Original Article

Prevalence and determinants of hyperuricemia in type 2 diabetes mellitus patients with central obesity in Guangdong Province in China

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This study investigated the prevalence and determinants of hyperuricemia in Chinese type 2 diabetes mellitus (T2DM) patients with central obesity. A multicentric hospital-based cross-sectional study was carried out in Guangdong Province between August 2011 and March 2012. At each hospital, Chinese T2DM patients with central obesity who were aged over 20 years, whose serum uric acid levels were measured, and who had lived in Guangdong Province for ≥1 year, were recruited. Hyperuricemia was defined as serum uric acid >420 µmol/L in men and >360 µmol/L in women. Binary logistic regression was used to assess associated risk factors for hyperuricemia. A total of 2,917 T2DM patients with central obesity took part. The overall prevalence of hyperuricemia was 32.6% (36.1% for women, 28.4% for men). Binary logistic regression analyses demonstrated that women (OR: 1.576; 95% confidence interval (CI): 1.231, 2.018), high BMI (OR: 1.228; 95% CI: 1.094, 1.379), waist circumference (OR: 1.135; 95% CI: 1.009, 1.276), hypertension (OR: 1.603; 95% CI: 1.263, 2.035), high total cholesterol (OR: 1.133; 95% CI: 1.002, 1.281), triglycerides (OR: 1.134; 95% CI: 1.069, 1.203), low HDL-cholesterol (OR: 0.820; 95% CI: 0.677, 0.995) and low estimated glomerular filtration rate (OR: 0.840; 95% CI: 0.815, 0.866) were risk factors associated with hyperuricemia. Hyperuricemia is prevalent in Chinese T2DM patients with central obesity and is significantly positively associated with women, cardiovascular risk factors such as obesity, hypertension and dyslipidemia, and low eGFR.

Key Words: prevalence, risk factors, hyperuricemia, type 2 diabetes mellitus, central obesity

INTRODUCTION

Uric acid is the end product of human purine metabolism. Hyperuricemia is a condition in which the subject has increased serum uric acid levels. Studies have noted that an elevated level of uric acid predicts the development of diabetes, obesity, hypertension and the metabolic syndrome. Uric acid levels tend to decrease with increasing plasma glucose levels in patients with type 2 diabetes mellitus (T2DM). Some cardiovascular risk factors, including obesity, hypertension, dyslipidemia and the metabolic syndrome, are more prevalent in patients with T2DM than in those without T2DM. The prevalence of hyperuricemia in patients with T2DM is high. Ogbera et al reported a 25% prevalence of hyperuricemia in Nigerian patients with T2DM.

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Manuscript received 13 March 2013. Initial review completed 29 March 2013. Revision accepted 13 July 2013. doi: 10.6133/apjcn.2013.22.4.16
T2DM is a chronic metabolic disease that is a major public health problem around the world. With rapid economic growth, increases in life expectancy and changes in lifestyle, the incidence of diabetes mellitus has increased from 0.67% in 1980 to 9.7% in 2008 among the Chinese. Obesity and weight gain are recognized causes of T2DM; approximately 63% of patients with T2DM are overweight or obese in China. Diabetes mellitus is considered a cardiovascular risk equivalent, and cardiovascular disease is the most common cause of death in patients with diabetes mellitus.

Hyperuricemia has recently gained attention as it has been reported that it not only plays an important role in the development of metabolic diseases but is also a cardiovascular risk factor. In China, the world’s most populous nation with approximately 92 million patients with diabetes, central obesity is a characteristic of Chinese obesity. However, the prevalence of hyperuricemia and associated risk factors in Chinese diabetic patients with central obesity has not been investigated. Therefore, this study was conducted to assess the prevalence of hyperuricemia and associated risk factors in Chinese T2DM patients with central obesity.

