Original Article

Positive Association between Hyperuricemia and Metabolic Syndrome: A Large Health Check-up Population in Taiwan

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Objectives: A high prevalence of hyperuricemia and metabolic syndrome has been reported in Taiwan. The association between hyperuricemia and specific components of metabolic syndrome is seldom studied. **Methods:** A cross-sectional study with records of 2006 to 2007 health screening check-up in Taoyuan was used. Hyperuricemia was defined as serum uric acid>7.7mg/dl for males, and> 6.6 mg/dl for females. Patients with metabolic syndrome were defined according to the ATP III criteria, except that one condition relating to the circumference of the waist was substituted by BMI$\geq$27kg/m^2. **Results:** A total of 27,774 records (71.4%) was used in this study. The prevalence of hyperuricemia was 15.7% (95% confidence interval (CI)=15.1–16.3%) for males and 12.3% (95%CI=11.8-12.8%) for females, respectively. The prevalence of metabolic syndrome was 25.4% (95% CI=24.6-26.2%) for males and 24.9% (95%CI=24.2-25.6%) for females, respectively. For both genders, metabolic syndrome and its components were significantly associated with hyperuricemia bivariately and multivariately. The adjusted odds ratio between hyperuricemia and metabolic syndrome was higher in females (2.92, 95% CI=2.64–3.24) than in males (2.04, 95% CI=1.84–2.25). **Conclusions**: A positive association between hyperuricemia and metabolic syndrome and between hyperuricemia and each component of metabolic syndrome was observed in adults with health check-ups in Taiwan. It is concluded that there is an association between hyperuricemia and metabolic syndrome and its components.

Key Words: Hyperuricemia, metabolic syndrome, prevalence, risk factors, health check-up

Introduction

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Hyperuricemia[1-9] and metabolic syndrome[1,10-15] have been reported to be highly prevalent in many countries. Hyperuricemia[16-18] and metabolic syndrome[16,18,19] have been reported as risk factors for cardiovascular disease. More importantly, hyperuricemia[20] can be treated and metabolic syndrome[21] can be reversed so that cardiovascular disease can be prevented.

Cross-sectional studies have identified a positive association between hyperuricemia and

metabolic syndrome[7,9,22-24]. Three cohort studies have reported that individuals with high serum uric acid (SUA) at baseline had an increase risk developing metabolic syndrome than those with low SUA[1,25,26]. However, one cohort study has reported multimetabolic disorders to be independent predictors for the development of hyperuricemia[27].

Nevertheless, few studies have explored the relationship between hyperuricemia and individual components of metabolic syndrome. The objective of this cross-sectional study was to investigate the possible association between hyperuricemia and metabolic syndrome, and between hyperuricemia and specific components of metabolic syndrome.

Material and Methods

Participants

Study subjects were Taoyuan residents, aged 40 years old or above, who participated in the adult health screening check-up from 2006 to 2007. The National Health Insurance provides adult health screening check-ups free of charge to Taiwan residents aged 40+ for primary prevention of chronic diseases.

This study was approved from the IRB of Chang Gung Memorial Hospital (95-0733B, 99-0654C).

Measurement and definition of condition abnormality

The health screening comprised a structured questionnaire, including demographic characteristics, lifestyle behaviors, disease histories, physical examination, and the collection of blood (for laboratory analysis of cholesterol, triglyceride, fasting plasma glucose and uric acid).

Hyperuricemia was defined as serum uric acid (SUA) >458.0μM (7.7mg/dl) for males and >392.6μM (6.6mg/dl) for females[14]. Because many studies use SUA > 7.0mg/dl for males and > 6.0mg/dl for females to define hyperuricemia[1,4-9], these cutoffs were also used to obtain the prevalence of hyperuricemia in order to compare the findings of our study with those of others.

Metabolic syndrome was defined using original and modified ATP III criteria, which include a reduced waist circumference for Asian people[28]. The original ATP III definition of metabolic syndrome requires three of the following criteria: waist circumference ≥ 102 cm (male) or ≥ 88 cm (female); blood pressure ≥ 130/85 mmHg; HDL-cholesterol < 40 mg/dL [1.04 mmol/L] (male) or < 50 mg/dL [1.30 mmol/L] (female); triglycerides ≥ 150 mg/dL [1.70 mmol/L]; fasting glucose ≥ 110 mg/dL [6.1 mmol/L]. Central obesity is defined by waist circumference, and varies among ethnic groups, with limits of 94 cm and 80 cm respectively for white European males and females, but 90 cm and 80 cm for South Asian or Chinese individuals[28]. This study used the body mass index (BMI≥27kg/m^2) instead of the waist circumference[14, 29], which is not measured in the health examination program. For individual component analysis, blood pressure was classified as hypertension (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg) and normotension (systolic blood pressure < 140 mmHg and diastolic blood pressure < 90 mmHg) [29].

