The Effect of Menopause on Serum Uric Acid Levels in Non-Obese Healthy Women

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Elevated circulating serum uric acid concentrations may be linked with an increased risk of coronary heart disease (CHD). We measured serum uric acid levels in 50 premenopausal and 88 postmenopausal non-obese white women who underwent an intravenous glucose tolerance test. The uric acid concentration was significantly higher in postmenopausal versus premenopausal women. Adjustment of the data to take into account a number of confounding variables, including the age and body mass index (BMI), revealed a highly significant independent difference between the groups. BMI was found to be a significant independent predictor of the uric acid concentration, but this was confined to premenopausal women. Postmenopausal women were found to be more insulin-resistant, and significant correlations were observed between components of the insulin resistance syndrome and uric acid in both groups. We conclude that increases in serum acid in postmenopausal women may result from changes in metabolism as a consequence of the menopause, and may be associated with the increased risk of CHD seen in these women.

EPIDEMIOLOGICAL EVIDENCE suggests that premenopausal women are at lower risk of coronary heart disease (CHD) than men of comparable age, and the relative cardiovascular protection is lost following the menopause.[1] This loss of protection can be linked to a loss of endogenous sex hormone production, both in women who have been oophorectomized[2] and in women undergoing natural menopause.[3] The cessation of sex hormone production has been shown to affect known markers of CHD risk, and atherogenic changes in lipid profiles have been reported between premenopausal and postmenopausal women.[4,5] Elevations in serum uric acid have also been linked with a number of risk factors for CHD.[6-8] Relative hyperuricemia has been associated with hypertension,[9] hyperlipidemia,[9,10] and obesity.[10,11] Most recently, hyperuricemia has been incorporated into the insulin resistance syndrome.[9,10]

Positive correlations between age and serum uric acid have only been found in women.[12-14] Because serum urate increases with age, postmenopausal women tend to have higher serum uric acid levels than premenopausal women. It has therefore been attractive to hypothesize that changes occurring at the menopause are the cause of this relative hyperuricemia. However, menopausal status was either undefined or determined by chronological age in these studies, so they cannot be regarded as conclusive in implicating the menopause per se. In addition, since the menopause is an age-dependent phenomenon, it is difficult to separate its effects from those of the chronological age, and this is true even of longitudinal studies. Indeed, the Framingham Study concluded that uric acid values increased with age in women, but it was unable to discuss this effect in terms of menopause.[12] An alternative design is to select age-matched groups of premenopausal and postmenopausal women, but it suffers from the difficulty that all participants are likely to be perimenopausal. Furthermore, there may be underlying metabolic differences between the two groups that have resulted in their reaching the menopause at differing chronological ages.

To overcome these problems, we have previously used an alternative approach. Using premenopausal and postmenopausal women of disparate age, we adjusted for the effects of age in the statistical analysis.[15] Using this approach, we investigated whether alterations in serum uric acid may be due to the menopause rather than age. Since we have previously demonstrated that the menopause is associated with significant alterations in insulin metabolism,[15] we investigated whether changes in insulin sensitivity are linked to alterations in serum uric acid.

SUBJECTS AND METHODS

Serum uric acid levels were measured in 138 healthy white women, all of whom were within 20% of their ideal body weight according to Metropolitan Life Tables. None were taking medication or had any clinical condition known to affect uric acid metabolism. Fifty were premenopausal with a regular menstrual cycle, and were studied between days 21 and 25. They were initially recruited over a three-year period to form the control group in a study of the metabolic effects of oral contraceptive use, and none had used hormonal contraception during the 3 months before the study. The remaining 88 were postmenopausal as assessed by amenorrhea and elevated gonadotropin levels (follicle-stimulating hormone > 40 IU/L; estradiol < 20 pg/mL), and were initially recruited for an investigation of the metabolic effects of hormone replacement therapy during the same period. Twenty-six had undergone hysterectomy and met the prior criteria for loss of ovarian function. The time since cessation of menses was ascertained in the other 62 and ranged from 6 to 72 months, with a median of 26.5. None received treatment with gonadal steroids during the 3 months prior to the study. All procedures were approved by the local Ethics Committee, and written informed consent was obtained in each case. On arrival in the morning after an overnight fast, the height, weight, and diastolic and systolic blood pressure were measured. A general medical history was taken by a clinician, including details of exercise habits, alcohol and tobacco consumption, and family history of diabetes mellitus and heart disease. A sample of blood was taken for serum preparation. The urate level was measured on an automated Miras station using a colorimetric assay based on uricase conversion of uric acid to allantoin (Roche, Herts, UK). Serum total cholesterol and triglyceride levels were measured by fully enzymatic procedures. The high-density lipoprotein (HDL) concentration was measured after

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precipitation with heparin and manganese ions.[16] Low-density lipoprotein (LDL) was calculated by the Friedewald formula.