MATERIALS AND METHODS

The study was a hospital-based multicentric cross-sectional study in Guangdong Province, China. Guangdong Province is divided into four districts according to their administration: 1) Pearl River Delta, with good economic conditions; 2) East of Guangdong, with medium economic conditions; 3) West of Canton, with relatively poor economic conditions; and 4) North of Guangdong, with poor economic conditions. A total of 60 hospitals were included in the study; 46 in Pearl River Delta, 6 in East of Guangdong, 3 in West of Canton, and 5 in North of Guangdong. Compared with the other three districts, Pearl River Delta has the largest population, the best economic conditions and a sufficiently high level of medical infrastructure. Therefore, the majority of hospitals included in the study are located in Pearl River Delta.

At each hospital, Chinese T2DM patients with central obesity, aged over 20 years, whose serum uric acid level had been measured, and who had lived in Guangdong Province for ≥1 year, were recruited between August 2011 and March 2012. Subjects with cancer, or who were pregnant, had severe psychiatric disturbances, hepatic failure or end-stage renal failure, were excluded. The Ethics Committee at each participating institution approved the study protocol. Written informed consent was obtained from each participant before data collection. And nurses and doctors, who participated in this present study, were unified trained.

For each participant, detailed demographic data including age, gender, address, education and occupation were recorded. History of any chronic disease including diabetes mellitus, hypertension, cerebrovascular disease and coronary artery disease were recorded. Information regarding regular diet (yes/no), regular physical activity (yes/no), current smoking pattern (yes/no) and current drinking pattern (yes/no) were also recorded.

All patients underwent a comprehensive medical examination, which included height, weight, waist circumference and blood pressure measurements. After anthropometric and blood pressure had been measured, fasting venous blood samples (drawn from the antecubital vein after at least an 8-hour overnight fast) were collected to determine serum uric acid, blood glucose, glycated hemoglobin (HbA1c), serum creatinine and serum lipid levels.

Anthropometric and laboratory measurements

Weight was measured using a balanced-beam scale with clothing. Height was measured using the clinic stadiometer, with the Frankfort plane held horizontal. The BMI was calculated as weight (kg) divided by squared height (m²). Blood pressure was the average of three measurements obtained by a sphygmomanometer at five minute intervals in one day.

Waist circumference was measured at the midpoint between the lowest rib margin and the iliac crest. In order to obtain accurate measurement data, patients were advised to take their normal breath, not to hold breath or take a deep breath. With appropriate tension, the tape was placed parallel to the floor depending on the metric unit at the midpoint between the lowest rib margin and the iliac crest.

Blood samples were measured at each hospital’s respective clinical laboratory department. Serum uric acid levels were measured by the uricase method. Fasting plasma glucose (FPG) and HbA1c levels were measured by the glucose oxidase method and high-performance liquid chromatography, respectively. Serum creatinine, total cholesterol (TC), triglycerides (TG), HDL-cholesterol and LDL-cholesterol were measured by the enzymatic method. Plasma glucose, serum creatinine, uric acid, TC, TG, HDL-cholesterol and LDL-cholesterol were measured using the Abbott Laboratories fully automatic biochemical analyzer. Estimated glomerular filtration rate (eGFR) was calculated with an equation developed by adaptation of the Modification of Diet in Renal Disease (MDRD) equation on the basis of data from Chinese chronic kidney disease patients.

Definitions and preferred cut-off values

The diagnostic criteria of DM were based on the 1999 WHO diagnostic criteria. The Chinese BMI cut-off points were used to define overweight and obesity: overweight (24 ≤ BMI < 28) and obese (BMI ≥ 28). Central obesity was defined as waist circumference ≥90 cm in men and ≥85 cm in women. Hyperuricemia was defined as serum uric acid >420 μmol/L in men and >360 μmol/L in women, respectively.

