Different Progressions of Hyperglycemia and Diabetes Among Hyperuricemic Men and Women in the Kinmen Study

KUAN-CHIA LIN, SHIH-TZER TSAI, HSIAO-YI LIN, and PESUS CHOU

ABSTRACT. ***Objective.*** A 7-year followup study among hyperuricemic subjects was conducted to investigate the association between longterm hyperuricemia and subsequent hyperglycemia and diabetes mellitus. The possible sex difference was also investigated.

Methods. A total of 641 hyperuricemic subjects aged 30 years and over (391 men, 250 women) screened from the community-based Kinmen Study in 1991-92 (the baseline study) were followed in 1997-98, with 75% followup rate. Demographic, clinical, and biochemical data were collected in both baseline and followup periods.

Results. After followup for 7 years, the distribution of plasma glucose concentrations changed moderately among male hyperuricemic subjects, but increased markedly among female subjects. The increase of uric acid levels during the followup period was correlated with subsequent diabetes only among hyperuricemic women. Moreover, a relatively higher incidence of diabetes was found in postmenopausal hyperuricemic women after 7-year followup.

Conclusion. Although the direct role and causality played by uric acid cannot be confirmed by this study, the findings, as applicable to a Chinese nondiabetic population, show that specific progressions of plasma glucose concentrations were significantly different between male and female hyperuricemic subjects. Hyperuricemia and persistent increase in uric acid levels among postmenopausal women should alert physicians to the possibility of subsequent hyperglycemia and diabetes. (J Rheumatol 2004;31:1159–65)

Key Indexing Terms:
HYPERURICEMIA HYPERGLYCEMIA DIABETES SEX DIFFERENCES

Relationships between hyperuricemia and the various stages of glucose intolerance are not uniform. Higher serum uric acid concentrations have been observed among those with prediabetic status or impaired glucose tolerance. But overt diabetes is reported to be associated with low uric acid concentrations in the absence of nephropathy[1-4]. Some studies found that a drop in uric acid concentration was particularly marked in male diabetic subjects[2-4]. In a large-scale study, the association between uric acid concentration and glucose concentration was different between the 2 sexes[4]: an increase in mean serum uric acid level with increasing glucose concentration up to 7.0 mmol/l in men, but above 9.0 mmol/l in women. In our previous study, we found a sex difference, in that serum uric acid level was associated with insulin resistance and plasma glucose levels more strongly in female than in male nondiabetics[5]. Indeed, the degree of hyperuricemia has now been incorporated into the insulin resistance syndrome[6-9]. Several longitudinal studies have reported that baseline hyperuricemia is a significant predictor of subsequent diabetes, but fewer studies have assessed this relationship separately for men and women[10-12].

We investigated the progression of subsequent diabetes in the natural history of hyperuricemia in men versus women.

In this prospective study, a community-based screening program conducted in Kin-Hu, Kinmen, in 1991-92 was used as the baseline study[13-15], and 641 subjects with hyperuricemia (391 men and 250 women) were identified and followed in 1996-97 to investigate the incidence of diabetes and possible sex difference.

MATERIALS AND METHODS

Study subjects. The Kinmen Study is a population survey that has been in progress since 1991. A series of topics on diabetes, hypertension, and coronary heart disease have been studied. During the period of 1991 through 1995, all residents over 30 years of age in 5 major townships of Kinmen (Kin-Hu[13-16], Kin-Chen[17], Kin-Sa, Kin-Nin, and Lieh-Yu) were surveyed by the Yang-Ming Crusade, a research effort organized by the medical students of National Yang-Ming University[18]. Most of the study that was related to epidemiology of diabetes and coronary heart disease was studied in Kin-

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Supported by grants from the National Science Council, ROC (NSC 89-2320-B-010-054), and the Yen Tjing-Ling Medical Foundation.

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Submitted April 28, 2003; revision accepted December 19, 2003.