Statistical Analysis

All data were expressed as mean ± standard deviation (SD) or as percentages. The 95% confidence interval (CI) was calculated for the age-specific rate of hyperuricemic or metabolic syndrome by gender. A Chi-square test or unpaired t-test was conducted for group comparisons where appropriate. Multiple logistic regression was conducted to obtain unadjusted or adjusted odds ratio (OR) of hyperuricemic on metabolic syndrome or its components. The odds ratio (OR) was presented with a 95% CI. Two-sided p<0.05 was consideredsignificant.

Results

From 2006 to 2007, 38,882 person-times participated in the adult health screening check-up in Taoyuan. The following records were excluded: 5,842 (15.0%) records not returned by the examination hospital, 2,543 (6.6%) repeated records more than once, 277 (0.7%) records of people age < 40, 1,861 (4.8%) missing or unreasonable data on

uric acid or metabolic syndrome components, and 585 (1.5%) records having self-reported cancer or stroke history, Thus, 27,774 records (71.4%) were included in this study. 12,717 (45.8%) subjects were male, while 15,057 (54.2%) participants were female. The mean age was 64.6±13.1 for males and 58.1±11.3 for females. The proportion of cigarette smoking for males (29.2%) was much higher than that for females (2.4%). The proportion of alcohol intake for males (25.8%) was also much higher than that for females (4.1%). The mean SUA level was 6.3 ±1.5mg/dL in males and 5.1±1.3mg/dL in females. The prevalence of hyperuricemia was higher in males (SUA >7.7 mg/dl: 15.7%, 95%CI=15.1– 16.3%) than in females (SUA >6.6 mg/dl: 12.3%, 95%CI=11.8-12.8%). In general, the prevalence of every component of metabolic syndrome was also higher in males than that in females, except for the abnormality of total cholesterol (Tables 1 and 2).

Although the overall prevalence of hyperuricemia was higher in males (15.7%) than in females (12.3%), age-specific prevalence of hyperuricemia behaved differently in the two genders. For males, the prevalence of hyperuricemia remained stable over age. For females, the hyperuricemia started from 4.8% in those aged 40–44, and increased slowly to 25.3% in those aged 80+ (Figure 1). The overall prevalence of metabolic syndrome was similar in both two genders (25.4%, 95%CI=24.6-26.2% for males and 24.9%, 95%CI=24.2-25.6% for females). However, the age-specific prevalence of metabolic syndrome behaved differently in the two genders. For males, the prevalence of metabolic syndrome rose gradually before age of 60, and decreased after then. For females, the rate of metabolic syndrome began at a low prevalence and slightly rose before the age of 50, and increased much more sharply after that time (Fig. 2).

For males and females, hyperuricemia was significantly and positively associated with metabolic syndrome and its components in our bivariate and multivariate analyses. Furthermore, female subjects had higher unadjusted and adjusted odds ratios of hyperuricemia on each component of metabolic syndrome and on metabolic syndrome. For instance, subjects with hyperuricemia had

a higher adjusted risk for hypertension than those without hyperuricemia (OR=2.09, 95% CI=1.88–2.33 for females and OR=1.71, 95% CI=1.54–1.89 for males, respectively). Subjects with hyperuricemia had a high adjusted risk for metabolic syndrome than those without hyperuricemia (OR=2.92, 95% CI=2.64–3.24 for females and OR=2.09, 95% CI=1.84–2.25 for males, respectively) (Table 3 and 4).

Discussion

Prevalence of Hyperuricemia

In this study, the prevalence of hyperuricemia (serum urate>7.7/6.6mg/dl) in individuals who participated in the health screening check-up for males (15.7%) (95%CI=15.1–16.3%) and females (12.3%) (95%CI=11.8-12.8%) was lower than those in previous studies in Taiwan. For instance, the prevalence of hyperuricemia was 20.3% for males and 14.9% for females over 30 years old in Puli township, Nantou County[3], 26% for males and
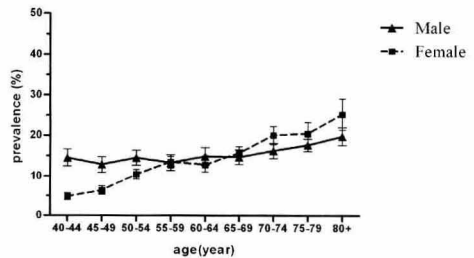