Intravenous Glucose Tolerance Test

All of the women underwent an intravenous glucose tolerance test. They were asked to consume more than 200 g/d carbohydrate in their diet for the preceding 3 days, to fast for at least 12 hours before the test, and to take only water and refrain from smoking on the morning of the test.

After resting for 15 minutes in a semirecumbent position, an indwelling catheter was inserted into an antecubital vein in each arm for injection and sampling, respectively. The sampling arm was rested on a heating pad to assist blood flow; prolonged venous stasis was avoided. Two successive blood samples were drawn into tubes containing lithium heparin for measurement of fasting plasma glucose, insulin, and C-peptide levels. Then, a glucose dose of 0.5 g/kg body weight was administered as an injection of 50% wt/vol dextrose over a period of 3 minutes. Blood samples for measurement of plasma glucose, insulin, and C-peptide levels were then taken at 3, 5, 7, 10, 15, 20, 30, 45, 60, 75, 90, 120, 150, and 180 minutes after commencement of the injection. Samples were obtained and immediately placed on ice; no more than 15 minutes elapsed between taking the sample and separating the plasma by centrifugation.

Plasma glucose was determined on the same day using a glucose oxidase procedure. Plasma insulin and C-peptide concentrations were measured (on samples stored at -20°C) using a double-antibody radioimmunoassay procedure and a radioimmunoassay kit supplied by Guildhall (Surrey, UK), respectively. Quality control was maintained by use of commercially available lyophilized sera and by participation in national schemes. Overall within- and between-batch coefficients of variation were 1.5% and 1.9% for glucose, 4.4% and 5.8% for insulin (mean of coefficients obtained in the range of 100 to 700 pmol/L), and 7.3% and 8.9% for C-peptide (mean of coefficients obtained in the range of 100 to 3,000 pmol/L). C-peptide at concentrations up to 2,800 pmol/L did not cross-react detectably in the insulin assay. Cross-reactivity of insulin in the C-peptide assay was less than 1%. Measurements of insulin sensitivity (Si) and the rate constant for non–insulin-dependent glucose disposal (Sg) were obtained using the minimal model of glucose disappearance.[17]

Statistical Design

Frequency histograms and normal probability plots were generated for the serum uric acid concentration in premenopausal and postmenopausal women and in the whole group. Uric acid was found to be normally distributed, so no transformation was performed before analysis. There were no outliers, defined as results deviating by greater than 4 SD from the mean.

Adjustment for the confounding effects of a number of variables (age, body mass index [BMI; kilograms per meter squared], parity, alcohol consumption, smoking behavior, exercise habit, family history of heart disease, and family history of diabetes mellitus) was made using multiple linear regression analysis.[18] Categorical variables were coded into an appropriate format. Tobacco use was assigned an integer in the range of 0 to 5 for none, less than five, five to 14, 15 to 24, 25 to 45, and greater than 45 cigarettes daily. Exercise was coded according to US Lipid Research Clinics criteria as 0, 1, or 2 for sedentary, regular strenuous aerobic exercise, and other regular activity, respectively. Only three premenopausal and two postmenopausal women met criteria for category 1, so codes 1 and 2 were amalgamated. The family history of heart disease was coded as follows. Indices were developed for the number of first- and second-degree relatives, with values of 0 to 2 for none, one, and more than one relative having the disease, and these indices were then summed to yield an integer in the range of 0 to 4. The family history of diabetes mellitus was coded in the same way.

Separate analyses within each group were made using the confounding variables as predictors. Validity of the analyses was confirmed by the study of residuals. Regression coefficients were used to adjust the data from premenopausal and postmenopausal groups to a common value for each predictor, the chosen value being the midpoint between the group means for that predictor. All variables were included regardless of whether a significant effect was found. Differences between the two groups were then examined using Student's t test for unpaired data. Comparison of the two groups in terms of the scores for the demographic variables (age, BMI, smoking, exercise, parity, alcohol consumption, family history of diabetes mellitus, and family history of heart disease) was undertaken using the Mann-Whitney test. All statistical analyses were made using BMDP statistical software.