Chen, Kin-Sa, Kin-Nin, and Lieh-Yu, while investigation of hyperuricemia and gout was mainly conducted in Kin-Hu. The characteristics of the target population and the methodology have been reported[18,19]. In 1991-92, a baseline survey was conducted in 3185 registered residents (1515 men, 1670 women) over 30 years of age in Kin-Hu (a major town of Kinmen). The prevalence of hyperuricemia (uric acid ≥ mg/dl in men and ≥ 6.0 mg/dl in women) was 25.8% (391/1515) for men and 15.0% (250/1670) for women. Six hundred forty-one hyperuricemic subjects were then followed in 1997-98 to study the natural history and associated disorders. Demographic and clinical data including body mass index (BMI, weight/height^2), smoking habit, drinking habit, verification of personal and family disease history, and systolic and diastolic blood pressure (averaged from 3 readings separated by at least 5 min) were measured and documented by the Yang-Ming Crusade, during individual interviews with structured questionnaires, both at baseline and during followup.

After interview, overnight fasting blood was drawn by a public health nurse. The blood was preserved with EDTA in NaF tubes, kept frozen (–20°C), and sent to the biochemical laboratory of Taipei Veterans General Hospital–Taipei for testing. Uric acid levels were determined using the enzymatic spectrophotometric method (reagent kits by bioMérieux, Chardonnieres-les-Dains, France). Fasting plasma glucose was determined by hexokinase-glucose-6-phosphate dehydrogenase method with a glucose (HK) reagent kit (Gilford, Oberlin, OH, USA). Fasting serum insulin was measured by radioimmunoassay (Incstar, Stillwater, MN, USA). The detection limit was 12.3 pM. The intra- and interassay coefficients of variation were 7.4% and 9.1%, respectively.

Definition of variables. Hyperuricemia was defined as uric acid ≥ 7.0 mg/dl for men and ≥ 6.0 mg/dl for women[20]. Subjects were considered to have type 2 diabetes if they met the 1999 World Health Organization criteria[21]. Subjects who gave a history of diabetes and who were under treatment with either insulin or oral antidiabetic agents were considered to have known diabetes regardless of their plasma glucose levels. For subjects without a history of diabetes, those with one fasting plasma glucose level (FPG) of ≥ 126 mg/dl were considered to have newly diagnosed diabetes. Subjects with FPG levels between 100 and 125 mg/dl received a 75 g oral glucose tolerance test; those with FPG levels of ≥ 126 mg/dl or 2-hour plasma glucose levels of ≥ 200 mg/dl were considered to have newly diagnosed diabetes. Three consecutive blood pressure readings at least 5 min apart were taken from the right arm with the person seated. Diastolic blood pressure was measured at the fifth phase. Hypertension was defined if the average of the 3 readings was ≥ 140/90 mm Hg[22]. Obesity was defined as BMI (weight/height^2) ≥ 25 kg/m^2 for men and women.

Statistical analysis. The progressions of plasma glucose levels among hyperuricemic subjects were observed separately for men and women by study periods. Age-specific and menopause-stratified incidence of diabetes among hyperuricemic subjects was observed. Differences in study variables among converts to diabetes and nonconverts were tested at baseline and during followup periods, respectively. Data were summarized as the mean ± standard deviation for continuous variables, and as proportions for categorical variables. Mann-Whitney U test (in view of the non-normal distribution of the results) and the chi-square test (no cells have expected count less than 5) were used, as appropriate, to analyze group differences. To estimate the influence of variable changes (including uric acid level change) between 2 data points in the development of diabetes, a logistic regression model including the absolute change of each variable was assessed in order to adjust the initial value. All statistics were analyzed by the Statistical Analysis System (SAS).

RESULTS

A total of 641 hyperuricemic subjects aged 30 years and over (391 men and 250 women) screened from the community-based Kinmen Study in 1991-92 (the baseline study) were followed up in 1997-98. Table 1 shows the baseline characteristics of hyperuricemic subjects. After intense screening, 482 hyperuricemic subjects (75%, including 310 men and 172 women) were followed up. Twenty-eight subjects with known diabetes or with prevalent cases of diabetes at baseline were excluded from analysis of incidence and risk factors.

Table 1. Baseline characteristics of hyperuricemic subjects aged 30 and over in Kin-Hu, Kinmen 1991–92. Continuous variables were expressed as mean ± standard deviation.