Hypertension was defined as systolic blood pressure (SBP) ≥130 mmHg or diastolic blood pressure (DBP) ≥80 mmHg at examinations, and also defined if the participant had a previous physician diagnosis. Dyslipidemia based on the recommendations for the prevention and treatment of dyslipidemia in China and the NECP-ATP III criteria, which was defined by one or more of the following conditions: TC ≥5.7 mmol/L, TG ≥1.7 mmol/L, LDL-cholesterol ≥3.6 mmol/L, HDL-cholesterol <1.29 mmol/L in women and <1.03 mmol/L in men. Dyslipidemia was also defined as a history of specific treatment for this lipid abnormality.
Alcohol drinking was defined as people who had drunk at least 30 g of hard liquor, or 360 g of beer, or 103 g of grape wine or 103 g rice wine at least once a week for 6 months or more. Smoking was defined as people who had smoked at least one cigarette per day for more than half one year. Regular physical activity was defined as participation in 30 or more minutes of moderate or vigorous activity per day at least 3 days per week.

Statistical analyses
Statistical analyses were performed using SPSS version 13.0 software. Quantitative data normality was assessed with the Kolmogorov–Smirnov test and is expressed as mean±SD. Categorical variables are expressed as percentages. Comparisons between quantitative data were conducted using independent-sample t tests and categorical variables were analyzed using chi-square tests. Binary logistic regression analyses were used to identify risk factors that were significantly associated with hyperuricemia in diabetic patients with central obesity. Data are presented as odds ratios (OR) with 95% confidence intervals (CI). A value of p<0.05 was considered statistically significant.

RESULTS

Study population
A total of 2,917 T2DM patients with central obesity were included in the study. Two underweight patients and 22 patients with end-stage renal failure were excluded. Among the 2,917 patients with T2DM, 2,896 patients were of Han nationality and 21 patients were of a minority nationality (one Chao Xian nationality, four Man nationality, two Hui nationality, 12 Yao nationality, one Li nationality, one Zang nationality). The mean age of patients was 59.6±13.2 years (20-90 years), and 1,317 (45.1%) patients were men and 1,600 (54.9%) were women.

The demographic and clinical features of patients stratified by gender are presented in Table 1. There was no significant difference in BMI, FPG, HbA1c and eGFR levels between genders. The duration of diabetes mellitus was significantly higher in women than men.

Some cardiovascular disease risk factors, for example, older age, higher waist circumference, smoking, drinking and family history of diabetes, were more prevalent in men, but hypertension, hypercholesterolemia, low blood HDL-cholesterol and high blood LDL-cholesterol were more prevalent in women.

Demographic and clinical features of patients with and without hyperuricemia
Table 2 shows the demographic and clinical features of patients with and without hyperuricemia. Compared with patients without hyperuricemia, patients with hyperuricemia were older, had a higher ratio of women, a longer duration of diabetes mellitus, lower HbA1c and FPG, higher waist circumferences and BMI, higher prevalence of hypertension and dyslipidemia, higher serum creatinine, lower eGFR, and a higher ratio of smokers and drinkers (Table 2).

Prevalence of hyperuricemia
The overall prevalence of hyperuricemia was 32.6%, and was significantly higher in women than in men (36.1% vs 28.4%, p<0.001) (Figure 1). The prevalence of hyperuricemia increased with increasing BMI in both sexes (p<0.001 in women, p=0.001 in men), and was significantly higher in women than in men (Figure 1).

The total prevalence of hyperuricemia significantly increased with BMI (p<0.001). The prevalence of hyperuricemia in patients with HbA1c <7% was significantly higher than in patients with HbA1c ≥7% (p<0.001). The prevalence of hyperuricemia in patients with hypertension was significantly higher than in patients without hypertension (p<0.001). The prevalence of hyperuricemia in patients with dyslipidemia was also significantly higher.

