data differed significantly between the first stream and midstream urine samples.

Epithelial cell and erythrocyte counts in midstream urine specimens changed significantly during the menstrual cycle (Fig. 1). Epithelial cell counts during the luteal phase were higher than those during the other three phases in midstream urine. Erythrocyte counts during the menstrual phase were higher than those during the other three phases. Other cell counts did not vary significantly with the menstrual cycle.

The values at the 90th percentiles of the results for the midstream urine samples during the menstrual, follicular, ovulatory, and luteal phases, respectively, were as follows:

- **Erythrocytes**: 506 × 10⁶, 21 × 10⁶, 30 × 10⁶, and 22 × 10⁶/L
- **Leukocytes**: 22 × 10⁶, 91 × 10⁶, 10 × 10⁶, and 74 × 10⁶/L
- **Epithelial cells**: 12 × 10⁶, 18 × 10⁶, 14 × 10⁶, and 40 × 10⁶/L
- **Casts**: 0.9 × 10⁶, 0.9 × 10⁶, 0.2 × 10⁶, and 1.4 × 10⁶/L
- **Bacteria**: 589 × 10⁶, 788 × 10⁶, 425 × 10⁶, and 1174 × 10⁶/L

The detection of epithelial cells is considered evidence that the first part of the voided urine has been collected (3). The first part of the voided urine contains considerable amounts of vaginal secretions (3). In agreement with this view, epithelial cell counts in midstream samples were significantly lower. In addition, our data provided evidence that the numbers of erythrocytes, leukocytes, and bacteria derived from contamination by vaginal secretions are reduced in midstream urine samples.

Epithelial cell counts in midstream urine differed in a phase-dependent manner. During the menstrual cycle, estrogen influences the proliferation and maturation of the vaginal epithelial cell layers, whereas progesterone is associated with shedding of the superficial epithelial cell layers; consequently, the number of epithelial cells in vaginal smears increases during the luteal phase (4, 5). These physiologic changes in vaginal secretions during the menstrual cycle could explain the significant cyclic variation in the number of epithelial cells in urine samples from women.

In conclusion, although the number of participants was limited and an investigation of the same individuals during the four menstrual phases will provide more appropriate and valid information, our study reconfirmed the importance of midstream collection for testing of urine from women by modern analytical methods. In addition, our results showed that the numbers of epithelial cells and erythrocytes in midstream urine vary significantly during the menstrual cycle.

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**References**


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**Sex and Age Differences in Serum Potassium in the United States, Diane K. Wysowski, Cynthia Kornegay, Parivash Nourjah, and Anne Trontell (Office of Drug Safety, Food and Drug Administration, Rockville, MD 20857; * address correspondence to this author at: Division of Drug Risk Evaluation, HDF-430, Food and Drug Administration, Parklawn Bldg., Room 15B-08, Rockville, MD 20857; fax 301-827-5190, e-mail wysowski@cdr.fda.gov)

An association between low serum potassium and prolongation of the electrocardiographic QT interval and cardiac arrhythmia has been known for some time (1–3). High serum potassium has also been found to be independently associated with increased cardiovascular mortality (4). However, population distributions of serum potassium have not been published recently, and as a result, physicians may not appreciate the prevalence of abnormal concentrations in the population. Knowledge of the prevalence of abnormal serum potassium concentrations is important when prescribing diuretics or drugs that are arrhythmogenic in the presence of hypo- or hyperkalemia. This report describes the distribution by age and sex of serum potassium concentrations in the US population and provides data on the prevalence of abnormal concentrations.

The National Health and Nutrition Examination Survey (NHANES) is a nationwide probability sample of the noninstitutionalized civilian population of the US. NHANES has been conducted on a periodic basis since the early 1970s. Baseline data collection usually includes a medical history, standardized medical examination, dietary assessment, laboratory tests, and anthropometric measurements. Serum potassium was measured in participants of the third survey (NHANES III), which was performed during the period 1988–1994. Frozen sera were collected and sent for analyses to the CDC. Potassium values were obtained only for participants ≥12 years of age. The range of observed values was 2.51–6.94 mmol/L.