Variable	Men, n = 391	Women, n = 250
Age, yrs	48.84 ± 12.13	54.46 ± 13.85
Uric acid, mg/dl	7.95 ± 0.95	7.06 ± 1.08
Fasting plasma glucose, mg/dl	99.35 ± 20.07	98.67 ± 20.34
Diabetes, %	5.1	6.0
Systolic blood pressure, mmHg	135.62 ± 21.43	138.46 ± 25.53
Diastolic blood pressure, mmHg	83.18 ± 13.38	81.79 ± 13.50
Hypertension, %	45.4	47.2
Body mass index, kg/m^2	24.14 ± 2.91	24.82 ± 3.86
Obesity, %	20.3	28.0
Waist-to-hip ratio	0.91 ± 0.06	0.87 ± 0.07
Triglyceride, mg/dl	118.15 ± 72.3	112.53 ± 62.05
Total cholesterol, mg/dl	214.40 ± 37.28	214.52 ± 39.87
HDL-C, mg/dl	49.53 ± 13.72	51.95 ± 13.04
Creatinine, mg/dl	0.97 ± 0.25	0.76 ± 0.22
Blood urea nitrogen, mg/dl	18.17 ± 6.43	17.88 ± 7.17

HDL-C: high density lipoprotein cholesterol.

Figures 1 and 2 show progression of plasma glucose concentrations from baseline to the conclusion of followup periods. The results revealed that the distribution of plasma glucose levels had changed moderately among hyperuricemic men after 7-year followup. However, among hyperuricemic women, the distribution of plasma glucose levels increased markedly and the number of overt cases of diabetes increased significantly. Table 2 shows the 7-year cumulative incidence of diabetes among hyperuricemic subjects. A relatively higher diabetes incidence was found in female than in male hyperuricemic subjects, especially among postmenopausal women (19.78%; p = 0.012, chi-square test). Table 2 also shows the major differences between converters to diabetes and nonconverters (all statistical inferences tested by Mann-Whitney U test), i.e., among those with asymptomatic hyperuricemia at baseline. The major differences included baseline and followup plasma glucose level, baseline and followup BMI, followup uric acid level, and followup insulin level. It should be noted that followup uric acid level increased significantly only in female converters, but seemed to be decreased among male converters.

To integrate the baseline and followup data and to determine the independent risk factors, we conducted logistic regression on the development of diabetes (Table 3) assessing the effect of risk profile change during 7-year followup. Based on the analysis of repeated measurement, model 1 was preliminarily conducted to estimate the effect

