

Gender Differences in the Relationships of Serum Uric Acid with Fasting Serum Insulin and Plasma Glucose in Patients without Diabetes

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ABSTRACT. Objective. To explore gender differences in the relationship of serum uric acid levels with fasting serum insulin and fasting plasma glucose concentrations among an adult Chinese nondiabetic population in Kinmen, Taiwan.

Methods. A total of 7483 nondiabetic subjects (4265 women, 3218 men, aged 30 to 89 years) were involved in a community based epidemiologic study. Those with known or newly diagnosed diabetes were excluded. Overnight fasting blood samples were drawn for serum uric acid, glucose, insulin, lipid, and other biochemical measurements. Demographic and clinical variables including body mass index (weight/height²), waist-to-hip ratio, and blood pressure were measured and documented during face-to-face interviews with structured questionnaires.

Results. Stratified analyses revealed that (1) serum uric acid levels were positively associated with hyperinsulinemia and HOMA-insulin resistance in both men and women after adjusting for hypertriglyceridemia, hypertension, obesity, and plasma glucose levels; and (2) serum uric acid levels were more strongly associated with hyperinsulinemia and plasma glucose levels in women than in men.

Conclusion. Hyperuricemia was positively associated with hyperinsulinemia among patients of both sexes without diabetes. Elevated levels of uric acid should alert physicians to the possibility of insulin resistance. The serum uric acid level was associated with insulin resistance and plasma glucose levels more strongly in females than in males in our study population. (*J Rheumatol* 2001;28:571–6)

Key Indexing Terms:
SERUM URIC ACID
PLASMA GLUCOSE

HYPERINSULINEMIA
INSULIN RESISTANCE

Resistance to insulin mediated glucose uptake may lead to a cluster of abnormalities associated with an increased risk of cardiovascular disease including glucose intolerance, hyperinsulinemia, hypertension, hypertriglyceridemia, and low plasma concentrations of high density lipoprotein-cholesterol (HDL-C)¹. The relationship between serum uric acid concentrations and insulin resistance is controversial²⁻⁷. Some reports support the notion that serum uric acid values are directly related to insulin resistance, independent of age, sex, excess body weight, fat distribution, and blood pressure²⁻⁴. But others indicate that this association may be due

predominantly to covariation of these variables with adiposity or hypertriglyceridemia⁷.

In addition, correlation of elevated uric acid with cardiovascular disease has been described in epidemiologic followup studies^{8,9}. It has been reported that elevated uric acid levels correlate with coronary artery disease in female rather than in male patients with diabetes, independent of hypertension and nephropathy¹⁰. The NHANES I epidemiologic followup study found no association between uric acid and ischemic heart disease among nondiabetic males, but the serum uric acid level was predictive of mortality from all causes and from ischemic heart disease among nondiabetic females¹¹.

We investigated whether the relationship of serum uric acid levels with insulin resistance and other metabolic disorders differs between men and women. Since overt diabetes is reportedly associated with low uric acid levels, patients with diabetes were excluded from this study. Our primary goals were to answer the following questions: (1) Is the serum uric acid level directly related to insulin resistance in men and women without diabetes? and (2) If such a relationship exists, does it differ significantly between the 2 sexes?

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MATERIALS AND METHODS

Study patients. The population of Kinmen, a group of islands lying very close to southern mainland China, has been the focus of a number of population based studies¹²⁻¹⁶ conducted by the Yang-Ming Crusade, a research effort organized by the medical students of National Yang-Ming University¹⁷. Kinmen has a population of about 45,000, most of whom reside on one principal island (Quemoy) and several nearby islets¹²⁻¹⁶. During the period 1991 through 1995, all residents over 30 years of age in 5 major townships of Kinmen (Kin-Hu¹²⁻¹⁵, Kin-Chen¹⁶, Kin-Sa, Kin-Nin, and Lieh-Yu) were surveyed by the Yang-Ming Crusade. The overall response rate was 62.5%, based on a target population of 20,185 by household registration. Because the data of fasting serum insulin were not available in the pilot survey conducted in the Kin-Hu study¹², the data from the remaining 4 townships were used for the current study. Patients with previously or newly diagnosed diabetes were excluded from the analyses.