The participant population of 29 314 consisted of 457 persons examined at home and the 28 857 persons examined in mobile examination centers. After 10 591 were excluded (9073 were ineligible children, 25 were missing values, and 1493 were for refusals, insufficient volume of
serum, or invalid concentrations), 18 723 (93%) of 20 241 persons had serum potassium for analysis.

We compared the sex, age, and health status of the 1493 individuals who refused or who had insufficient volume of serum or invalid concentrations with the 18 723 persons who were included in the analysis. Compared with those included, individuals not included were more likely to be female (56% vs 52%), slightly younger (mean age, 38 vs 40 years), and very similar in self-reported health status (very good to good). As a result of this comparison, we do not believe that the serum potassium results are biased as a result of large differences between participants and nonparticipants.

NHANES III used a complex weighting scheme to make the sample nationally representative; therefore, a weighting variable was used to construct the distribution of serum concentrations that would be nationally representative. The total number of weighted observations was nearly 193 million individuals, with 51.7% female and 48.3% male. The age range for the sample was 12 to >90 years. Individuals ≥90 years of age were coded as 90 years. A total of 124 persons (representing a total population of 525 957) were ≥90 years of age. A total of 2227 individuals (representing a total population of 19 578 700) were 12–17 years of age at the time of the examination. The mean age was 40.8 years, and the median age was 40 years.

Weighted analyses were performed using the NHANES recommended weights and the inverse of these weights. Statistical analyses were performed using SAS, Ver. 6.12 (SAS Institute). DESCRIB and REGRESS procedures in SUDAAN (Research Triangle Institute) were used to examine serum potassium concentrations between males and females and across age groups. This software package takes into account the complex sampling design of the survey.

The distribution of serum potassium concentrations for the US population for 1988–1994 from NHANES III is presented in Fig. 1A. The reference interval for serum potassium is 3.5–5.0 mmol/L. The majority of the US population, 185.8 million (96.3%) of ~193 million people, fell into the range of 3.5–4.9 mmol/L. By contrast, 5.9 million people, representing ~3.1% of the US population, had low serum potassium (<3.5 mmol/L), and 1.3 million, or ~0.7%, had borderline high and high serum potassium (≥5.0 mmol/L).

The distribution of serum potassium concentrations by age and sex is presented in Fig. 1B. A smaller proportion of US females than males had serum potassium within the reference interval, and a larger proportion had hypokalemia. Approximately 4.3 million (4.3%) of 99.8 million US females were hypokalemic, whereas only 1.6 million (1.7%) of 93.2 million US males were hypokalemic. Serum potassium was lower for those 21–30 years of age than for those 12–20; however, controlling for sex, after age 30, serum potassium increased significantly with age (slope for linear relation of age and serum potassium was statistically significant, P < 0.0001). Serum potassium was lower for all age groups of females compared with males (Fig. 1B). After adjusting for age, we found a statistically significant difference in serum potassium between males and females (P < 0.0001).

Analyses of serum potassium values from a 1988–1994 representative cross-sectional sample of the population revealed that hypokalemia affects millions of persons in the US. Approximately 5.9 million individuals, comprising ~3% of the population, were hypokalemic, whereas ~1.3 million individuals, comprising 0.7% of the population, were hyperkalemic. Women, in whom the frequency of hypokalemia was 4%, were disproportionately affected.

We did not have as our objective identification of factors such as food intake, disease entities, and medications that affect serum potassium concentrations, nor did we attempt to identify factors that could explain the differences in concentrations between younger and older individuals and women and men. Further study would be required to explain these differences. However, it is known that women are more susceptible to development...
of QT prolongation (1–3) and that QT prolongation is associated with hypokalemia (5). Thus, higher frequencies of QT prolongation in women compared with men may be attributable in part to the higher frequency of hypokalemia in women.

Hypokalemia is a condition that affects millions of persons (especially young women) in the US. Because of its prevalence, it may be prudent to measure electrolytes before prescribing diuretics or drugs that are arrhythmogenic in the setting of electrolyte disorders. This is especially important for women who have conditions such as eating disorders or who take medications that affect electrolyte concentrations.