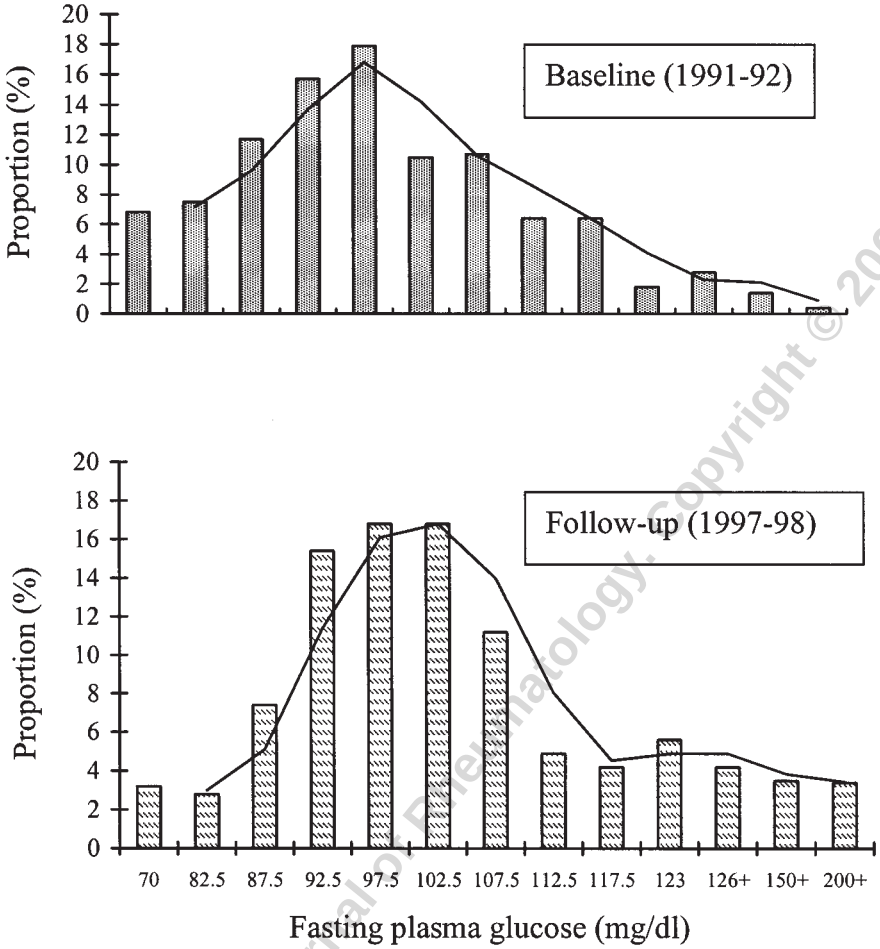

Figure 1. Distribution and progression of fasting plasma glucose among hyperuricemic men from baseline (1991-92) and followup periods (1997-98).

of uric acid level on the development of diabetes. We found each 1 mg/dl increase in uric acid level during followup period was significantly associated with subsequent diabetes in female hyperuricemia subjects independently of menopause effect. On the other hand, model 2 was further analyzed based on the multivariate modeling procedure. Fasting serum insulin data and C-peptide data were not available in the Kin-Hu study survey (i.e., baseline measures[13]); the remaining and initial correlates analyzed in multiple regression included: age, fasting plasma glucose, uric acid, BMI, menopause status (women), high density lipoprotein cholesterol, systolic blood pressure, diastolic blood pressure, serum creatinine, triglyceride, total cholesterol, and fasting serum insulin (only followup values for serum insulin were available).

Multivariate refutation and forward procedure (based on 5% type I error) was used to study and measure the independent correlates of subsequent diabetes. The model 2 results showed that the risk factors of subsequent diabetes among male hyperuricemic subjects were baseline fasting plasma glucose level and baseline BMI. But in female hyperuricemic subjects, the significant variables included baseline fasting plasma glucose level, baseline BMI, menopausal status, and increased uric acid level.

DISCUSSION

This followup study is from the community-based Kinmen Study in 1991-92 (the baseline survey). The overall followup rate was 75% and the reasons for dropouts included known diabetes or prevalent cases of diabetes at baseline (n = 28), death (n = 31), change of residence or migration (n = 82), and serious disability (n = 18). As there were no significant differences in uric acid concentration or other risk profiles at baseline between respondents and nonrespondents, the loss to followup bias would not be considered important. The findings of our followup study have revealed 2 important points: (1) The progressions of plasma glucose levels were significantly different between male and female hyperuricemic subjects. (2) A relatively higher diabetes incidence was found in postmenopausal