Demographic and clinical data including body mass index (weight/height²), waist-to-hip ratio, and systolic and diastolic blood pressure (averaged from 3 readings separated by at least 5 min) were measured and documented during face-to-face interviews with structured questionnaires by the Yang-Ming Crusade.

Overnight fasting blood samples were drawn for serum uric acid, plasma glucose, insulin, lipid, and other biochemical measurements. Uric acid levels were determined using the enzymatic spectrophotometric method (reagent kits by BioMerieux, Chardonnieres-les-Dains, France). Fasting plasma glucose was determined by the hexokinase-glucose-6-phosphate dehydrogenase method with the glucose (HK) reagent kit (Gilford, Oberlin, OH, USA). Fasting serum insulin levels were measured by radioimmunoassay (Instar Co., Stillwater, MN, USA). The detection limit was 12.3 pM. The intra and interassay coefficients of variation were 7.4 and 9.1%, respectively.

Definitions of variables. Hyperuricemia was defined as a uric acid level \geq 7.0 mg/dl for men or \geq 6.0 mg/dl for women¹⁸. The definition of diabetes was adopted from the World Health Organization, with modifications¹⁹. Patients with a history of diabetes were considered to have known diabetes. For patients without a history of diabetes, those with one fasting plasma glucose level (FPG) \geq 140 mg/dl were considered to have newly diagnosed diabetes. Subjects with FPG levels between 100 and 140 mg/dl received a 75 g oral glucose tolerance test; those with FPG levels \geq 140 mg/dl or 2 hour plasma glucose levels \geq 200 mg/dl were considered to have newly diagnosed diabetes. Patients with systolic blood pressure \geq 140 mm Hg or diastolic blood pressure \geq 90 mm Hg, and those taking antihypertensive medication, were considered to have hypertension²⁰. Hyperinsulinemia was defined as fasting serum insulin level greater than the 90th percentile of general population distribution in Kinmen (corresponding to a fasting serum insulin level $>$ 20.5 μ U/ml). Insulin resistance was calculated by the homeostasis model assessment (HOMA) using the formula: insulin resistance (HOMA IR) = [fasting insulin (μ U/ml) \times fasting glucose (mmol/l)]/22.5, as described by Matthews, *et al*²¹. Thus, low HOMA IR values indicate a high insulin sensitivity, whereas high HOMA IR values indicate low insulin sensitivity (insulin resistance).

Statistical analysis. All statistical analyses were carried out using the SAS statistical package. Data are summarized as the mean \pm standard deviation for continuous variables and as proportions for categorical variables. Student's t test and the chi-square test were used to analyze group differences. Multiple regression analysis was used to model the outcome (fasting plasma glucose, fasting serum insulin or HOMA insulin resistance) as a function of covariates, including age, gender, uric acid, HDL-C, body mass index, triglycerides, blood pressure, total cholesterol, creatinine and blood urea nitrogen. Values for fasting serum insulin were log-transformed to improve normality. An interaction term (gender \times uric acid) was added into each model to investigate the gender difference. Finally, the stepwise procedure was applied to model selection and possible statistical collinearity was detected by the Durbin-Watson test.

RESULTS

After excluding those with known and newly diagnosed diabetes (540 women and 350 men), the total number of subjects analyzed was 7483 (4265 women and 3218 men). Their mean age was 49.5 years (range 30 to 89 yrs). Table 1 shows the cardiovascular risk profiles of nondiabetic patients stratified by sex. In the univariate analysis, men and women with hyperuricemia were significantly more likely than those without to have hyperinsulinemia and hypertension, and also had significantly higher levels of fasting plasma glucose, body mass index, creatinine, waist-to-hip ratio, triglycerides and lipids. Among women, hyperuricemia seemed to correlate more with increased age and higher levels of fasting serum insulin, fasting plasma glucose, and hyperinsulinemia than it did with men.

