Significance of Low Concentrations of Creatinine in Serum from Hospital Patients

Peter Hagemann and Sidney N. Kahn

We present an analysis of the clinical significance of creatinine concentrations ≤4 mg/L (35 μmol/L) in serum as measured by a specific enzymatic method. In an unselected hospital patient population, 4% of whom had serum creatinine concentrations this low, a value of 5 mg/L (44 μmol/L) or higher was obtained on repeat analysis for a third of these patients, but the remaining two-thirds had persistently low values. Associated clinical conditions included low body mass, pregnancy, insulin-dependent diabetes mellitus, and total immobilization, but 12% of the patients, all female, had no obvious cause for the persistently low creatinine concentration. We conclude that low concentrations of creatinine in serum have no profound clinical significance.

Additional Keyphrase: multilayer-film analysis

The traditional normal reference interval for creatinine in serum, based on values obtained by the Jaffé reaction, includes a component (2–4 mg/L (17–35 μmol/L)) derived from noncreatinine chromogens. Therefore, when the only widely used methods were all Jaffé reaction-based, creatinine values of 4 mg/L (35 μmol/L) or lower were rarely seen in serum, even in the absence of clinical conditions that would have been expected to lower the serum creatinine concentration significantly. After we adopted the creatinine-specific Kodak Ektachem dry-film enzymatic method in our laboratory, concentrations ≤4 mg/L were found in approximately 4% of the measurements of serum creatinine. We studied the prevalence of creatinine values this low in sera from an unselected patient population in a large teaching hospital and performed a selective retrospective analysis of associated clinical factors.

Materials and Methods

The patients' data were derived from 16,628 unselected values for serum creatinine stored in the laboratory computer system at the Hospital of the University of Pennsylvania. Of these, 682 were ≤4 mg/L, from which we selected without conscious bias 85 patients' records for review.

To measure the concentration of creatinine in serum, we used the two-slide creatinine method in a Kodak Ektachem 700 multilayer-film analyzer (Eastman Kodak Co., Rochester, NY 14650). The method is based on the colorimetry of bromphenol blue reacting with the ammonia released from creatinine by enzymatic hydrolysis. A blank for serum ammonia is obtained for each sample by using a slide without enzyme. Our current reference intervals, which were derived from a population study of healthy adults, are 7–13 mg/L (62–115 μmol/L) for men, and 4–10 mg/L (35–88 μmol/L) for women.

As a measure of leanness, we calculated the Quetelet (body mass) index (I).

Results

Of the 16,628 values for serum creatinine, 650 (3.8%) were between 2 and 4 mg/L and 32 (0.2%) were ≤2 mg/L (18 μmol/L) (Figure 1). Of the 85 cases selected for analysis, 69 (81%) were female; the low values were persistent in 58 (68%). Table 1 lists the major clinical associations, which included low body mass, pregnancy, total immobilization, and insulin-dependent diabetes mellitus. Figure 2 illustrates the distribution of values for multiply-repeated assays of creatinine in serum of four patients with different clinical conditions. In pregnancy, the modal value was 4 mg/L (35 μmol/L). Emaciated patients showed the most markedly decreased values [≤2 mg/L (18 μmol/L)]. We observed moderately decreased values [3–4 mg/L (26–35 μmol/L)] in association with total immobilization and (or) artificial respiration. There was no obvious explanation for the persistently low concentration of creatinine in 12% of the patients, but all were female.

Twenty-seven (32%) of the patients had a single low value, which was not confirmed on retesting. Most of these were women, and most had one value of 4 mg/L (35 μmol/L) among values ranging from 5 to 7 mg/L (44–62 μmol/L).

Discussion

Specific methods for creatinine in serum can be expected to produce slightly lower values than those obtained by the less-specific alkaline picrate (Jaffé) method. The resulting bias (approximately 3 mg/L (26 μmol/L)) may not be obvious for above-normal and most normal concentrations of creatinine, but samples with genuinely low concentrations, analyzed by a specific method, may give results that are significantly below previously accepted reference limits and cause physicians to doubt their accuracy.

When an apparently spurious result is obtained for a patient's sample, analytical interference and inaccuracy
Table 1. Clinical Correlates of Low Creatinine Concentrations (<4 mg/L [35 μmol/L]) in Serum

<table>
<thead>
<tr>
<th>Clinical condition</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low body mass (Quetelet index &lt;18.5)</td>
<td></td>
</tr>
<tr>
<td>Pregnancy (second &amp; third trimester)</td>
<td>18</td>
</tr>
<tr>
<td>Insulin-dependent diabetes mellitus</td>
<td>9</td>
</tr>
<tr>
<td>Malignancy with weight loss</td>
<td>10</td>
</tr>
<tr>
<td>Total immobilization and (or) artificial respiration</td>
<td>9</td>
</tr>
<tr>
<td>None identified (idiopathic)</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>85</td>
</tr>
</tbody>
</table>

must be ruled out. The Ektachem method is relatively resistant to interference (2, 3) and its analytical accuracy for samples with concentrations of creatinine <5 mg/L is documented (4).

Apart from random error, analytical imprecision is an additional component that must be considered. The recent introduction of a single-slide Ektachem creatinine method may improve the precision over that of previous enzymatic creatinine methods, which are insufficiently precise, especially at low concentrations (2, 5). The standard deviation of the two-slide method at a concentration of 5.2 mg/L was found to be 1 mg/L (2), which is partly the result of rounding values expressed in conventional units to one decimal place, both in calibration and reporting of results. Cumulative error of this type can result in shifts of up to 2 mg/L at these low concentrations. Expression of results in molar concentration units would be a definite advantage in this regard.

Low creatinine concentrations in serum can be expected in several physiological conditions. Because creatinine is formed by spontaneous, irreversible cycling of muscle phosphocreatine at a steady rate of 3% per day, creatinine formation correlates with muscle mass, as illustrated by the lower values seen for women. However, the reported weak correlation with total body weight (6) has recently been disputed (7). In aging, decreasing muscle mass leads to decreased formation of creatinine, which is, however, compensated for by decreased excretion (8). The increased glomerular filtration rate during pregnancy results in increased urinary excretion of creatinine in the face of constant production (9). Other minor physiological factors which affect serum creatinine concentration include circadian rhythms (10, 11), menses (12), and seasonal variations (13, 14).

Pathologically decreased concentrations of serum creatinine may be the result of decreased production or increased excretion, as in the increased glomerular perfusion of insulin-dependent diabetics (15). In patients with muscle wasting (e.g., muscular dystrophy, cachexia) or decreased muscular activity (e.g., immobilization, paralysis), muscle creatine is decreased, with a concomitant decrease in the formation and serum concentration of creatinine.

Although low serum creatinine concentrations have no profound clinical significance, it is important for clinicians to be aware that improved analytical methods not only require revision of reference ranges but that results that superficially appear physiologically improbable truly reflect pathophysiological processes.

Fig. 2. Distribution of values for multiple analyses of serum creatinine in four patients with different clinical conditions

References