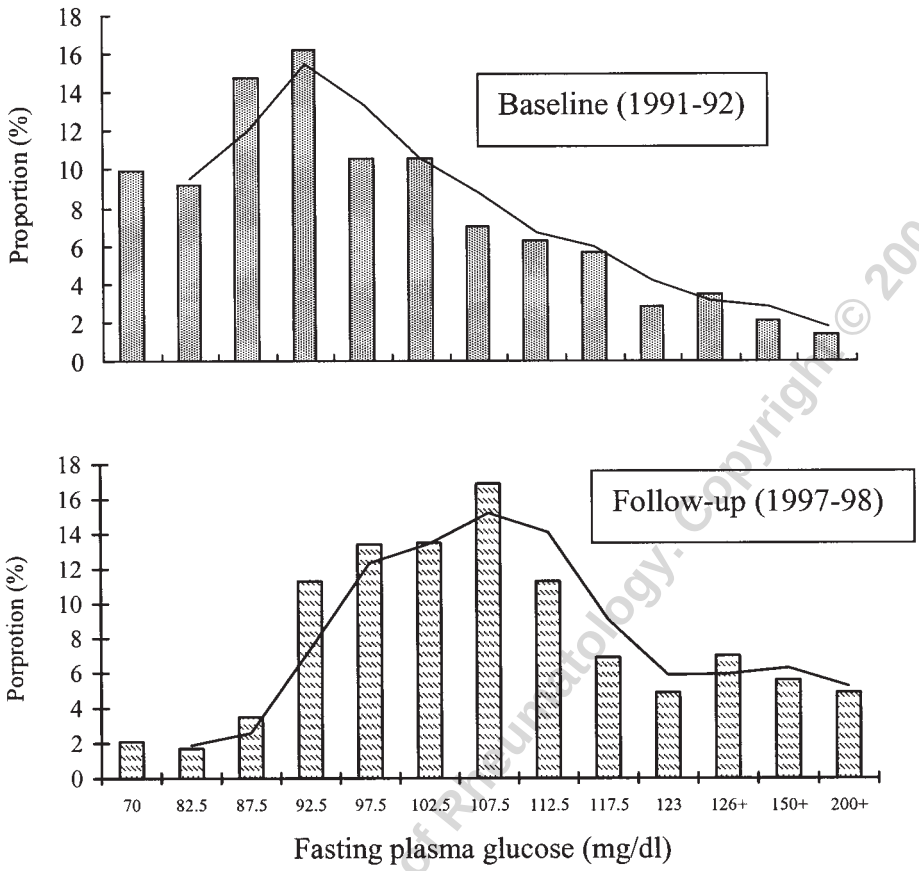

Figure 2. Distribution and progression of fasting plasma glucose among hyperuricemic women from baseline (1991-92) and followup periods (1997-98).

hyperuricemic women after 7-year followup.

Hyperuricemia is related to the overproduction and decrease in urinary clearance of uric acid, and it has a worldwide distribution[20,23-27]. Although hyperuricemia is generally accepted as the primary risk factor for the development of gout, most hyperuricemic subjects are asymptomatic, especially women[15,17,23]. Since the importance of asymptomatic hyperuricemia in the general population remains

Table 2. The 7 year cumulative incidence of diabetes and major differences of converters and non-converters to diabetes among hyperuricemic subjects from baseline (1991-92) to followup periods (1997-98).

Variables	Men			Women		
	Age < 50 yrs	Age ≥ 50 yrs	p value	Pre-menopause	Post-menopause	p value
Cumulative incidence of diabetes, %	9.52 (16/168)	8.80 (11/125)	0.832	5.41 (4/74)	19.78 (17/87)	0.008
	Non-converters	Converters	p value	Non-converters	Converters	p value
Fasting plasma glucose, mg/dl						
Baseline	95.29 ± 12.69	104.96 ± 9.30	0.002	93.15 ± 12.81	103.47 ± 18.32	0.023
Followup	100.42 ± 11.30	173.09 ± 33.23	< 0.001	102.19 ± 12.43	161.88 ± 31.42	< 0.001
Uric acid, mg/dl						
Baseline	7.85 ± 0.89	7.97 ± 0.89	0.619	6.88 ± 0.81	7.04 ± 0.88	0.368
Followup	7.98 ± 1.26	7.65 ± 1.31	0.524	6.86 ± 1.33	7.95 ± 1.98	0.018
Body mass index kg/m^2						
Baseline	24.23 ± 2.72	26.88 ± 2.72	0.002	24.82 ± 3.34	27.75 ± 3.38	0.005
Followup	25.10 ± 2.90	27.25 ± 3.16	0.042	25.19 ± 3.67	28.04 ± 3.85	0.003
Fasting serum insulin, mg/dl						
Followup	11.27 ± 8.03	18.48±8.92	< 0.001	10.50 ± 6.80	20.54 ± 8.49	< 0.001

Table 3. Logistic regression analysis on diabetes among hyperuricemic subjects in Kin-Hu, Kinmen. Assessment of the impact of risk profile change during 7 year followup. In model 2, body mass index at increase at followup and baseline uric acid was not significantly associated with subsequent diabetes and had been dropped from model 2 by forward procedure.