Figure 1 displays the relationships between serum uric acid and fasting plasma glucose and fasting serum insulin in both men and women. The fasting insulin concentration was positively associated with serum uric acid levels in both sexes, but increased more obviously with increasing serum uric acid levels in women than in men. The slope of linear relationship between serum uric acid levels and fasting insulin concentration was 1.06 in women ($p < 0.001$) and 0.84 in men ($p < 0.001$). However, the relationship between fasting plasma glucose and serum uric acid levels differed markedly between the sexes. First, there was a significant interaction effect that the mean values of fasting plasma glucose according to the serum uric acid levels of postmenopausal women and men crossed over approximately at the value of 6 mg/dl. Second, the fasting plasma glucose increased with increasing uric acid levels in both premenopausal and postmenopausal women ($p < 0.001$, tested by linear regression model), but not in men.

Table 2 (both groups, combined model) and Table 3 (sex-specific models) show the results of multiple regression analysis for correlates of fasting plasma glucose (Model 1), fasting serum insulin (Model 2), and HOMA insulin resistance (Model 3). The significant correlates of fasting plasma glucose were age, gender, fasting serum insulin, HDL-C, body mass index, and triglycerides. Uric acid level was independently and significantly correlated with fasting plasma glucose only in women. Factors significantly associated with fasting serum insulin included age, gender, serum uric acid, fasting plasma glucose, HDL-C, body mass index, triglycerides, and blood pressure. In Model 3, serum uric acid, HDL-C, body mass index, triglycerides, and blood pressure were significantly related to HOMA insulin resistance. After adjusting for age and other potential confounding factors, the interaction term (gender \times uric acid) remained statistically significant in all 3 models.

DISCUSSION

Our study utilized a population survey in Kinmen. Selection bias due to nonresponse is inevitable. It was found in a

Table 1. Characteristics of risk profile among hyperuricemic and nonhyperuricemic patients aged 30 and over in Kinmen, 1991-5.

Variable	Men		Women	
	Hyperuricemia (UA \geq 7.0 mg/dl) (n = 987)	Normal UA (UA < 7.0 mg/dl) (n = 2231)	Hyperuricemia (UA \geq 6.0 mg/dl) (n = 892)	Normal UA (UA < 6.0 mg/dl) (n = 3373)
Age (yr)	50.98 \pm 12.64	50.29 \pm 12.58	53.45 \pm 13.73	46.86 \pm 12.62
Fasting insulin (μ U/ml)	13.20 \pm 7.61	11.01 \pm 5.95	15.36 \pm 8.23	12.43 \pm 6.51
Hyperinsulinemia (%)	14.13	6.41	16.83	5.86
Fasting plasma glucose (mg/dl)	99.21 \pm 13.92	97.82 \pm 13.93	101.96 \pm 12.68	94.37 \pm 13.76
Systolic blood pressure (mm Hg)	134.62 \pm 18.91	129.26 \pm 17.98	133.77 \pm 21.35	123.76 \pm 19.36
Diastolic blood pressure (mm Hg)	85.41 \pm 12.30	82.58 \pm 11.48	80.94 \pm 12.38	77.02 \pm 10.10
Hypertension (%)	42.46	29.56	38.13	21.39
Body mass index (kg/m ²)	24.81 \pm 4.01	23.08 \pm 3.65	24.88 \pm 4.32	23.11 \pm 3.68
Waist-to-hip ratio	0.89 \pm 0.05	0.87 \pm 0.05	0.86 \pm 0.06	0.83 \pm 0.06
Triglyceride (mg/dl)	127.22 \pm 69.21	95.12 \pm 49.03	120.15 \pm 71.34	88.89 \pm 46.62
Total cholesterol (mg/dl)	212.83 \pm 40.42	200.78 \pm 38.28	209.75 \pm 40.34	193.34 \pm 36.26
HDL-C (mg/dl)	52.97 \pm 17.19	55.91 \pm 18.66	55.97 \pm 19.64	59.08 \pm 16.64
Creatinine (mg/d)	0.98 \pm 0.32	0.89 \pm 0.81	0.81 \pm 0.35	0.67 \pm 0.23
Blood urea nitrogen (mg/dl)	18.84 \pm 5.73	17.50 \pm 5.61	18.04 \pm 7.03	15.41 \pm 4.03

Data are mean \pm standard deviation unless otherwise indicated. UA: uric acid.