References

Serum CrossLaps Compared with Other Markers of Bone Turnover in Severely Malnourished Children before and after Refeeding, Patricia M. Crofton,1,2, Nancy Evans,2 and Rhona Stephen2 (1 Department of Paediatric Biochemistry, Royal Hospital for Sick Children, Sciennes Rd., Edinburgh EH9 1LF, United Kingdom, 2 Section of Child Life and Health, Department of Reproductive and Developmental Sciences, University of Edinburgh, Sylvan Place, Edinburgh EH9 1UW, United Kingdom; * address correspondence to this author at: Department of Paediatric Biochemistry, Royal Hospital for Sick Children, Sciennes Rd., Edinburgh EH9 1LF, United Kingdom; fax 44-131-536-0410, e-mail patricia.crofton@luht.scot.nhs.uk)

In growing children, bone turnover is generally high. There are several biochemical markers of bone formation and resorption that have been validated in adults by bone histomorphometry and calcium kinetics. Markers of bone formation are all measured in plasma and include bone-specific alkaline phosphatase (ALP), osteocalcin, and the C-terminal propeptide of type I collagen (PICP). Their use as markers of growth and bone formation in children is now well established (1, 2). However, most markers of bone resorption are measured in urine, including total pyridinoline (Pyd) and the more bone-specific deoxypyridinoline (Dpd). The main problems associated with the urinary markers in pediatric practice are high within-individual biological variation and the need for either timed collections (frequently impossible in children) or, for random urine samples, expressing results as a ratio to creatinine. Creatinine is itself subject to biological variation and changes with muscle mass. Dpd:creatinine excretion in children is highly variable (3) and hence relatively insensitive to therapeutic interventions.

Until recently, only one commercially available marker of bone resorption could be measured in plasma, the cross-linked telopeptide of type I collagen (ICTP). Plasma ICTP appears to be less sensitive than some of the other markers to changes in bone resorption in certain clinical situations (e.g., bisphosphonate treatment), perhaps because of metabolism by osteoclastic cathepsin K (4). There is now a new marker for bone resorption that can be measured in serum or plasma, serum CrossLaps™ (5), for which we have recently reported pediatric reference data (6). The CrossLaps assay is specific for the amino acid sequence EKAHD-β-GGR where the aspartic acid residue (D) is β-isomerized. It detects only cross-linked degradation products of C-terminal telopeptides of type I collagen and is therefore specific for bone resorption. It has been clinically evaluated in adults in whom changes in CrossLaps were inversely correlated with changes in bone mineral density in postmenopausal women treated with bisphosphonates and hormone replacement therapy (7). CrossLaps has not yet been clinically evaluated in children.

Markers of bone formation and resorption usually change in parallel, for example, during childhood growth (longitudinal bone growth and modeling) (1, 2) and during bone remodeling when the processes of bone resorption and formation are usually tightly coupled. However, it has been reported that in malnourished adolescents and adults with anorexia nervosa, there is uncoupling of bone remodeling, with a relative excess of resorption over formation (8, 9). In a recent study of severely malnourished children, we have similarly reported a marked discrepancy between low markers of bone formation and high concentrations of ICTP at presentation, consistent with such uncoupling (10). The latter study provides an appropriate clinical context in which to evaluate serum CrossLaps by examining its response to severe malnourishment and refeeding in comparison with that of other markers of bone resorption and bone formation.

We measured serum CrossLaps in a representative subgroup of 10 patients (7 boys) from an earlier larger study of 141 severely malnourished children undergoing refeeding in Dhaka, Bangladesh (10). Full details of the patients and the refeeding program are given elsewhere (10). The median age of our subgroup was 13.0 months (range, 7–36 months). For the original study, consent was obtained in Bengali from the primary caregiver of each child, and the study was approved by the Paediatrics and Reproductive Medicine Research Ethics SubCommittee of Lothian Health (Edinburgh), the Ethics Committee of the International Centre for Diarrhoeal Disease Research (Bangladesh), and the Dhaka Shishu Children’s Hospital.

We analyzed plasma and urine (stored at −20 °C until analysis) from paired blood and urine samples collected at presentation (day 1) and after 30 days of refeeding.