The relationship between uric acid and potassium in normal subjects

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SUMMARY The serum uric acid concentration in normal healthy subjects has been studied in relation to sex, height, weight, lean body mass measured from total body potassium and predicted from the Hume-Weyers formula (1971), total body potassium, plasma potassium and urea, and packed cell volume. The strongest correlation was found with sex, but height, weight, total body potassium, lean body mass (measured and predicted) also correlated significantly with serum uric acid concentration. However, when the sex variable was removed, the other factors lost their significant correlation. Finally, total red blood cell and plasma volumes were predicted (Hume and Goldberg, 1964) and from these an estimate of total plasma uric acid, total plasma potassium, and total red blood cell potassium obtained. Measured total body potassium was found to correlate well with total plasma potassium and total red blood cell potassium independent of sex. Total plasma uric acid correlated well with measured total body potassium when both sexes were considered and when separated into male and female groups the males retained a significant correlation as did the female group.

Serum uric acid concentrations, although subject in the individual to marked fluctuation, are distributed unimodally in large scale population studies (Mikkelsen *et al.*, 1965) and it would seem from twin studies that the major determinant of serum uric acid levels are environmental rather than genetic (Boyle *et al.*, 1967). Several contributing factors, in addition to dietary intake, have been studied; haemoglobin concentration and alcohol consumption (Evans *et al.*, 1968) and psychological traits (Brooks and Mueller, 1966; Kasl *et al.*, 1966) have all been reported to be related to the serum uric acid concentration.

That serum uric acid and body bulk are inter-related has been documented in several races with a variety of geographic, ethnic, and demographic characteristics (Dunn *et al.*, 1963; Prior *et al.*, 1964; Mikkelsen, 1965; Mikkelsen *et al.*, 1965; Acheson and O'Brien, 1966; Burch *et al.*, 1966; O'Brien *et al.*, 1966; Prior and Rose, 1966), although different measures of body bulk have yielded varying

relationships to serum uric acid concentration (Evans *et al.*, 1968). Evans *et al.* (1968) found that ponderal index bore a slightly better relationship to serum uric acid than did body weight, but the relative importance of body fat or lean body mass in determining serum uric acid has never been fully explored.

In the present report, serum uric acid has been studied in relation to lean body mass, as represented by direct measurements of total body potassium, similarly the relationship of total body potassium to parameters of blood potassium have been investigated.

Materials and methods

SUBJECTS

Fifty-seven normal healthy subjects were studied of whom 30 were female (mean age 27.6 years $\pm$ SEM 1.87, range 18 to 52 years) and 27 were male (mean age 29.7 years $\pm$ 1.90, range 21 to 57 years). Each subject was receiving a normal solid and fluid diet and none had taken alcohol within the 24 hours preceding the study. Height (cm) and weight (kg) were measured and a sample of serum was separated

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for uric acid estimation (standard colorimetric autoanalyser technique employing phosphotungstic acid).

In 14 normal males and 11 females (mean age $32.2 \text{ years} \pm \text{SEM } 2.1$, range 18 to 57) a further sample of venous blood was obtained for the determination of plasma urea and potassium concentration, red cell potassium (Boyd, 1970), and packed cell volume.

Total body potassium was measured in each subject using the Merlin mobile shadow-shield whole-body monitor (Boddy, 1967). The subject counting rate in the potassium-40 photopeak ($1.36\text{--}1.56 \text{ MeV}$) was expressed as mmol of potassium without the administration of a radioactive isotope, using the procedure described in detail elsewhere (Boddy *et al.*, 1971). The estimated coefficient of variation of this procedure was shown to be $\pm 3.9\%$ for a subject having 3600 mmol potassium.

By employing the formulae and tables of Hume and Goldberg (1964), it was possible to obtain an estimate of total blood volume, total red blood cell volume, and total plasma volume. Subsequently from these figures an estimate of total plasma uric acid could be obtained for all the control subjects and total plasma potassium and total red cell potassium in the 14 male and 11 female subjects where plasma and red blood cell potassium results were available.

