Reprinted from
ARTHRITIS AND RHEUMATISM
Vol. 27, No. 6, June 1984

Printed in U.S.A.

BRIEF REPORT

HYPERURICEMIA IN THE INHABITANTS OF THE MARSHALL ISLANDS

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Elevated serum uric acid (SUA) levels are common among Pacific populations, and modifying environmental factors have been investigated as a cause for this finding (1). We have studied SUA levels of people living in the Marshall Islands, which are located in eastern Micronesia, and have found elevated values similar to those reported for other Micronesian populations (2–4). The nearly Gaussian distribution of individual serum uric acid values for men, and for women ≤45 years of age, indicates that the elevation is due to a regularized increase in serum uric acid rather than to a subpopulation that has pathologic hyperuricemia. The higher serum uric acid levels appear, therefore, to be normal for the Marshallese, a conclusion supported by the infrequency of clinical gout in the population tested.

Patients and methods. Annual medical examinations are conducted by Brookhaven National Laboratory (BNL) for a population of Marshallese who were accidentally exposed to radioactive fallout in 1954, for a comparison population, and for all inhabitants of the atolls of Rongelap and Utirik (5). Disease surveillance includes analysis of serum samples, which are collected, frozen within a few hours of collection, and returned to BNL for testing.

In 1974 and 1977 SUA and serum proteins were determined for 384 Marshallese. Analyses were performed colorimetrically using the Technicon Auto Analyzer I (Technicon Corp., Tarrytown, NY). The testing procedure for uric acid is based on a carbonate method utilizing a phosphotungstate reaction of Folin-Denis reagent (6). A modification of the biuret reaction was used for total protein analysis. Serum protein electrophoresis was performed on a Quick Scan Electrophoresis Analyzer using Titan III cellulose acetate plates (Helena Laboratories, Beaumont, TX). Albumin and globulin fractions were calculated by multiplying the relative percents of each by the total protein and dividing by 100.

Medical records were reviewed to extract pertinent clinical data, and individuals were classified according to diabetic status, blood pressure readings, and obesity at the time of SUA testing. The diagnosis of diabetes was based on World Health Organization guidelines (7). An individual was listed as hypertensive if a diastolic reading of 90 mm Hg or greater was noted on 2 occasions separated by an interval of at least 1 year. Obesity was estimated using the formula that divides weight in kilograms by the height in meters squared (the body mass index [BMI]). A value greater than 27 was considered an indication of obesity (8). Clinical entries were reviewed for recorded evidence of gout, defined as acute, recurrent monarticular arthritis, at the time of, and 5 years subsequent to, SUA testing.

Virtually all subjects resided on 1 of 4 islands. Because of their remoteness, those people living on Rongelap and Utirik atolls tend to be traditional in customs, diet, and economy. Local foods (fish, breadfruit, pandanus, and coconut) are, however, heavily supplemented by foods supplied by the U.S. Department of Agriculture (rice, canned meats), and import-

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Submitted for publication May 17, 1983; accepted in revised form January 19, 1984.

Table 1. Mean serum uric acid values in a Marshallese population*

	Men (n)	Women (n)	Women ≤ 45 years of age (n)
Age			
15–24	6.6 ± 1.0 (53)	5.1 ± 1.2 (41)	
25–34	6.9 ± 1.3 (41)	5.2 ± 1.1 (49)	
35–44	6.5 ± 1.7 (26)	5.4 ± 1.4 (35)	
>44	6.5 ± 1.4 (68)	6.2 ± 1.3 (71)	
Total	6.6 ± 1.3 (188)	5.6 ± 1.4 (196)	
Island†			
Rongelap	6.1 ± 1.0 (37)	5.1 ± 1.3 (31)	4.7 ± 0.9 (23)
Utirik	6.5 ± 1.4 (68)	5.7 ± 1.1 (64)	5.6 ± 1.1 (39)
Ebeye	6.9 ± 1.4 (45)	5.5 ± 1.6 (63)	5.1 ± 1.5 (39)
Majuro	6.9 ± 1.2 (29)	5.8 ± 1.3 (32)	5.5 ± 1.1 (22)
Radiation exposure			
High	6.7 ± 1.0 (29)	5.5 ± 1.3 (35)	
Low	6.4 ± 1.3 (45)	5.8 ± 1.3 (62)	
None	6.6 ± 1.4 (55)	5.4 ± 1.5 (60)	

* Values represent the mean ± 1 SD.
† Excluded are 15 people who lived elsewhere.

ed alcoholic beverages are not permitted. Those living on the islands of Ebeye and Majuro are more closely associated, socially and economically, with the United States. They receive no U.S. Department of Agriculture food. The 3 subgroups evaluated in this study can also be classified according to history of radiation exposure (5). The "high" exposure group (Table 1) refers to those individuals who received an average total-body gamma radiation dose of 69–175 rads, and those in the "low" exposure group received about 14 rads. The individuals having no exposure ("none") are from a selected comparison population that has an age and sex composition statistically similar to the exposed groups. Only persons aged 15 years or older at the time of SUA testing have been included in this analysis.

