siveness to thyroliberin stimulation and, together with information on peripheral thyroid hormone concentrations, is sufficient for the diagnosis of overt hyperthyroidism and borderline hyperthyroidism. Moreover, in addition to values for peripheral thyroid hormone, the basal thyrotropin value is a sufficient diagnostic parameter for monitoring thyroid hormone therapy in euthyroid goiter and after removal of thyroid carcinoma.

In comparing basal thyrotropin values and changes in thyrotropin, the correlation coefficient of 0.77 was in the same range as described by Seidel et al. (6), which indicates that the extent of thyrotropin response may be predicted from the basal thyrotropin value.

Whereas euthyroidism and hyperthyroidism can be clearly distinguished by measurement of basal thyrotropin with this assay, the value of results for basal thyrotropin in diagnosis of borderline hypothyroidism needs to be investigated in further clinical studies.

References


**Factors Influencing Normal Reference Intervals for Creatinine, Urea, and Electrolytes in Plasma, as Measured with a Beckman Astra 8 Analyzer**

R. Stuart C. Rodger, Michael F. Laker, Kate Fletcher, Trevor F. White, Alex Heaton, Michael K. Ward, and David N. S. Kerr

In a study of 514 healthy adults, we used a Beckman Astra 8 Analyzer to establish normal reference intervals for plasma creatinine, urea, and electrolytes. For potassium and chloride these were considerably lower and higher, respectively, than previously reported ranges. All of these analytes showed significant sex-related differences; all except chloride showed age-related changes. The relationship of these biochemical indices to fasting, cigarette smoking, alcohol intake, regular exercise, and the contraceptive pill— independent of these age- and sex-related differences—was assessed by multiple linear regression. The effect was significant in each case. Our results underline the importance of regular review of reference values.

**Additional Keyphrases:** variation, source of, sex- and age-related effects, effects of smoking, alcohol, exercise, hyperkalemia

Since the introduction of multi-channel analyzers to hospital practice, many laboratories offer simultaneous measurement of creatinine, urea, and electrolytes in plasma or serum. Such data are widely used to help assess renal function, acid–base status, and extracellular volume and composition, although their value for screening has been criticized, particularly regarding routine measurements of chloride and bicarbonate ions (1, 2). Plasma electrolytes show remarkable intra- and inter-individual consistency, although large-scale surveys have demonstrated statistically significant but clinically unimportant age- and sex-related differences (3–8). Concentrations of urea and creatinine in plasma of healthy adults are more variable, changing with changes in age, muscle mass, and protein intake (5–9).

Our clinical practice has suggested certain inconsistencies in the normal reference values for these and other analytes, even though the ranges are based on large numbers of samples. We therefore designed a study to better establish normal ranges for various biochemical and hematological variables in a large, well-documented population. Here we report our results for creatinine, urea, and electrolytes in plasma.

**Materials and Methods**

We collected data on 524 adults, 10 of whom were later excluded because of they were being treated with diuretics (9) or potassium (1) (Table 1). Members of the study population were recruited from the staff of the University of Newcastle upon Tyne, preclinical medical students (ages 18–21 years), and members of a local retirees club (ages
Table 1. Population Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>260</td>
<td>264</td>
<td>524</td>
</tr>
<tr>
<td>Age, years *</td>
<td>41 ± 15</td>
<td>37 ± 14</td>
<td>39 ± 14</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.91 ± 0.13</td>
<td>1.63 ± 0.15</td>
<td>1.76 ± 0.20</td>
</tr>
<tr>
<td>Obese, % b</td>
<td>7</td>
<td>20</td>
<td>14</td>
</tr>
<tr>
<td>White persons, %</td>
<td>96</td>
<td>96</td>
<td>96</td>
</tr>
<tr>
<td>Fasting, %</td>
<td>44</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>Smokers, %</td>
<td>17</td>
<td>24</td>
<td>21</td>
</tr>
<tr>
<td>Alcohol intake, units/week c,d</td>
<td>11.4 (0–70)</td>
<td>5.7 (0–40)</td>
<td>8.5</td>
</tr>
<tr>
<td>Vigorous exercise, hours/week c</td>
<td>1.9 (0–15)</td>
<td>1.25 (0–20)</td>
<td>1.6 (0–20)</td>
</tr>
<tr>
<td>Taking oral contraceptives, %</td>
<td>—</td>
<td>27</td>
<td>14</td>
</tr>
</tbody>
</table>

*Mean ± SD.

Obese = body mass index (kg/m²) >27 (males) or >25 (females).

One unit = 250 mL beer = 120 mL wine = 30 mL spirits.

Range indicated in parentheses.

>65). Volunteers described their smoking, drinking, exercise habits, etc. in response to a brief questionnaire, which was kept confidential by a system of code number identification so that the answers would be unknown to the analyst but persons with abnormal results could be recalled. About 100 mL of blood was collected by venepuncture (at 08:30–09:30 hours). To do so we used a “butterfly” needle (Venessystems, gauge 19; Abbott Ireland Ltd., Sligo, Republic of Ireland), plastic syringes (Plastipak; Becton Dickinson and Co. Ltd., Dunlaoghaire Co., Dublin, Ireland), and a tourniquet, with heparin as anticoagulant. Creatinine, urea, and electrolytes were measured in the plasma the same day in an Astra 8 analyzer (Beckman RIIC Ltd., High Wycombe, Bucks, U.K.), which was calibrated with primary aqueous standards. Table 2 summarizes the methods used and their precision, for lyophilized bovine serum (Wellcome Research Ltd., Hither Green Lane, London, U. K.).