STATISTICAL METHODS

A step-wise regression and Principal Component Analysis was carried out using two BMD packages on the Oxford 1906 computer of the serum uric acid concentration on sex, total body potassium, and serum urea. Linear regressions of total serum uric acid on total body potassium, of total red cell potassium and total serum potassium on total body potassium were calculated by the method of least squares. The rationale of the step-wise regression is to take the variable most highly correlated with

serum uric acid and analyse that regression, then to add the second variable that is most highly correlated after adjustment for the first variable and give the analysis, and then to add the third next highest correlated variable, and so on. The rationale of the Principal Component Analysis is to construct a new set of variables which are linearly related to the original variables, in this study being 11 in number, such that the first few variables should contain as much 'information' as possible. For example, in this study the first principal component accounted for 67% of the total variance, but when taken with the second principal component accounted for 79% of the total variance, etcetera.

Results

The mean, SEM, and range of each parameter measured in the normal subjects is shown in Table 1 and each is in accord with values obtained in our own and in other Caucasian studies.

The results of the regression analysis of serum uric acid concentration on height, weight, sex, lean body mass (measured and predicted), and total body potassium (measured and predicted) in 57 subjects and on the plasma urea, plasma potassium, and intra-red blood cell potassium concentrations in 25 subjects on whom it was possible to obtain the measurements are shown in Table 2. It can be seen that a significant regression exists for serum uric acid on height, weight, sex, lean body mass and total body potassium (both measured and predicted) but not for serum uric acid on plasma urea, potassium, and intra red blood cell potassium concentrations.

The step-wise regression and principal component analysis results indicated that sex was the variable most highly correlated with the serum uric acid concentration and when adjustment was made for this all other factors did not show a significant correlation with the serum uric acid concentration. Fig. 1 illustrates the plot of measured total body

Table 1 Clinical and laboratory data expressed as mean $\pm$ SEM in 57 normal subjects

	Height (cm)	Weight (kg)	Measured TBK (gm)	LBM from TBK (kg)	Uric acid (mg/100 ml)	Plasma K (mmol/l)	Red blood cell K (mmol/l)	Plasma urea (mg/100 ml)	Packed cell volume (%)
Males	173 ± 1.4	69.8 ± 2.4	146.1 ± 3.4	56.3 ± 0.67	6.2 ± 0.16	3.95 ± 0.15	45 ± 0.68	32.5 ± 1.7	43.6 ± 0.39
Females	159.4 ± 1.0	59.3 ± 1.7	96.7 ± 2.1	43.4 ± 0.5	4.3 ± 0.14	3.86 ± 0.1	42.2 ± 1.1	29.4 ± 2.9	40.3 ± 0.57

TBK = total body potassium. LBM = lean body mass.

Conversion: traditional to SI units—Uric acid: $1 \text{ mg}/100 \text{ ml} \approx 0.595 \text{ mmol}/\text{l}$. Plasma potassium and red blood cell potassium: $1 \text{ mEq}/\text{l} = 1 \text{ mmol}/\text{l}$. Plasma urea: $1 \text{ mg}/100 \text{ ml} \approx 0.166 \text{ mmol}/\text{l}$. Packed cell volume: $1 \text{ vol } \% = 0.01$.

Table 2 The separate regressions of serum uric acid concentration on the independent variables measured in the population studied, where β is the regression

Independent variable	Slope (β)	SE (β)	df	t	P
Height (cm)	0.064	0.016	57	3.93	<0.001
Weight (kg)	0.047	0.013	57	3.77	<0.001
Sex	1.898	0.222	57	8.50	<0.001
Lean body mass (LBM)	0.113	0.018	57	6.34	<0.001
Total body potassium (TBK)	0.027	0.005	57	5.93	<0.001
Height, weight, age, TBK (predicted)	0.029	0.005	57	5.78	<0.001
Height, age, TBK (predicted)	0.028	0.005	57	5.22	<0.001
Height, weight, LBM*	0.095	0.016	57	6.06	<0.001
Plasma urea concentration	0.087	0.021	25	0.97	NS
Plasma potassium concentration	0.372	0.446	25	0.83	NS
Intra-red blood cell potassium (male)	0.068	0.095	14	0.72	NS
Intra-red blood cell potassium (female)	0.002	0.061	11	0.04	NS

*Lean body mass obtained from the height-weight formula of Hume and Weyers (1971).