RESULTS

Characteristics of the study population are shown in Table 1. The postmenopausal women were significantly older ($P<.001$) and had a higher BMI ($P<.001$) than the premenopausal women. They also smoked more ($P<.001$) and had a greater number of pregnancies ($P<.001$). There were no differences between the groups for the family history of diabetes mellitus, family history of heart disease, alcohol consumption, or the number of subjects taking regular exercise.

Simple correlation and multiple regression coefficients between uric acid and predictor variables are shown in Table 2. There was no significant correlation between age and uric acid in either premenopausal or postmenopausal women. A positive correlation was seen in the postmenopausal group between uric acid and family history of heart disease. Overall, the BMI was the most consistent predictor of uric acid concentration, showing a highly significant positive correlation in simple correlation analysis that was independent of the effects of the other covariates.

Postmenopausal women had 10% higher serum uric acid concentrations than premenopausal women (Table 3). Following adjustment for confounding variables, this difference achieved greater statistical significance and increased to 16%.

Correlations were also established between components of the insulin resistance syndrome and serum uric acid (Table 4). Significant correlations were observed in premenopausal women between serum uric acid and triglycerides and diastolic blood pressure. In the postmenopausal group, serum uric acid was associated with the insulin area and fasting C-peptide. Although postmenopausal women were not significantly different in terms of insulin sensitivity versus the premenopausal group, there was a trend toward higher insulin resistance.

DISCUSSION

Elevations in serum uric acid have been linked with a number of risk factors for CHD.[6-8] Epidemiological studies have revealed an age-related increase in serum urate in women.[12-14] It has been hypothesized that this change in serum urate, which does not occur in men, is due to the menopause. We have used a statistical approach to investigate whether increased serum uric acid levels in postmenopausal women can be linked to the menopause. After adjustment for a number of variables, our results indicate a significant increase in serum uric acid levels between premenopausal and postmenopausal women that is independent of increasing chronological age. We found a significant correlation between BMI and uric acid in premenopausal but not postmenopausal women. This observation is of interest, as significant correlations between serum uric acid

Table 1. Study Group Characteristics

Characteristic	Premenopausal		Postmenopausal	
	Range	Mean ± SD	Range	Mean ± SD
Age (yr)	21-45	32.1 ± 6.1	43-61	52.3 ± 3.4
BMI (kg/m^2)	15.8-28.4	21.8 ± 2.4	19-27.9	23.5 ± 2
Fasting glucose (mmol/L)	4.3-5.8	4.9 ± 0.05	4.3-6.5	5.1 ± 0.04
Fasting insulin (pmol/L)	12.1-108.1	38.7 ± 10.4	9.1-138.9	44.9 ± 6.4
Fasting C-peptide (pmol/L)	55.5-330.5	173.7 ± 343.3	55-415.4	138.6 ± 346.3
Insulin area (min · nmol/L)	3.25-32	13.4 ± 0.009	4.6-36.8	15 ± 0.008
Glucose area (min · mmol/L)	148-679.3	374.8 ± 114.2	204.5-803.9	430.2 ± 134.4
Insulin sensitivity ($10^5 \cdot min^{-1} \cdot$ pmol/L)	0.3-14.3	5.7 ± 0.007	0.48-22.9	6.0 ± 0.006
Glucose effectiveness ($10^{-2} \cdot min^{-1}$)	0.5-6.1	1.9 ± 1.6	0.3-4	1.6 ± 1.7
Systolic blood pressure (mm Hg)	80-120	105.6 ± 1.6	90-150	115.8 ± 1.6
Diastolic blood pressure (mm Hg)	45-85	68.1 ± 1.3	56-102	74.2 ± 1.03
Total HDL (mmol/L)	0.9-2.4	1.5 ± 0.3	1-2.8	1.7 ± 0.3
LDL (mg/dL)	44.6-185.8	99.1 ± 3.6	72.6-221.8	137.1 ± 3.3
Triglycerides (mmol/L)	0.3-2.3	0.6 ± 0.02	0.3-2.9	0.8 ± 0.002
Alcohol intake (U/wk)	0-28	4.5*	0-28	3.0*
% Smokers (never/previous/current)		47/16/37		69/14/17
% Exercisers (none/nonaerobic/aerobic)		51/4/45		47/2/51
% Family history				
Diabetes mellitus				
0, 1, or ≥2 first-degree relatives		89/11/0		87/12/1
0, 1, or ≥2 second-degree relatives		80/18/2		82/17/1
Heart disease				
0, 1, or ≥2 first-degree relatives		70/27/3		52/42/6
0, 1, or ≥2 second-degree relatives		67/27/6		82/12/6
% Parity (0/1/2/3/4)		75/12/10/3/0		12/15/38/25/10