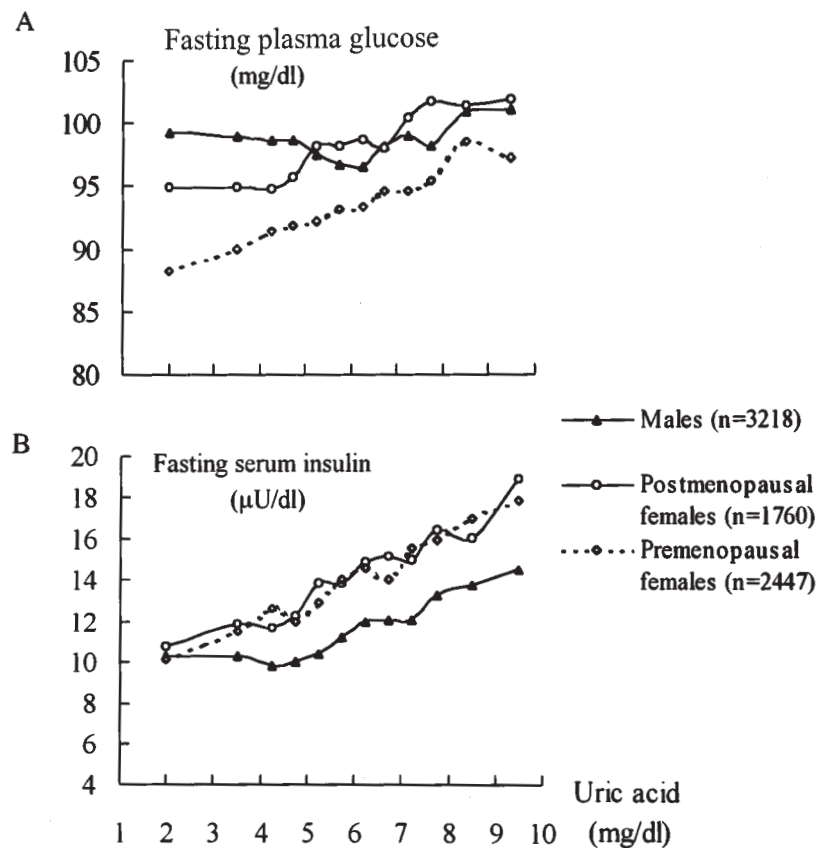


Figure 1. Relationships between serum uric acid and fasting plasma glucose (A), and between serum uric acid and fasting serum insulin (B), in male and female nondiabetic residents of Kinmen, 1991-5. The fasting plasma glucose increased with increasing uric acid levels in women (in both premenopausal and postmenopausal women; $p < 0.001$ tested by linear regression model), but not in men. The fasting insulin was positively associated with serum uric acid levels in both women (slope = 1.06, $p < 0.001$) and men (slope = 0.84, $p < 0.001$).

Table 2. Multiple linear regression analysis for correlates of fasting plasma glucose level, fasting insulin level, and HOMA insulin resistance among nondiabetic patients aged 30 and over, 1991–5.