Table 3 The correlation coefficient between serum uric acid (SUA) concentration and height and weight in 57 subjects and intra-red blood cell potassium (RBC K) concentration and plasma potassium (K) concentration in 25 subjects in the study

Correlates	Males (n = 27)	Females (n = 30)	Total (n = 57)
SUA/ height	r = 0.08 P > 0.1	r = 0.15 P > 0.1	r = 0.47 P < 0.001
SUA/ weight	r = 0.22 P > 0.1	r = 0.2 P > 0.1	r = 0.45 P < 0.001
SUA/ RBC K concentration	r = 0.2 P > 0.1	r = 0.12 P > 0.1	r = 0.34 P > 0.05
SUA/ plasma K	r = 0.45 P > 0.05	r = 0.52 P > 0.05	r = 0.13 P > 0.1

value in males (0.043 ± 0.001 SEM) was not significantly different ($P < 0.05$) from that in the female subjects (0.044 ± 0.001).

When total plasma potassium is correlated with total body potassium (Fig. 2) in the 14 male and 11 female subjects, the correlation coefficient is significant in both males ($r = 0.83$, $P < 0.01$) and females ($r = 0.69$, $P < 0.05$). Similarly, with total body potassium and total red blood cell potassium there is a significant correlation in both male ($r = 0.74$, $P = 0.01$) groups (Fig. 3).

Discussion

Many studies have been carried out to ascertain the influence of a multitude of factors on serum levels of uric acid. Reed *et al.* (1972) showed that serum uric acid levels were positively associated with measures of blood pressure, obesity and serum triglyceride levels in Micronesians which confirmed the previous observation of Burch *et al.* (1966) of the importance of the geographical factor in serum uric acid. Other studies have also confirmed this association in other areas of the world (Healey and Jones,

Fig. 1 The correlation between total plasma uric acid and total body potassium in 30 female (●) and 27 male (○) subjects studied. $r = 0.84$; $P < 0.001$.

potassium against total plasma uric acid and it can be seen that for the group as a whole there is a significant correlation ($r = 0.84$, $P < 0.001$) and when the group is broken down for sex the correlation persists for males ($r = 0.64$, $P < 0.01$), and for the female group ($r = 0.45$, $P < 0.01$). These results contrast with the lack of correlation between serum uric acid and plasma potassium concentration (mmol/l) and also intra-red blood cell potassium concentration (Table 3) in the total group or when these are split into male and female groups.

It is of interest that there is a significant correlation between serum uric acid and height and weight when males and females are considered as a single group but when divided by sex, this significance disappears confirming the trend noted in the step-wise regression and principal component analysis. When serum uric acid concentration was expressed as g^{-1} total body potassium, the mean

Fig. 2 The correlation between total plasma potassium and total body potassium in 10 female (●) and 14 male (○) subjects studied. $r = 0.83$; $P < 0.001$ for males. $r = 0.69$; $P < 0.05$ for females.

Fig. 3 The correlation between total red blood cell potassium and total body potassium in 10 female (●) and 14 male (○) subjects studied. $r = 0.71$; $P < 0.01$ for males. $r = 0.74$; $P < 0.01$ for females.

1971; O'Brien *et al.*, 1966; Zalokar *et al.*, 1972; Laing and Murray, 1973).