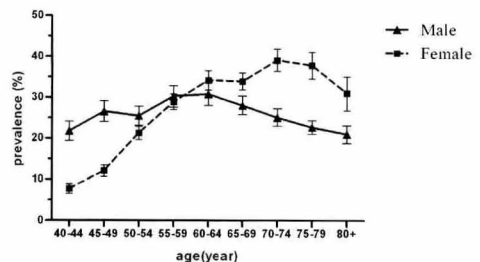Figure 1. Hyperuricemia Prevalence in Taoyuan, Taiwan 2006–2007 (n=27,774)

Figure 2. Metabolic Syndrome Prevalence in Taoyuan, Taiwan, 2006–2007 (n=27,774)

Table 1. Age, Serum Uric Acid, Metabolic Syndrome Components in Male population in Taoyuan, Taiwan, 2006–2007 (n=12,717)

Age (mean ± SD)	64.6±13.1	**BMI** (kg/m^2)	24.8±3.4
Age stratums		Abnormal (BMI≥27)	23.2%
40-44	9.0%	**Systolic BP** (mm Hg)	133.7±20.3
45-49	9.2%	Abnormal (≥140 mm Hg)	35.7%
50-54	10.9%	**Diastolic BP** (mm Hg)	79.9±12.9
55-59	9.2%	Abnormal (≥90 mm Hg)	20.9%
60-64	8.2%	**Total cholesterol** (mg/dl)	196.2±37.1
65-69	11.8%	Abnormal (>200 mg/dl)	43.5%
70-74	12.5%	**Triglyceride** (mg/dl)	133.1±93.3
75-79	18.9%	Abnormal (>150 mg/dl)	28.4%
80+	10.4%	**Fasting glucose** (mg/dl)	102.0±36.6
Cigarette smoking	29.2%	Abnormal (>126mg/dl)	19.4%
Alcohol intake	25.8%	**Metabolic syndrome**	3229 (25.4%)
Serum urate (mg/dl)	6.3±1.5	0	14.4%
Abnormal (>7.7)	15.7%	1	31.0%
Abnormal (>7.0)	28.4%	2	29.2%
Hypertension	6343 (49.9%)	3	17.1%
History	3038 (23.9%)	4	7.0%
New cases	3305 (26.0%)	5	1.3%
Diabetes mellitus	2745 (21.6%)		
History	1026 (8.1%)		
New cases	1719 (13.5%)		

Table 2. Age, Serum Uric Acid, Metabolic Syndrome Components in Female Population in Taoyuan, Taiwan, 2006–2007 (n=15,057)

Age (mean ± SD)	58.1±11.3	**BMI** (kg/m^2)	24.6±3.7
Age stratums		Abnormal (BMI≥27)	23.2%
40-44	13.5%	**Systolic BP** (mm Hg)	129.2±21.4
45-49	14.3%	Abnormal (≥140 mm Hg)	29.1%
50-54	17.1%	**Diastolic BP** (mm Hg)	78.4±12.8
55-59	14.8%	Abnormal (≥90 mm Hg)	17.7%
60-64	10.5%	**Total cholesterol** (mg/dl)	207.4±38.6
65-69	13.1%	Abnormal (>200 mg/dl)	55.3%
70-74	8.1%	**Triglyceride** (mg/dl)	122.9±84.2
75-79	5.6%	Abnormal (>150 mg/dl)	24.3%
80+	3.2%	**Fasting glucose** (mg/dl)	99.4±35.9
Cigarette smoking	2.4 %	Abnormal (>126mg/dl)	15.7%
Alcohol intake	4.1%	**Metabolic syndrome**	3754 (24.9%)
Serum urate (mg/dl)	5.1±1.3	0	17.7%
Abnormal (>6.6)	12.3%	1	30.6%
Abnormal (>6.0)	19.7%	2	26.7%
Hypertension	5972 (39.7%)	3	16.4%
History	2708 (18.0%)	4	7.0%
New cases	3264 (21.7%)	5	1.6%
Diabetes mellitus	2536 (16.8%)		
History	918 (6.1%)		
New cases	1618 (10.7%)		

Table 3. Risk of Hyperuricemia on Metabolic Components for Males: Bivariate and Multivariate Results (n=12,717)