Statistical analysis was performed utilizing BMDP statistical software as described in the BMDP Statistical Software 1981 Manual (University of California Press).

Results. One hundred seventy persons had SUA determinations in both 1974 and 1977. The mean SUA values for the 2 years were identical, 6.0 mg/dl. A paired *t*-test indicated no significant differences in SUA values between 1974 and 1977 ($t = 1.15$, $df = 169$, $P = 0.25$). For this reason, the total number of persons evaluated included persons tested in either or both years (n = 384).

The mean SUA was 6.6 ± 1.3 SD for men (n = 188), and 5.6 ± 1.3 SD for women (n = 196). The normal range obtained using the same technique in the same laboratory for an unselected adult U.S. population is 5.6 ± 0.9 SD for men, and 4.4 ± 0.8 SD for women. Mean age-specific values were similar for men, whereas SUA levels increased with age in women, especially after age 45 (Table 1). The cumulative frequency probability plot of SUA values for men was nearly Gaussian, but was skewed toward higher values for women. Skewness nearly disappeared after deletion of values of those women who were over 45 (Figure 1).

A significant correlation was noted between SUA and total serum protein. This was due to the albumin component (Table 2). The mean serum albumin of the Marshallese, however, was lower than that

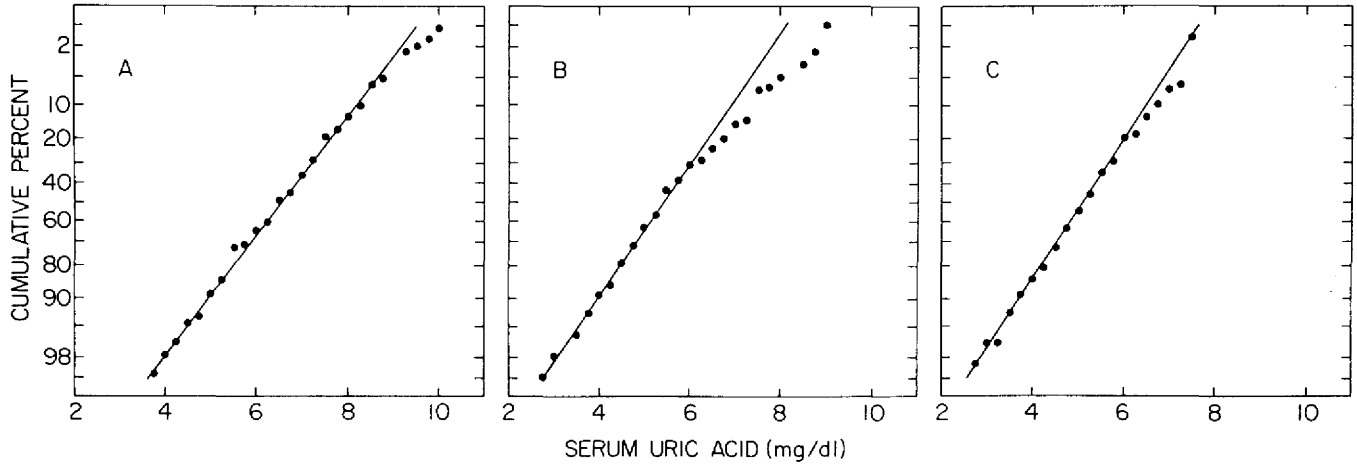

Figure 1. Cumulative probability plots of serum uric acid (SUA) (in mg/dl) for A men, B women, and C women 45 years of age and under. The straight lines are drawn through the lower, and therefore more likely normal, SUA range in order to highlight deviations in the high range.

Table 2. Correlations between serum uric acid (SUA) and serum proteins*

	No. persons tested	Correlation coefficient	Probability†
Total protein			
Men	156	0.1697	0.05
Women	169	0.1768	0.05
Total	325	0.1300	0.02
Total globulin			
Men	149	0.0905	NS
Women	167	0.1139	NS
Total	316	−0.0275	NS
Albumin			
Men	151	0.1957	0.02
Women	168	0.1412	0.05
Total	319	0.2541	0.01

* Outlying values (arbitrarily selected as a SUA >9.5 mg/dl for men and >8.5 mg/dl for women) were excluded in this analysis.
† NS = not significant.

of the U.S. population followed at BNL (4.4 ± 0.5 SD [n = 319], versus 4.7 ± 0.4 SD, respectively), whereas total globulin levels were higher in the Marshallese (3.7 ± 0.6 SD [n = 316], versus 2.6 ± 0.7 SD). Outlying values (arbitrarily selected as a SUA >9.5 mg/dl for men and >8.5 mg/dl for women) were excluded in these correlations because the purpose was to study the effect of protein binding on normal SUA in the general population.