Variables	Men		Women	
	OR	95% CI	OR	95% CI
Model 1				
Uric, acid, mg/dl, baseline	1..06	0.64–1.70	1.58	0.81–3.05
Uric acid, each 1 mg/dl increase during followup period	0.85	0.66–1.25	1.46	1.15–2.12
Menopause, yes vs no	NA	NA	4.53	1.36–9.73
Model 2				
Uric acid, each 1 mg/dl increase during followup period	0.76	0.51–1.22	1.44	1.13–2.25
Menopause, yes vs no	NA	NA	3.88	1.92–7.91
Body mass index, kg/m^2, baseline	1.25	1.08–1.47	1.36	1.12–1.97
Fasting plasma glucose, mg/dl, baseline	1.07	1.03–1.12	1.08	1.04–1.15

OR: odds ratio; CI: confidence interval; NA: not available.

unclear[8,28-30], if the gouty symptom does not occur, people with hyperuricemia are usually unaware of subsequent complications such as hypertension, coronary heart disease, renal disease, and diabetes. Recent evidence from many epidemiologic studies suggests that serum uric acid concentration is an important marker of these diseases, and sex differences have also been reported in previous epidemiologic findings[2,31,32]. On the other hand, relationships between serum uric acid and diabetes have been reported in many studies[1-4]. All the authors conclude that in diabetes the serum uric acid level is reduced, but it is particularly marked in diabetic men. Indeed, there are fewer studies assessing the relationship between hyperuricemia and subsequent diabetes separately for men and women. To consider the different cut off values in the spectrum between uric acid level and plasma glucose concentration in the 2 sexes[5], different progressions of hyperglycemia and diabetes may exist in the natural history of hyperuricemia between men and women.

It is well accepted that type 2 diabetes is associated with insulin resistance and with impaired insulin secretion[33]. Here insulin secretion increases initially and overcomes the effect of insulin resistance, but ultimately fails, thereby allowing blood glucose levels to increase through abnormal glucose tolerance to overt diabetes. Hyperuricemia itself has now been widely discussed in several studies, regarding its relationship with insulin resistance (syndrome X)[6-9,34]. More recently, it has been noted that the main components associated with hyperuricemia are identical to those of insulin resistance syndrome. Cappuccio, *et al* proposed altered tubular sodium handling and uric acid metabolism consistent with hyperinsulinemia, insulin resistance being the possible pathophysiological link[35].

We conducted a multiple regression analysis and forward procedure to study the independent correlates of subsequent diabetes. After adjusting for fasting plasma glucose at baseline and baseline BMI, increasing uric acid during followup still independently and significantly correlated with subsequent diabetes among female hyperuricemic subjects. Nevertheless, the direct role and causality played by uric acid cannot be confirmed in the current study, due to a lack of baseline insulin and C-peptide measurements; and baseline uric acid levels were not significantly associated with an increased risk of diabetes in either men or women. In spite of this, it was interesting to find that increased uric acid levels during followup were significantly correlated with followup insulin level, especially in hyperuricemic women. Hyperuricemia and a persistent increase in uric acid levels, possibly indicating a trend of insulin resistance, could reflect a connection through common underlying pathophysiological processes of subsequent diabetes. This is supported by evidence that increased serum uric acid levels correlate with decreases in insulin-stimulated glucose uptake and they correlated plasma insulin response to oral glucose loading[6-9,35,36]. Moreover, it has been suggested that uric acid might be cytotoxic to the beta cells and may be a marker of a genetic and/or environmental susceptibility to diabetes[37,38].

It was interesting that increased uric acid concentrations during the followup period correlated with subsequent diabetes only among hyperuricemic women. The uric acid changes from baseline to followup between converters to diabetes and nonconverters were also significantly different in both sexes. The possible explanation of these sex differences may be the sex-distinct associations between uric acid level and plasma glucose concentration. It is reported that high plasma glucose levels could lower serum uric acid concentration by enhancing renal excretion of uric acid,

which was more notable in men than in women[2-5]. The results of our study support our previous finding of a stronger association in women than in men of serum uric acid with hyperinsulinemia and plasma glucose levels[5].

Another noteworthy finding is a relatively higher incidence of diabetes found among postmenopausal hyperuricemic women. The changing level of serum uric acid concentration in women at menopause suggests an interaction with sex hormones. Previous research has indicated that increased serum uric acid levels are apparent in postmenopausal women, and this may be associated with menopause itself, as no correlation between age and urate was observed[39]. Therefore, the increase of serum uric acid levels may result from menopause-related changes in metabolism, which are associated with subsequent diabetes[40,41]. In our study, however, after adjustment for menopausal effect, we still found a strong and independent association between increased uric acid levels and subsequent diabetes in women. For this reason, the menopause effect seems not to be a possible confounding factor.