*Median.

level and BMI have been reported in a number of studies in men.[19,20]

However, in a recent study that showed correlations between BMI and uric acid in 38-year-old healthy non-obese men and women using simple and partial correlation analysis, the relationship was lost in both genders after multiple linear regression.[21] In the women, a significant relationship was observed between the waist to hip ratio and serum uric acid following multiple regression analysis. This finding was suggestive that the relationship between BMI and uric acid in a predominantly premenopausal group of women was due to fat distribution. The fact that the relationship between BMI and uric acid was retained in premenopausal women in our study following multiple regression is probably due to the condition that menopausal status was assigned in our group. The relationship may have been lost in the study by Cigolini et al[21] due to the presence of postmenopausal or perimenopausal women. It has previously been demonstrated that metabolic alterations occurring as a result of the menopause cause significant changes in body fat distribution such that postmenopausal women have a more "male" fat distribution pattern.[22] Given that Cigolini et al observed no relationship in men between uric acid and fat distribution, a plausible explanation for the lack of correlation between BMI and uric acid in our postmenopausal women is a menopause-related change in fat distribution.

We also found significant correlations between components of the insulin resistance syndrome and serum uric acid in both groups. In accordance with other published results, premenopausal women showed significant correlations between diastolic blood pressure, triglycerides, and serum uric acid.[21] These correlations were not observed in the postmenopausal group, but the insulin area and fasting C-peptide were significantly associated with serum uric acid. Although insulin sensitivity did not correlate with serum uric acid in either group, there was a trend toward greater insulin resistance in postmenopausal women.

Table 2. Correlation Coefficients for Serum Urate in Premenopausal and Postmenopausal Women

Group	Age	BMI	Parity	Alcohol	Smoking	Exercise	FHDM	FHHD
Simple regression								
Premenopausal	−.05	.31*	−.30*	.18	−.16	−.12	.17	.07
Postmenopausal	.05	.16	.05	.19	−.11	.08	.04	.25*
Multiple regression								
Premenopausal	−.11	.31*	−.28	.12	−.22	.15	.18	−.08
Postmenopausal	−.02	.11	.07	.15	−.09	.08	−.04	.25*

Abbreviations: FHDM, family history of diabetes mellitus; FHHD, family history of heart disease.
*$P < .05$.

Table 3. Results of *t* Tests Comparing Premenopausal and Postmenopausal Serum Uric Acid Concentrations (mean ± SEM, μmol/L)

Condition	Premenopausal	Postmenopausal
Unadjusted	201 ± 6.25	220 ± 5.90*
Adjusted	188 ± 5.29	218 ± 5.52†

*$P < .05$.
†$P < .001$.

Serum uric acid levels are dependent on uric acid production and excretion. It has previously been demonstrated that estrogen does not directly influence renal elimination of urate.[23] Our data are consistent with the hypothesis that complex metabolic alterations associated with the menopause, rather than the age, are linked to the observed increase in serum uric acid. A plausible explanation would be that the menopause causes changes in body fat distribution that lead to a more insulin-resistant state. This, in turn, concomitantly influences serum uric acid levels. A mechanism for the link between the serum uric acid level and insulin resistance has yet to be established, although reductions in renal elimination of uric acid have been observed in association with increased insulin resistance.[24] However, there is currently no experimental evidence to conclusively demonstrate that this change in renal elimination can significantly affect serum urate levels. Alternative explanations may involve insulin actions on urate production.[25]

Table 4. Simple Correlation Coefficients of Uric Acid With Components of the Insulin Resistance Syndrome

Variable	All Subjects	Premenopausal	Postmenopausal
Fasting glucose	.05	−.04	.03
Fasting insulin	.10	.11	.26*
Fasting C-peptide	.18*	.23	.26*
Glucose area	.13	.28	.03
Insulin area	.27†	.14	.30†
Sg	−.12	−.26	−.02
Si	−.13	.02	−.2
SBP	.03	.11	−.09
DBP	.12	.36*	−.08
LDL	.14	.22	.00
HDL	.00	.14	−.12
Triglycerides	.18*	.39†	.04

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; Sg, rate constant for non–insulin-dependent glucose disposal; Si, insulin sensitivity.
*$P < .05$.
†$P < .01$.

Our results indicate that relative to premenopausal women, increased serum uric acid levels are apparent in postmenopausal women, and this may be associated with the menopause itself, as no correlation between age and urate was observed. This relative hyperuricemia may be linked to alterations in body fat composition and insulin sensitivity.

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