| Table 1. The demographic and clinical features of the patients by gender |
|---------------------------------|-----------------|-----------------|-----------------|
| | Men (n=1317) | Women (n=1600) | p value* |
| Age (years) | 56.5±14.3 | 62.2±11.6 | <0.001 |
| College or high level of education (%) | 25.1 | 8.5 | <0.001 |
| Family history of DM (%) | 30.3 | 26.4 | 0.028 |
| Duration of DM (years) | 5.94±6.03 | 7.81±6.94 | <0.001 |
| Regular physical activity (%) | 40.6 | 38.7 | 0.326 |
| Smoking (%) | 45.2 | 2.7 | <0.001 |
| Drinking (%) | 27.7 | 1.5 | <0.001 |
| Body mass index (kg/m²) | 27.3±2.90 | 27.1±3.30 | 0.079 |
| Waist circumference (cm) | 99.5±7.69 | 95.2±8.19 | <0.001 |
| Hypertension (%) | 83.7 | 86.7 | <0.025 |
| Fasting plasma glucose (mmol/L) | 8.93±4.06 | 8.94±3.46 | 0.915 |
| HbA1c (%) | 8.95±2.59 | 8.87±2.34 | 0.392 |
| Hypercholesterolemia (%) | 29.0 | 38.0 | <0.001 |
| Hypertriglyceridemia (%) | 55.6 | 55.9 | 0.904 |
| High blood LDL- cholesterol (%) | 24.3 | 30.3 | <0.001 |
| Low blood HDL- cholesterol (%) | 47.4 | 60.1 | <0.001 |
| Dyslipidemia (%) | 80.7 | 87.0 | <0.001 |
| eGFR (mL/min/1.73 m²) | 92.6±38.1 | 90.2±37.3 | 0.104 |

DM, diabetes mellitus; eGFR, estimated glomerular filtration rate.

*Independent-sample t tests for continuous variables (mean±SD) and chi-square tests for categorical variables (%)
Hyperuricemia in patients with diabetes

We carried out binary logistic analyses to evaluate the risk factors for hyperuricemia. The presence of hyperuricemia was a dependent parameter. Independent parameters were associated with the presence of hyperuricemia in bivariate analyses with a p value of <0.05 (Table 2). All the independent parameters were pooled into the analysis together and adjusted ORs were calculated with enter method. As shown in Table 4, the results revealed that the presence of hyperuricemia was significantly associated with women, high BMI and waist circumference, high TC and TG, low HDL-cholesterol, and low eGFR.

**DISCUSSION**
Among Chinese T2DM patients with central obesity, the results of the current study showed prevalence of hyperuricemia in patients with diabetes was significantly higher than in patients without dyslipidemia (p<0.001) (Table 3).

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uricemia in women as 36.1% and in men as 28.4%. Liu et al. systematically analyzed the prevalence of hyperuricemia in general Chinese populations using the meta-analysis method, and reported that the prevalence in women was 8.6% and 21.6% in men. The prevalence of hyperuricemia in Chinese T2DM patients with central obesity as observed in the current study is dramatically higher than in general Chinese general populations as reported by Liu et al.20

Previous studies have reported that men had a higher percentage of hyperuricemia compared with women.20,21 Inconsistent with these reports, the findings of the current study suggest the prevalence of hyperuricemia in women was significantly higher than in men (36.1% vs 28.3%, p<0.001). There are several possible reasons that may explain these conflicting results. First, the mean age of women was significantly higher than that of men (62.2±11.6 vs 56.5±14.3 years, p<0.001) in the present study. 83.8% of women patients were older than 50 years and it is possible that the majority of them were menopausal. Although serum uric acid increases with advancing age;22 this increasing trend is more obvious especially after attainment of menopause;23,24 menopausal women have higher serum uric acid levels than premenopausal women.25 In this study, the prevalence of hyperuricemia in menopausal women was dramatically higher than in premenopausal women (37.7% vs 26.0%, p=0.001). Estrogen is known to promote excretion of serum uric acid. Studies have shown that estrogen could reduce serum uric acid levels, and reduce the prevalence of hyperuricemia in postmenopausal women with hyperuricemia by hormone replacement therapy.26,27 Second, the current study suggests that higher TC (OR, 1.134), higher TG (OR, 1.133) and lower HDL-cholesterol (OR, 0.822) are risk factors associated with hyperuricemia. The prevalence of dyslipidemia in women was dramatically higher than in men (87.0% vs 80.7%, p<0.001). In addition, higher waist circumference was also a risk factor associated with hyperuricemia, and waist circumference was more significantly associated with serum uric acid in women than in men (r²=0.167, p<0.001 in women; r²=0.103, p=0.001 in men). Further studies are needed to clarify these findings.