We studied a Chinese nondiabetic population to further examine if women with hyperuricemia and increased uric acid levels had a relatively increased burden of hyperinsulinemia and hyperglycemia. Although the direct role and causality of uric acid cannot be confirmed, our study, as applicable to a Chinese nondiabetic population, shows that specific progressions of plasma glucose concentrations were significantly different between male and female hyperuricemic subjects. A relatively higher incidence of diabetes was found in postmenopausal hyperuricemic women after 7-year followup. Hyperuricemia and persistent increase in uric acid concentrations among postmenopausal women should alert physicians to the possibility of subsequent hyperglycemia and diabetes.

REFERENCES

1. Cook DG, Shaper AG, Thelle DS, Whitehead TP. Serum uric acid, serum glucose and diabetes: relations in a population study. Postgrad Med J 1986;262:1001-6.
2. Tuomilehto J, Zimmet P, Wolf E, Taylor R, Ram P, King H. Plasma uric acid level and its association with diabetes mellitus and some biologic parameters in a biracial population of Fiji. Am J Epidemiol 1988;127:321-6.
3. Herman JB, Goldbourt U. Uric acid and diabetes: observation in population study. Lancet 1982;2:240-3.
4. Whitehead TP, Jungner I, Robinson D, Kolar W, Pearl A, Hale A. Serum urate, serum glucose and diabetes. Ann Clin Biochem 1992;29:159-61.
5. Chou P, Lin KC, Lin HY, Tsai ST. Gender differences in the relationships of serum uric acid with fasting serum insulin and fasting plasma glucose in non-diabetic subjects. J Rheumatol 2001;28:571-6.
6. Modan M, Halkin H, Karasik A, Lusky A. Elevated serum uric acid: a facet of hyperinsulinemia. Diabetologia 1987;30:713-8.
7. Facchini F, Chen YD, Hollenbeck CB, Reaven GM. Relationship between resistance to insulin-mediated glucose uptake, urinary uric acid clearance, and plasma uric acid concentration. JAMA 1991;266:3008-11.
8. Zavaroni I, Mazza S, Fantuzzi M, et al. Change in insulin and lipid metabolism in males with asymptomatic hyperuricemia. J Intern Med 1993;234:25-30.
9. Vuorinen-Markkola H, Yki-Jarvinen H. Hyperuricemia and insulin resistance. J Clin Endocrinol Metab 1994;78:25-9.
10. Chou P, Li CL, Wu GS, Tsai ST. Progression to type 2 diabetes among high-risk groups in Kin-Chen, Kinmen. Diabetes Care 1998;21:1183-7.
11. Hara H, Egusa G, Yamakido M. Incidence of non-insulin-dependent diabetes mellitus and its risk factors in Japanese-Americans living in Hawaii and Los Angeles. Diabetic Medicine 1996;13:S133-S142.
12. Balkau B, King H, Zimmet P, Raper R. Factors associated with the development of diabetes in the Micronesian population of Nauru. Am J Epidemiol 1985;122:594-605.
13. Chou P, Liao MJ, Kuo HS, Hsiao KJ, Tsai ST. A population survey on the prevalence of diabetes in Kin-Hu, Kinmen. Diabetes Care 1994;17:1055-8.
14. Chen CH, Lin HC, Kuo HS, Chang MS, Chou P. Epidemiology of hypertension in Kin-Hu, Kinmen. Am J Hypertens 1995;8:395-403.
15. Lin KC, Lin HY, Chou P. Community-based epidemiological study on hyperuricemia and gout in Kin-Hu, Kinmen. J Rheumatol 2000;27:1045-50.
16. Chen CH, Chuang JH, Kuo HS, Chang MS, Wang SP, Chou P. A population-based epidemiological study on cardiovascular risk factors in Kin-Chen, Kinmen. Int J Cardiol 1995;48:75-88.
17. Lin KC, Lin HY, Chou P. The interaction between uric acid level and other risk factors on the development of gout among asymptomatic hyperuricemic men in a prospective study. J Rheumatol 2000;27:1501-5.
18. Chou P, Liao MJ, Kuo HS, et al. Program description and preliminary health survey data in Kin-Hu, Kinmen. Chin Med J Taipei 1993;52:241-8.
19. Chou P, Kuo HS, Chen CC, Lin HC. Characteristics of non-participants and reasons for non-participation in a population survey in Kin-Hu, Kinmen. Eur J Epidemiol 1997;13:195-200.
20. Darmawan J, Valkenburg HA, Muirden KD, Wigley RD. The epidemiology of gout and hyperuricemia in a rural population of Java. J Rheumatol 1992;19:1595-9.
21. Alberti KGMM, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications: Part 1. Diagnosis and classification of diabetes mellitus: provisional report of a WHO consultation. Diabet Med 1998;15:539-53.
22. Anon. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Arch Intern Med 1997;157:2413-46. Erratum in: Arch Intern Med 1998;158:573.
23. Hall AP, Barry PE, Dawber TR, McNamara PM. Epidemiology of gout and hyperuricemia. Am J Med 1967;42:27-37.
24. Chang SJ, Ko YC, Wang TN, Chang FT, Cinkotai FF, Chen CJ. High prevalence of gout and related risk factors in Taiwan's Aborigines. J Rheumatol 1997;24:1364-9.
25. Klemp P, Stansfield SA, Castle B, Robertson MC. Gout is on the increase in New Zealand. Ann Rheum Dis 1997;56:22-6.
26. Zimmet P, Whitehouse S, Jackson L, Thoma K. High prevalence of hyperuricaemia and gout in an urbanised Micronesian population. BMJ 1978;1:1237-9.
27. Mikkelsen WM, Dodge HJ, Valkenburg HA. The distribution of serum uric values in a population unselected as to gout or hyperuricemia, Tecumseh, Michigan, 1959-1960. Am J Med 1965;39:242-51.
28. Duffy WB, Senekjian HO, Knight TF, Weinman EJ. Management of asymptomatic hyperuricemia. JAMA 1981;246:2215-6.
29. Campion EW, Glynn RJ, DeLabry LO. Asymptomatic hyperuricemia: risks and consequences in the Normative Aging Study. Am J Med 1987;82:421-6.