Variable	Model 1		Model 2		Model 3	
	Parameter (β)	p	Parameter (β)	p	Parameter (β)	p
Age (yr)	0.159	< 0.001	0.002	0.012	0.002	0.322
Gender (female/male)	-4.815	0.002	0.181	0.002	0.359	0.086
Uric acid (mg/dl)	0.215	0.112	0.022	< 0.001	0.112	< 0.001
Gender (female/male) × uric acid	0.578	0.005	0.005	0.041	0.032	0.038
HDL-C (mg/dl)	-0.042	< 0.001	-0.004	< 0.001	-0.008	< 0.001
Body mass index (kg/m ²)	0.226	< 0.001	0.036	< 0.001	0.133	< 0.001
Triglyceride (mg/dl)	0.024	< 0.001	0.001	< 0.001	0.005	< 0.001
Systolic blood pressure (mm Hg)	0.004	0.725	0.002	< 0.001	0.006	< 0.001
Diastolic blood pressure (mm Hg)	0.024	0.408	0.002	0.002	0.008	0.006
Total cholesterol (mg/dl)	0.031	0.616	0.001	0.256	0.013	0.553
Creatinine (mg/dl)	0.173	0.526	0.062	0.792	0.018	0.609
Blood urea nitrogen (mg/dl)	0.056	0.140	0.007	0.284	0.006	0.635

Model 1: Using the fasting plasma glucose (mg/dl) as dependent variable. Model 2: Using the log fasting serum insulin as dependent variable. Model 3: Using the HOMA insulin resistance (HOMA IR) as dependent variable.

Table 3. Sex-specific multiple linear regression analysis for correlates of fasting plasma glucose level, fasting insulin level, and HOMA insulin resistance among nondiabetic patients aged 30 and over, 1991-5.

Variable	Model 1				Model 2				Model 3			
	Men		Women		Men		Women		Men		Women	
	Parameter (β)	p	Parameter (β)	p	Parameter (β)	p	Parameter (β)	p	Parameter (β)	p	Parameter (β)	p
Age (yr)	0.172	< 0.001	0.149	< 0.001	0.003	0.016	0.002	0.042	0.002	0.382	0.004	0.185
Uric acid (mg/dl)	0.240	0.218	0.782	< 0.001	0.018	0.008	0.029	0.001	0.079	0.001	0.124	< 0.001
HDL-C (mg/dl)	-0.067	< 0.001	-0.021	0.016	-0.003	< 0.001	-0.002	0.001	-0.008	< 0.001	-0.005	< 0.001
Body mass index (kg/m ²)	0.262	< 0.001	0.198	< 0.001	0.038	< 0.001	0.035	< 0.001	0.127	< 0.001	0.135	< 0.001
Triglyceride (mg/dl)	0.023	< 0.001	0.025	< 0.001	0.001	< 0.001	0.002	< 0.001	0.005	< 0.001	0.005	< 0.001
Systolic blood pressure (mm Hg)	0.006	0.714	0.008	0.625	0.002	< 0.001	0.003	0.018	0.007	0.003	0.004	0.037
Diastolic blood pressure (mm Hg)	0.013	0.238	0.012	0.677	0.002	0.028	0.002	0.035	0.008	0.033	0.007	0.044
Total cholesterol (mg/dl)	0.031	0.516	0.016	0.550	0.005	0.356	0.001	0.286	0.014	0.413	0.011	0.630
Creatinine (mg/dl)	0.193	0.106	0.138	0.726	0.021	0.340	0.012	0.772	0.021	0.509	0.016	0.339
Blood urea nitrogen (mg/dl)	0.049	0.302	0.056	0.181	0.006	0.071	0.002	0.112	0.007	0.189	0.004	0.079

Model 1: Using the fasting plasma glucose (mg/dl) as dependent variable. Model 2: Using the log fasting serum insulin as dependent variable. Model 3: Using the HOMA insulin resistance (HOMA IR) as dependent variable.

previous study²² that the respondents were younger and healthier than the nonrespondents. Although our study might have underestimated findings in the elderly portion of the population, we did have a good overall response rate of 62.5%. Our findings with this large scale homogeneous nondiabetic Chinese population revealed 2 important points: (1) the serum uric acid level was positively and independently associated with hyperinsulinemia in both sexes, even after adjusting for hypertriglyceridemia, hypertension, obesity, and plasma glucose level; and (2) the associations of serum uric acid with hyperinsulinemia and plasma glucose were stronger among women than men.