Other findings included:

1) a significant correlation between SUA values and BMI (men: $r = 0.230$ [n = 110], $P < 0.02$; women: $r = 0.274$ [n = 137], $P < 0.01$).
2) a significantly higher mean SUA value in hypertensive subjects than in nonhypertensives (6.7 mg/dl [n = 32], versus 6.0 mg/dl [n = 356], $P = 0.02$). When values of obese individuals were removed, however, this difference was lost (6.3 mg/dl [n = 16], versus 6.0 mg/dl [n = 262], $P = 0.54$).
3) a lower mean SUA value in diabetic subjects than in nondiabetics, but the difference was not statistically significant (5.7 mg/dl [n = 35], versus 6.1 mg/dl [n = 353], $t = 1.48$, $df = 41$, $P = 0.15$).
4) a difference in SUA values for men according to island of residence (f [3,175] = 3.03, $P = 0.03$), with the population centers having higher mean values than the remote islands; for women, $P = 0.09$.
5) no significant difference, by one-way analysis of variance, between the groups exposed to radiation and those not exposed (Table 1).

Gout was present in 2 men at the time of SUA testing, and 2 more developed clinical gout over the ensuing 5 years, giving a current prevalence of 1.7%. No patient had gouty tophi.

Discussion. Uric acid is tightly bound to an α_1-α_2-globulin, although only in small quantities (about 0.1–0.2 mg/dl) (9). Other protein binding is considered to be loose, thus permitting glomerular filtration of uric acid. The finding of a significant correlation between SUA and albumin values suggests that albumin is one determinant of SUA levels. This is supported by in vitro studies indicating 1 gm/dl of albumin will bind 0.6 mg/dl of uric acid (10). Data in this report also show that the elevated globulin levels often encountered in tropical areas do not contribute significantly to the SUA level, and thus do not explain the higher values found in the Marshallese.

Another factor influencing SUA is menopause, at which time the SUA level increases (11). In the present series, 67 of 196 women (34.2%) were over age 45. The mean SUA value for all women was 5.6 mg/dl, whereas the value was 5.2 mg/dl for women ≤45 years of age. This difference is reflected in the cumulative frequency distribution (Figure 1).

The distributions of SUA values in these Micronesians were not bimodal, a point that has been noted by others (2,4). Instead, the cumulative frequency distributions, when graphed on probability paper, were nearly straight lines for men and for women under 46 years of age (Figure 1), suggesting that the SUA distribution is Gaussian rather than leptokurtic (12). It is therefore unnecessary, when selecting a "normal" range, to correct for skewness by using percentile cutoffs. For Marshallese men the normal range of SUA (based on the mean ±2 SD) is 4.0–9.2 mg/dl, and for women under 46 years of age, 2.8–7.6 mg/dl. The upper limits of normal are at least 1 mg/dl higher than those reported in U.S. studies using nonenzymatic SUA assays.

A positive correlation between SUA values and both body weight and ponderal index has been reported (13). The present data indicate a similar correlation with another index of obesity, the BMI. The lack of correlation of hypertension with SUA levels (after deletion of values from obese persons), and the lower mean SUA levels in diabetics than in nondiabetics has been reported in other populations (14). While men had higher SUA values in the population centers than on the remote islands, we have insufficient data to

gauge the effect of alcohol or diet on this difference. Additionally, there is considerable interisland travel, which makes it more difficult to isolate specific environmental factors that might account for the difference. As expected, no significant difference was noted among the 3 groups classified according to radiation exposure.

In the Framingham study (15), the prevalences of gout at mean ages of 44 and 58 were 0.2% and 1.5%, respectively, with the minimum age on entry into the study being 30 years. Applying the same minimum age cut-off to the Marshallese at the time of SUA testing, the prevalence of gout was 0.85% at a mean age of 50, and 1.7% at 55. In this population, then, gout was encountered about as commonly as in the Framingham study.

It is not clear, at least from the present data, that the Marshallese belong to the "one gouty family" described by Kellgren for Pacific populations (16). First, the prevalence and 5-year followup data on clinical gout are not too different from those reported in the U.S. Second, although mean SUA values were high in the Marshallese, the cumulative frequencies of values for men and for women 45 years of age or less approach a normal distribution, indicating a higher normal range than that found in the U.S. Hyperglobulinemia, often found in tropical areas, does not contribute to the higher levels.

These findings may not accurately reflect the true prevalence of hyperuricemia in the Marshall Islands because of the nonrandom nature of the investigation. Nevertheless, since inhabitants of the Marshall Islands presently number about 32,000, our findings describe more than 1% of that population.

Acknowledgment. We gratefully acknowledge the secretarial services of Mrs. Geraldine Callister.

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