30. Klinenberg JR, Gonick HC, Dornfeld L. Renal function abnormalities in patients with asymptomatic hyperuricemia. Arthritis Rheum 1975;18:725-30.
31. Fang J, Alderman MH. Serum uric acid and cardiovascular mortality. The NHANES I Epidemiologic Follow-up Study, 1971-1992. JAMA 2000;283:2404-10.
32. Rathmann W, Hauner H, Dannehl K, Gries FA. Association of elevated serum uric acid with coronary heart disease in diabetes mellitus. Diabetes Metab 1993;19:159-66.
33. Reaven GM. Role of insulin resistance in human disease: Banting lecture. Diabetes 1988;37:1595-607.
34. Reaven GM. The kidney: an unwilling accomplice in syndrome X. Am J Kidney Dis 1997;30:928-31.
35. Cappuccio FP, Strazzullo P, Farinaro E, Trevisan M. Uric acid metabolism and tubular sodium handling. Results from a population-based study. JAMA 1993;270:354-9.
36. Sinagra D, Greco D, Scarpitta AM, Bonaventura V. Serum uric acid, insulin secretion and resistance in nonhyperuricemic and hyperuricemic obese female subjects. Int J Obesity 1996;20:1041-3.
37. Orchard TJ, Dorman JS, LaPorte RE, Ferrell RE, Drash AL. Host and environmental interaction in diabetes mellitus. J Chron Dis 1986;39:979-99.
38. Mohan V, Snehalatha C, Jayashree R, et al. Serum uric acid concentrations in offspring of conjugal parents. Metabolism 1984;33:869-71.
39. Wingrove CS, Walton C, Stevenson JC. The effect of menopause on serum uric acid levels in non-obese healthy women. Metabolism 1998;47:435-8.
40. Walton C, Godsland IF, Proudler AJ, Wynn V, Stevenson JC. The effect of the menopause on insulin sensitivity, secretion and elimination in non-obese, healthy woman. Eur J Clin Invest 1993;23:466-73.
41. Matthews KA, Meilahn E, Kuller LH, Kelsey SF, Caggiula AW, Wing RR. Menopause and risk factors for coronary heart disease. N Eng J Med 1989;321:641-6.