The current study examined T2DM patients with central obesity with a mean BMI of 27.2 kg/m² and a mean waist circumference of 97.2 cm, and revealed that the total prevalence of hyperuricemia was 32.6%. This prevalence is much higher than the 25% prevalence reported in a study examining Nigerian patients with T2DM with a median BMI of 28.3 kg/m² and a mean waist circumference of 93.5 cm.2 However, the prevalence is much lower than the 44.6% prevalence reported in another study examining obese Indian patients with a median BMI of 44.1 kg/m².21

Studies have reported that the prevalence of hyperuricemia was positively associated with BMI and waist circumference.19,21,23,28-30 Consistent with these studies, the current study revealed that the risk of hyperuricemia increased 1.248-fold and 1.136-fold for every 3.1 kg/m² increase in BMI and every 8.2 cm increase in waist circumference, respectively. Higher BMI and waist circumference are associated with higher leptin production and insulin resistance,29,31 and both have been shown to be inversely correlated with renal clearance of urate. The differences in BMI and waist circumference between our study and other studies1,21 may partly explain the different prevalence of hyperuricemia.

Nan et al reported that serum uric acid levels tended to decrease with increasing plasma glucose levels in patients with T2DM.2 Li et al reported that serum uric acid was negatively correlated with HbA1c (correlation coefficient= -0.24, p<0.001) and FPG levels (correlation coefficient= -0.26, p<0.001) in patients with T2DM.32 Consistent with these studies, the current study showed that the risk of hyperuricemia decreased 0.928-fold and 0.962-fold for every 1% increase in HbA1c and every 1 mmol/L increase in FPG, respectively. Both glycemic control and the function of beta cells worsen with increasing duration of diabetes mellitus; the rate of renal filtration in patients with diabetes increases gradually. Hyperfiltration by glomeruli caused by the hyperglycemic state, which promotes the excretion of uric acid, may partly explain the

| Table 4. Associations between risk factors and hyperuricemia among patients assessed by a binary logistic regression analysis |
|---------------------------------|-----------------|-----------------|-----------------|
| Risk factor                      | Odds ratio      | 95% confidence interval | p value         |
| Age (years)                      | 0.994           | 0.985, 1.005       | 0.189           |
| Gender (women vs. men)           | 1.568           | 1.224, 2.069       | <0.001          |
| Duration of diabetes mellitus (years) | 1.004         | 0.988, 1.020       | 0.663           |
| Current smoking (yes vs no)      | 0.862           | 0.638, 1.165       | 0.330           |
| Current drinking (yes vs no)     | 1.014           | 0.717, 1.434       | 0.939           |
| Body mass index, per 3.1 kg/m² increase | 1.248        | 1.112, 1.401       | <0.001          |
| Waist circumference, per 8.2 cm increase | 1.136       | 1.011, 1.277       | 0.033           |
| Hypertension (yes vs no)         | 1.209           | 0.883,1.654       | 0.236           |
| HbA1c (%)                        | 0.928           | 0.884, 0.973       | 0.002           |
| Fasting plasma glucose (mmol/L)  | 0.962           | 0.932, 0.994       | 0.021           |
| eGFR, per 10 mL/min/1.73 m² increase | 0.836       | 0.811, 0.862       | <0.001          |
| Total cholesterol (mmol/L)       | 1.134           | 1.003,1.282       | 0.045           |
| Triglycerides (mmol/L)           | 1.133           | 1.068, 1.201       | <0.001          |
| LDL-cholesterol (mmol/L)         | 0.822           | 0.679, 0.995       | 0.044           |
| HDL-cholesterol (mmol/L)         | 1.036           | 0.901, 1.192       | 0.619           |