Data were stored on a Spires Database and analyzed by use of the Statistical Package for the Social Sciences (10). Statistical analyses were performed by using the regression equation, Student’s t test, and stepwise multiple linear regression. Reference ranges were obtained by using the percentile technique (11).

Results

Our results for plasma creatinine, urea, and electrolytes (Table 3) showed significant sex-related differences. With increasing age, concentrations of sodium and bicarbonate increased in women, potassium and creatinine increased and sodium decreased in men, and urea increased in both sexes.

Table 4 summarizes the correlations of height, weight, body surface area (BSA), and body mass index (BMI) with age and concentrations of the analytes in plasma. In men, height and BSA correlated with the concentrations of sodium and chloride, respectively, and BMI correlated inversely with the concentrations of bicarbonate. In women, height and BSA correlated with creatinine, and BMI with potassium and bicarbonate.

The effects of fasting, cigarette smoking, alcohol intake, exercise, and the contraceptive pill were assessed by multiple linear regression for each sex separately (Table 5). Bicarbonate concentrations were lower in fasting men and in women who were taking oral contraceptives. Urea concentrations were lower in smoking than in nonsmoking men, and plasma potassium increased with alcohol intake in men. Independently of age-related changes, regular exercise was associated in both sexes with higher concentrations of creatinine and in men with higher potassium and lower sodium and chloride concentrations. The reference ranges derived from these results (2.5th–97.5th centile) are shown in Table 6.

Discussion

The reference values we derived differ in several important respects from previous series. We have attempted to define the influence of demographic factors on the values for these analytes. Information about the volunteers, from whom a “healthy population” was derived, was obtained from their questionnaire response without further verification. The population was also biased towards the upper social class, although this per se has not been shown to affect these biochemical indices. With these limitations, we systematically studied a well-documented population.

Our results for plasma potassium are lower than those quoted in most standard references (3–8). For a quarter of the subjects the plasma potassium was <3.6 mmol/L; only 13% had a value >4.0 mmol/L. This may be partly explained by our careful sampling to avoid hemolysis and by the judicious brief use of a tourniquet (12), which was aided by a warm environment and the use of butterfly needles; however, we doubt that these factors could account for all of the discrepancy. Hypokalemia is associated with various degrees of muscle weakness and cardiac arrhythmia, although the view that fatal ventricular arrhythmias result from hypokalemia is controversial (13, 14) and the putative benefit of potassium supplementation in patients after myocardial infarction remains unproven. Our results suggest that plasma potassium is often lower in health than is generally recognized, and that many patients (e.g., some receiving diuretics for hypertension) are thus treated unnecessarily for spurious hypokalemia.

The chief value in measuring chloride, the dominant anion of the extracellular fluid, is in the assessment of organic acid load, the “anion gap.” Most published reference ranges for chloride show a lower limit of 96–100 mmol/L (5–7), but in our population the lower limit for 95% confidence limits was 103 mmol/L. These differences may be due to differing methodology, previously published ranges for chloride having been mostly based on continuous-flow chemical analysis whereas in the Astra analyzer a coulometric technique is used. In addition, we used primary aqueous standards rather than serum-based calibrators.

The sex-related differences in chloride probably arise secondarily to differences in bicarbonate concentrations, which reflect the relatively mild respiratory alkalosis present in women (15), and this decrease of bicarbonate was accentuated in women who were taking oral contraceptives.

Reasons for the differences in electrolyte concentrations related to fasting, alcohol intake, or exercise are unclear,

CLINICAL CHEMISTRY, Vol. 31, No. 2, 1985
although the concentrations of lactate and ketone bodies may have been altered in these subjects. The minor sex-related differences in sodium and potassium concentrations and their discordant changes with age are of uncertain significance, the latter having not been reported previously.

Differences in dietary or metabolic factors between smokers and non-smokers are in dispute (16, 17). We observed lower concentrations of plasma urea in male smokers than non-smokers regardless of age, which might reflect a reduced protein intake by this group.

Doolan et al. (9) described a diurnal variation in plasma creatinine, an increase in the afternoon by as much as 18%, which should be taken into account because all our subjects were sampled in the morning. Creatinine concentrations were not affected by fasting, and correction for BSA negated most of the differences between the sexes. The correlation of plasma creatinine with muscle mass (9) might explain the higher values for persons taking regular exercise. Glomerular filtration rate and muscle mass, factors that have opposing effects on plasma creatinine concentration, decline with age (18, 19); we observed an increase in creatinine with age in men but not in women, in whom, presumably, the loss of muscle mass is more marked.

This study demonstrates minor but significant associations between demographic factors and some biochemical
Table 6. Reference Intervals (2.5th–97.5th centiles)

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Range</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺, mmol/L</td>
<td>138–145</td>
<td>&gt;50 yrs 139–145</td>
</tr>
<tr>
<td>K⁺, mmol/L</td>
<td>3.2–4.4</td>
<td>&gt;50 yrs 3.4–4.6</td>
</tr>
<tr>
<td>Cl⁻, mmol/L</td>
<td>103–110</td>
<td>&gt;50 yrs 103–109</td>
</tr>
<tr>
<td>HCO₃⁻, mmol/L</td>
<td>20.7–29.9</td>
<td>&gt;50 yrs 21.1–30.2</td>
</tr>
<tr>
<td>Urea, mmol/L</td>
<td>2.8–7.2</td>
<td>&gt;50 yrs 3.0–9.2</td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td>61–111</td>
<td>&gt;50 yrs 72–127</td>
</tr>
</tbody>
</table>

variables. Although the disparities between these and other previously reported normal ranges may be partly ascribed to different methods of sampling and analysis, our results emphasize the need for regular review of reference values to take into account changes in the health and lifestyle of the population.

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References