Variables	UA≤7.7 Normal (%)	UA>7.7 Abnormal (%)	Bivariate# OR (95 % CI)	Multivariate# OR (95 % CI)
Metabolic syndrome	23.1	37.9	2.04 (1.84, 2.26)*	2.04 (1.84, 2.25)*
Obesity (BMI >27)	21.4	32.5	1.76 (1.59, 1.96)*	1.78 (1.61, 1.98)*
Hypertension	48.1	62.5	1.80 (1.63, 1.98)*	1.71 (1.54, 1.89)*
Hyperlipidemia	54.7	66.8	1.67 (1.51, 1.84)*	1.74 (1.57, 192)*
Hypercholesterolemia	42.6	48.2	1.26 (1.14, 1.38)*	1.29 (1.18, 1.43)*
Hypertriglyceridemia	25.8	42.4	2.12 (1.92, 2.34)*	2.26 (2.04, 2.50)*
DM	21.0	24.9	1.25 (1.12, 1.40)*	1.17 (1.05, 1.32)*

UA: urate concentration (mg/dl)
Multivariate analyses, adjusted for age, smoking and alcohol
#: UA≤7.7 as reference group
*: p-value<0.01

Table 4. Risk of Hyperuricemia on Metabolic Components for Females: Bivariate and Multivariate Results (n=15,057)

Variables	UA≤6.6 Normal (%)	UA>6.6 Abnormal (%)	Bivariate# OR (95 % CI)	Multivariate# OR (95 % CI)
Metabolic syndrome	21.6	49.0	3.50 (3.16, 3.86)*	2.92 (2.64, 3.24)*
Obesity (BMI >27)	20.6	41.4	2.73 (2.46, 3.02)*	2.49 (2.25, 2.76)*
Hypertension	37.0	61.3	2.70 (2.44, 2.98)*	2.09 (1.88, 2.33)*
Hyperlipidemia	61.3	77.6	2.18 (1.95, 2.45)*	1.88 (1.67, 2.11)*
Hypercholesterolemia	54.1	63.9	1.50 (1.36, 1.66)*	1.34 (1.21, 1.48)*
Hypertriglyceridemia	21.1	46.5	3.24 (2.93, 3.58)*	2.84 (2.57, 3.15)*
DM	15.1	29.5	2.36 (2.11, 2.63)*	1.88 (1.68, 2.11)*

UA: urate concentration (mg/dl)
Multivariate analyses, adjusted for age, smoking and alcohol
#: UA≤6.6 as reference group
*: p-value<0.01

17% for females over 19 years old in the 1993-1996 National Nutrition and Health Survey[2]. When SUA of 7.0/6.0mg/dl was used as the cutoff, the prevalences of hyperuricemia for males (28.4%)(95%CI=27.6-29.2%) and for females (19.7%)(95%CI=19.1-20.3%) in this study similar to those reported for Japan (20–25%)[6] and Iran (27.5%)[7] and higher than USA (17%)[1], Beijing (11.3–15.4% for males, 8.4–11.0% for females, age 40–58)[4], Shanghai (14.2% for males, 7.1% for females)[5], Thailand (18.4% for males, 7.8% for females)[9] and Iran (8.4%)[8]. Thus, ethnic differences were noted.

Men and women had different age-specific rates of hyperuricemia . In this study, the hyperuricemia rate remained stable over age for males, and increased with the advancement of age. Compared with Thailand where hyperuricemia was defined as SUA >7.0mg/dl for males and >6.0mg/dl for females, the rate also increased as age the advancement of age, but the prevalence was higher in males than in females (18.4% vs. 7.8%)[9].

Prevalence of Metabolic Syndrome and Its Components

The rate of metabolic syndrome in males (25.4%) (95%CI=24.6-26.2%) and females (24.9% (95%CI=24.2-25.6%) for females) in this study was higher than those who received self-paid health check-ups in 2000-2001 (10.6% for males and 8.1% for females, aged 20+)[13], higher than those who participated self-paid health check-ups and aged 20-95 in 2005-2007 (15.1% for males and 10.6% for females) [14], and lower than residents aged 40+ in the representative sample of Taichung in 2004-2005 (35.2% for males and 43.2% for females)[15].

The rate of metabolic syndrome in this study was similar to those in American surveys (23.7%, aged over 20) [10], but higher than Canada (15.7%

overall, 18.2% male, 13.2% female, 20–74 years old)[11], and Irish (20.7% overall, 21.8% male, 21.5% female, 50–69 years old) [12].

