diabetic end-stage renal disease; the remaining 11 patients (45.8%) had no diabetes. Of the 24 control patients, 1 (4.2%) had high peritoneal transport, 11 (45.8%) had low-average transport, and 12 (50.0%) had high-average transport.

Table I compares the index patient with the control group. The 1st and 4th clearance measurements for the index patient took place before the start of fenofibrate and 2 months after its discontinuation respectively; the 2nd and 3rd measurements were obtained while the patient was taking the drug. The patient’s total Cr at the 2nd measurement and his S Cr at the 3rd measurement, plus the measured Cr excretion and the measured-to-predicted Cr excretion at both the 2nd and 3rd measurements were above the corresponding 95% CIs in the control group. For the index patient, all other variables were within the 95% CIs of the control group (Table I). By 2 months after cessation of the fenofibrate, the index patient’s S Cr and measured-to-predicted Cr excretion returned to within the 95% CIs of the control group, and the Cr excretion, although lower than that measured while the patient was taking fenofibrate, remained slightly above the 95% CI of the control group (Table I).

Figure 1 shows the linear regression comparison of estimated Cr production and age in all 24 patients of the control group. One estimate of Cr production in the index patient while he was taking fenofibrate (3rd study) was above the 95% CI from that regression. Regressions were also performed separately in control group patients with and without diabetes mellitus. The correlation between age and Cr production was nonsignificant in the diabetic group. Figure 2 shows the regression obtained in the group without diabetes.

For the index patient, Cr production in study 3 was also above the 95% CI of that regression. Of 13 Cr
production estimates in patients with diabetes, 4 (30.8%) were below the 95% CI of the regression obtained in the group without diabetes.

**Discussion**

As this case illustrates, not only a decrease in total \( C_{Cr} \) [usually as a consequence of loss of residual renal function if the PD schedule is not altered (7)], but also increases in the production and excretion rates of Cr may be responsible for rises in \( S_{Cr} \) in PD patients. If Cr production is constant, only changes in total \( C_{Cr} \) determine steady-state changes in \( S_{Cr} \). The expected rise in \( S_{Cr} \) after a drop in total \( C_{Cr} \) can be then estimated. The rise should be less than its estimate from the change in total \( C_{Cr} \) because a progressively larger fraction of the Cr produced will be eliminated through the metabolic pathway as \( S_{Cr} \) increases (Equation 2). If Cr production had remained the same in the index patient, the expected \( S_{Cr} \) value as a result of the observed decrease in total \( C_{Cr} \) between the 1st (pre-fenofibrate) and 3rd (peak \( S_{Cr} \)) clearance studies would be 11.09 mg/dL if all Cr produced were excreted through the renal and peritoneal routes and 10.53 mg/dL if metabolic Cr elimination were added. The \( S_{Cr} \) in the 3rd clearance study was, at 16.73 mg/dL, substantially higher than either of the foregoing estimates. Therefore, in addition to the documented drop in total \( C_{Cr} \), either Cr production or the amount of Cr available for excretion, or both, must also have increased between the 1st and 3rd clearance studies. Increases in Cr production and excretion require investigation.

One condition that may cause an increase in the amount of Cr available for excretion without any change in Cr production is the presence of an unsteady state—for example, if a patient missing 1 or more PD exchanges resumes the regular PD schedule on the day of the clearance study. The observation of Cr excretion values higher than those predicted from population studies in subjects with chronic kidney disease was proposed as a means of detecting noncompliance with the PD schedule (6). However, a theoretical analysis concluded that the foregoing methodology is insensitive in detecting noncompliance (8,9). Subsequent clinical studies confirmed the methodology’s lack of accuracy (10,11). Furthermore, one study found good clinical outcomes in PD patients with high measured-to-predicted Cr excretion (12). That finding is consistent with the concept that Cr production, and consequently its excretion in the steady state, is a marker of somatic nutrition, which is the main long-term determinant of Cr production. However, short-term increases in Cr production during the course of PD are not always beneficial.

In PD patients, Cr production is temporarily increased by either potentially beneficial influences such as meat consumption (13) or adverse influences, for example, myopathy caused either by endogenous processes (muscle disease, neuropathies, muscle infarcts) or by exogenous noxious influences including chemicals such as fenofibrate. Fenofibrate administration to patients with proteinuria and early chronic kidney disease was associated with an average increase of 14% in \( S_{Cr} \), with no change in \( C_{Cr} \) (14). In another study, administration of fenofibrate to subjects with normal renal function was associated with rises in \( S_{Cr} \) and proportional increases in renal Cr excretion, but without any change in renal blood flow or the glomerular filtration rate. Muscle enzymes were elevated in the serum of only 2 of the 13 patients studied (15). An increase in the metabolic production of Cr was proposed as the mechanism of this fenofibrate effect (15).

In the index patient of the present report, the estimated Cr production increased when muscle symptoms developed during fenofibrate treatment and decreased after cessation of treatment (Figures 1 and 2). The long-term effects and histologic picture of muscles during this increase in Cr production are not clarified, but it is prudent to stop the medication if patients develop symptoms or if the increase in Cr production is not trivial. Notably, the package insert for fenofibrate suggests that the drug is contraindicated in patients with a Cr clearance less than 30 – 50 mL/min. If fenofibrate is used in PD patients, we suggest the exercise of extreme caution in monitoring muscle symptoms, muscle enzymes, \( S_{Cr} \), and Cr excretion and production during treatment.

**Conclusions**

In addition to decreases in total \( C_{Cr} \), various mechanisms of increased Cr production may lead to rises in \( S_{Cr} \) during the course of PD. Estimating the potential changes in Cr production and excretion, and investigating the underlying mechanisms, constitutes a critical part of the evaluation process in PD patients who are developing increases in \( S_{Cr} \) and should be used to guide potential changes in treatment.
Disclosures
The authors have no financial conflicts of interest to declare.

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