Insulin resistance syndrome (syndrome X) refers to a cluster of metabolic abnormalities including glucose intolerance, hyperinsulinemia, hypertension, hypertriglyceridemia, and low plasma levels of HDL-C. This syndrome may substantially increase the risk of atherosclerotic disease^{1,23}. These features of insulin resistance syndrome are observed not only in patients with diabetes and prediabetes, but also in a large proportion of people with insulin resistance who are relatively euglycemic and who may never develop Type II diabetes^{24,25}.

In this study, we used both the fasting serum insulin and homeostasis model assessment (HOMA) insulin resistance

to represent the hyperinsulinemia and degree of insulin resistance. The HOMA has been proposed to assess insulin resistance and validated by insulin clamp (true insulin sensitivity)^{21,26}. We have shown that high serum uric acid levels were directly associated with hyperinsulinemia and HOMA insulin resistance among nondiabetic patients of both sexes. This is in agreement with studies that proposed elevated serum uric acid levels as a feature of insulin resistance syndrome^{2-4,27}.

A previous study exploring physiologically feasible explanations for the association between hyperuricemia and insulin resistance concluded that regardless of the mechanism relating hyperuricemia to hypertriglyceridemia and insulin resistance, the serum uric acid level is independently and strongly correlated with the degree of insulin resistance²⁷. Furthermore, increases in insulin concentration may acutely enhance renal tubular sodium reabsorption, which in turn reduces urinary excretion of uric acid and increases the serum uric acid concentration^{2,28,29}. Thus, insulin resistance appears to modulate serum uric acid concentration at the level of the kidney. Our findings, based on an epidemiologic point of view, provide further evidence for the independent relationship between uric acid metabolism and hyperinsulinemia^{2,29}.

The relationship between serum uric acid and cardiovascular mortality has been reported in recent studies⁸⁻¹¹. Insulin resistance may also partly explain this association²⁷. Alternatively, we were interested to find that the associations of serum uric acid with hyperinsulinemia and fasting plasma glucose were stronger in women than in men. These gender dependent relationships were further investigated using multiple regression analysis and were confirmed by the significant interaction (gender × uric acid level) term. Consistent with this gender difference, many studies have found that serum uric acid levels are predictive of coronary artery disease among women, but not men without diabetes^{11,30-32}. The cross-sectional association between the prevalence of ischemic heart disease and serum uric acid is also stronger among women. Moreover, elevated uric acid levels correlate with the presence of coronary artery disease in women, but not men, with diabetes, and this correlation is independent of hypertension and nephropathy¹⁰.

Although the reasons for these gender differences are still unclear, sex hormones may play a role³³. In postmenopausal women, for example, increased serum uric acid levels may result from menopause related changes in metabolism, and may be associated with an increased risk of coronary artery disease³⁴. However, in our study, after adjustment for menopausal effect, both premenopausal and postmenopausal women with hyperuricemia had higher levels of fasting serum insulin. The fasting plasma glucose increased with increasing uric acid levels in both premenopausal and postmenopausal women, but not in men (Figure 1). For this reason, the menopause effect did not appear to be a possible

confounding factor. Furthermore, fasting plasma glucose was positively associated with the full spectrum of serum uric acid levels in women, but not men. Therefore, we hypothesize that women with hyperuricemia have a relatively increased burden of hyperinsulinemia and hyperglycemia, and we propose that the serum uric acid level is more important for predicting the degree of insulin resistance in women than in men. In addition the significant sex differences in the relationships of serum uric acid with insulin resistance and fasting plasma glucose may explain part of this stronger association between serum uric acid and coronary artery disease in women.

In conclusion, the serum uric acid level should be regarded as an independent marker of hyperinsulinemia among nondiabetic subjects of both sexes, and elevated levels of uric acid should alert physicians to the possibility of insulin resistance. The serum uric acid level was associated with insulin resistance and plasma glucose levels more strongly in nondiabetic women than in men in our study population.

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