Our age-specific rates of metabolic syndrome were similar to those of previous surveys[14]. The rate of metabolic syndrome increased with age. The rates of metabolic syndrome in males rose gradually with age up to age 59, and higher than females. For females, the rate of metabolic syndrome increased with age, increasing most rapidly after 50 years old, and the rates were higher than males over 60 years old.

Association between hyperuricemia and metabolic syndrome and its components

Similar to previous studies[7,9,22-24], we also saw a positive association between hyperuricemia and metabolic syndrome, and between hyperuricemia and individual components of metabolic syndrome, for both genders in our bivariate and multivariate analyses. Due the cross-sectional nature of this study, we cannot address there lationship between hyperuricemia and metabolic syndrome over time.

Whether hyperuricemia has a causative role in the development of metabolic syndrome and cardiovascular disease is unclear. Several review articles suggest the following. (1) The vascular effects of uric acid may involve complex pathways that are able to induce oxidative stress, inflammation and endothelial dysfunction[30]. (2) Endothelial dysfunction may cause insulin resistance and hyperinsulinemia, which are both considered the main hallmarks of the metabolic syndrome[31]. (3) The relationship between insulin resistance and uric acid is reciprocal, not independent. Insulin resistance is able to induce hyperuricemia by interfering with urate reabsorption in the kidney[31]. (4) Uric acid may have a role in the pathogenesis of the metabolic syndrome due to high-fructose diet[30,32]. Fructose intake rapidly raises uric acid levels through the activation of fructokinase, ATP consumption, intracellular phosphate depletion and stimulation of AMP deaminase. The increase in uric acid reduces endothelial nitric oxide, which may produce an insulin-mediated vasoconstriction in the skeletal muscle after meals as well as in a reduced glucose uptake and in a consequent increased insulin secretion, with hyperinsulinemia and insulin resistance.

Limitations

This study has some limitations. First, an unrepresentative sample may jeopardize the prevalence of hyperuricemia or metabolic syndrome. Although all residents aged 40 years or older were invited to take health examinations, the participation rate was only 32.2%[33]. Participants who pay attention to their own health, those with enough time, and those with some preclinical symptoms, are generally most likely to take the health examination. Therefore, the prevalence of hyperuricemia or metabolic syndrome might have been overestimated. Second, no correction was performed for the medication effect on hyperuricemia and metabolic components, because medication information for hyperuricemia or metabolic syndrome was not available. Third, although ethnicity may affect the result, 3.9% of research samples involved aboriginal cases (n=1085), so the influence might be minor. Another limitation was that data for fructose intake, which might have influenced serum uric acid levels, were unavailable for the analyzed subjects. However, this limitation is common to all other studies.

Conclusion

Hyperuricemia and metabolic syndrome is common in adults who undertook health check-ups in Taiwan. There is a positive association between hyperuricemia and metabolic syndrome and between hyperuricemia and each component of metabolic syndrome.

Acknowledgments

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Original Article

高尿酸血症和代謝症候群之正相關性-台灣大規模成人健康檢查資料分析

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目標：在台灣高尿酸血症及代謝症候群有很高的盛行率。而高尿酸血症和代謝症候群的子診斷項目之間的關係較少被探討。**方法：**本研究採橫斷研究，對2006-2007年桃園縣社區民眾健康篩檢資料作統計分析。高尿酸血症的定義則是男性以血清尿酸值>7.7mg/dl，女性> 6.6 mg/dl作界定。代謝症候群的定義乃依據ATP III標準，除了腰圍以身體質量指數（BMI ≥27 kg/m²）代替。**結果：**共27,774例（71.4%）的健康篩檢資料作分析。高尿酸血症的盛行率：男性為15.7%（95%信賴區間=15.1–16.3%），女性為12.3%（95%信賴區間=11.8-12.8%）。而代謝症候群的盛行率：男性為25.4%（95%信賴區間=24.6-26.2%），女性為24.9%（95%信賴區間=24.2-25.6%）。不論性別，其雙變量分析與多變量分析皆呈現高尿酸血症和代謝症候群和其相關症狀皆顯著相關。高尿酸血症和代謝症候群的調整勝算比（adjusted odds ratio）皆是女性（2.92, 95%信賴區間=2.64–3.24）高於男性（2.04, 95%信賴區間=1.84–2.25）。**結論：**台灣成人健康檢查資料顯示，高尿酸血症和代謝症候群及其子診斷項目具有正相關。本研究顯示高尿酸血症和代謝症候群以及其相關症狀的出現具相關性。

關鍵詞：高尿酸血症、代謝症候群、盛行率、危險因子、健康檢查

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