eGFR, estimated glomerular filtration rate
inverse relationship between serum uric acid and HbA1c, and FPG. Studies have reported that elevated levels of uric acid predict the development of hypertension, and 25-60% of patients with untreated essential hypertension had hyperuricemia. In the current study, the prevalence of hyperuricemia in patients with hypertension was dramatically higher than in patients without hypertension (34.3 vs 24.3, \( p<0.001 \)). However, hypertension was not an independent risk factor associated with hyperuricemia (OR, 1.209; 95% CI, 0.883, 1.654). The use of antihypertensive medications could be a confounding reason for this. The frequency of antihypertensive medication use in patients with hyperuricemia was dramatically higher than in those without hyperuricemia (69.8% vs 53.4%, \( p<0.001 \)).

Numerous studies have reported that TC and TG are positively associated with serum uric acid. In agreement with these studies, dyslipidemia in the current study was more prevalent in patients with hyperuricemia than in those patients without hyperuricemia (35.0% vs 20.6%, \( p<0.001 \)). The current study also revealed that the risk of hyperuricemia decreased 0.822-fold for every 1 mmol/L increase in HDL-cholesterol, and the risk of hyperuricemia increased 1.133-fold and 1.134-fold for every 1 mmol/L increase in TC and TG, respectively.

Uric acid is primarily a purine metabolic waste product. About 70% of uric acid is excreted by the kidneys, and decreased excretion is one of the main causes of hyperuricemia. Li et al and Hiroyuki et al reported that serum uric acid levels were negatively correlated with eGFR in Chinese and Japanese T2DM patients, respectively. Consistent with these studies, it was observed in the current study that the risk of hyperuricemia decreased 0.836-fold for every 10 mL/min per 1.73 m\(^2\) increase in eGFR.

To the best of the authors' knowledge, this is the first large-sample study investigating the prevalence of, and risk factors associated with, hyperuricemia in Chinese T2DM patients with central obesity. However, there are several limitations to this study. First, as this was a cross-sectional investigation, it only allows conclusions on associated factors for hyperuricemia, and does not allow conclusions on risk factors. Second, although this was a hospital-based multicentric study of Guangdong Province, hospital distribution was uneven. The majority of hospitals were distributed in Pearl River Delta; however, Pearl River Delta has the largest population, better economic conditions and a sufficiently high level of medical infrastructure to allow for study implementation. Third, the results of laboratory examinations were from 60 different hospitals. Although plasma glucose, serum creatinine, uric acid, TC, TG, HDL-cholesterol, and LDL-cholesterol were measured using an Abbott Laboratories full automatic biochemical instrument, HbA1c was estimated by high pressure liquid chromatography. The results of laboratory examinations from different hospitals may also contain some errors.

Hyperuricemia is prevalent in Chinese T2DM patients with central obesity and is significantly positively associated with women, cardiovascular risk factors such as obesity, hypertension and dyslipidemia, and low eGFR. Hyperuricemia is an important public health problem in Chinese T2DM patients with central obesity. Strategies aimed at the prevention and treatment of hyperuricemia are needed.