In this study we have shown that when the group of subjects are considered *in toto*, the serum uric acid concentration correlates significantly with height, weight, lean body mass, and total body potassium. Krizek (1966) also demonstrated a linear relationship between serum uric acid concentration and weight in a population of male and female subjects. However, when this group was divided into male and female subgroups, a significant correlation still existed for males ($r = 0.6$) and females ($r = 0.42$) in contrast to the present findings of the loss of significant correlation when the subjects in our study were considered in terms of male and female subgroups. Acheson and O'Brien (1966) in a

study of the relationship of serum uric acid to other corporeal factors also showed significant correlations between serum uric acid and ponderal index in men and serum uric acid and weight in women. However, it is important to note that Krizek's population had an age range of 18–70 years and his subjects were chosen by reason of obesity and/or because they suffered from one of a variety of 'rheumatic diseases' in contrast to our younger normal subjects. Similarly the population studied by Acheson and O'Brien (1966) had a much higher mean age (46.4 years) in contrast to our group (males—27.6 years, females—29.7 years), suggesting that the former study probably contained a considerable number of postmenopausal subjects. Since the serum uric acid concentration in postmenopausal women is known to be higher than in premenopausal women (Mikkelsen *et al.*, 1965), it is not unlikely that, when contrasting the female populations, where there is a significant difference in age, varying results are likely to emerge.

The difficulties in interpreting correlating factors in epidemiological studies of serum uric acid concentrations are highlighted by the study of Acheson and Florey (1969) who investigated 5047 male army recruits from Argentina, Brazil, Columbia, and the United States. They found that serum uric acid correlated significantly with weight in the Argentinian and American populations, although the coefficients were small, $r = 0.189$ and $r = 0.21$, respectively, whereas no correlation was noted for the Columbian and Brazilian populations.

Similarly, Emmerson *et al.* (1969) in a study of 80 male and 133 female subjects found no correlation between serum uric acid and height, weight, or surface area in the male population. A slight significant correlation was noted between serum uric acid and weight in the females ($r = 0.17$);

no significance was noted between serum uric acid and height or surface area. This contrasts with other workers who found a significant correlation between ponderal index and serum uric acid in a young male population, although this correlation was low (Kasl *et al.* 1970).

Nicholls *et al.* (1973) found that on treating transsexual men with oestrogen therapy the serum uric acid concentration fell and urinary uric acid rose suggesting that hormonal differences were responsible for the known age and sex differences in serum uric acid concentration. However, there was no record in this study of weight change or estimation of lean body mass/fat ratio which might be expected to change with oestrogen therapy. These would certainly be of significance since several workers have found correlations between serum uric acid concentration and body weight (Krizek, 1966) body bulk as measured by the ponderal index (Evans *et al.*, 1968) and weight loss (Nicholls and Scott, 1972).

It therefore seemed to us that perhaps the difference of serum uric acid concentration between the two sexes might be due to a variation in lean body mass rather than simply a hormonal effect.

The results (Fig. 1) certainly demonstrate, for the group as a whole, a clear correlation, between total body potassium and total serum uric acid—rather than the simple uric acid concentration and since it has been shown (Boddy *et al.*, 1972) that total body potassium is proportional to lean body mass, this would suggest that the uric acid concentration in the body as a whole is related to lean body mass. However, this cannot alone account for the differences in sex, since, although when separated into male and female subjects, the correlation is still significant the lines of regression for each group diverge. A further piece of evidence against sex *per se* as the only criterion in determining differences in uric acid concentrations between male and female subjects is the fact that there was no significant differences between either group when serum uric acid was expressed as per grams total body potassium.

These findings contrast with those for potassium in which the mean concentration of potassium in serum was not significantly different between males and females ($P > 0.05$). The mean concentration of potassium in erythrocytes was significantly different, however, in males and females ($P < 0.05$). A significant correlation was obtained between the total serum potassium and total body potassium and also between the total erythrocyte potassium and total body potassium.

These latter findings confirm those of Boddy *et al.* (1976) and in view of the anomalies noted in a

study of potassium in patients with rheumatoid arthritis (Nuki *et al.*, 1975) this method would seem to provide a simple basis for assessing further the status of potassium in this and possibly other disease situations.

The results of this study suggest that serum uric acid is a multifactorial determinant and that lean body mass is but one of these factors and cannot by itself account for differences in levels found between the sexes. The study also shows that expression of plasma and red cell potassium in total levels illustrates a correlation between these and total body potassium which is not demonstrable when comparing blood potassium concentration.

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