ACKNOWLEDGEMENTS

The study was supported by the following hospitals: Zhuijiang Hospital of Southern Medical University, The First Affiliated Hospital of Sun Yat-sen University, Sun Yat-sen Memorial Hospital of Sun Yat-sen University, The Second Affiliated Hospital of Shantou University Medical College, The First Affiliated Hospital of Sun Yat-sen University Medical College, Wu Jing Zong Dui Hospital of Guangdong Province, The People's Hospital of Jiangmen, Jiangmen Central Hospital, The People's Hospital of Shenzhen, Zhongshan People's Hospital, Guangdong General Hospital, Affiliated Hospital of Guangdong Medical College, The first Affiliated Hospital of Clinical Medicine of GDPU, The Second Affiliated Hospital of Guangzhou Medical University, The First Affiliated Hospital of Guangzhou Medical University, The Third Affiliated Hospital of Guangzhou Medical University, General Hospital of Guangzhou Military Command of People's Liberation Army, Guangzhou First Municipal People's Hospital, The First Affiliated Hospital of Jinan university, The Third Affiliated Hospital of Southern Medical University, Guangdong NO.2 Provincial People's Hospital, The Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou Red Cross Hospital, The 458th Hospital of PLA, Clifford Hospital, Shantou Central Hospital, People's Hospital of Boan District of Shenzhen City, Peking University Shenzhen Hospital, People's Hospital of Futian District of Shenzhen City, The Second People's Hospital of Shenzhen, People's Hospital of Nanshan District of Shenzhen City, Longgang Central Hospital, Chaozhou Central Hospital, The People's Hospital of Dongguan, Shenzhen Donghua Hospital, People's Hospital of Nanhai District of Foshan City, The First People's Hospital of Foshan, Foshan Hospital of Traditional Chinese Medicine, Mingjing Diabetic Hospital of Shunde, The People's Hospital of Heshan, Huizhou Central Hospital, Wuyi Hospital of Traditional Chinese Medicine, The People's Hospital of Xinhui, Xinhui Hospital of Traditional Chinese Medicine, The People's Hospital of Jieyang, Kaiping Central Hospital, Kaiping Hospital of Traditional Chinese Medicine, The People's Hospital of Qingyuan, The People's Hospital of Shanwei, The People's Hospital of Xinxing, The People's Hospital of Yangjiang, The People's Hospital of Yuebei, The People's Hospital of Lechang, The First People's Hospital of Zhaoqing, Chenxinhai Hospital Affiliated to Guangdong Medical College, The Second People's Hospital of Zhubai, The Fifth Affiliated Hospital of Sun Yat-sen University, Zhongshan Hospital of Traditional Chinese Medicine, Sanxiang Hospital of Zhongshan, Maoming People's Hospital, Meizhou People's Hospital, Zhongshan Hospital of Traditional Chinese Medicine.

AUTHOR DISCLOSURES

The authors declare that they have no competing interests.

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coronary heart disease and renal dysfunction in patients with
Prevalence and determinants of hyperuricemia in type 2 diabetes mellitus patients with central obesity in Guangdong Province in China

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中国广东省腹型肥胖 2 型糖尿病患者高尿酸血症的患病率及危险因素分析

本研究旨在探讨高尿酸血症在中国 2 型糖尿病合并腹型肥胖患者中的患病率，并分析其相关危险因素。2011 年 8 月至 2012 年 3 月期间，在广东省内进行多中心、以医院为基础的横断面调查。在广东省内居住满一年且年龄在 20 岁以上，确诊 2 型糖尿病合并腹型肥胖且检测血尿酸水平的患者纳入本研究。高尿酸血症定义：男性血尿酸 >420 µmol/L 或女性血尿酸 >360 µmol/L。采用二分类 logistic 回归分析高尿酸血症的危险因素。共 2917 名 2 型糖尿病合并腹型肥胖的患者纳入本研究。高尿酸血症的患病率为 32.6%(女性为 36.1%，男性为 28.4%)。二分类 logistic 回归分析显示，女性、高体重指数和腰围、高血压、高总胆固醇和甘油三酯、低高密度脂蛋白胆固醇和低肾小球滤过率是高尿酸血症的危险因素。高尿酸血症在中国 2 型糖尿病合并腹型肥胖患者中盛行，与女性、心血管危险因素如肥胖、高血压、血脂异常症和低肾小球滤过率呈显著相关。

关键词：患病率、危险因素、高尿酸血症、2 型糖尿病、腹型肥胖