

Original Article

Clinical value of serum lipid profile and renal function for the management of hyperuricemia in adults in southern China

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Abstract: Aim: To examine associations of serum lipid profile and estimated glomerular filtration rate (eGFR) with hyperuricemia (HUA) and to identify the clinical value of serum lipid profile and renal function for the management of HUA. Method: A Chinese Han population of 11,501 residents (6229 men, 5272 women) aged over 18 years who visited the Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China, for routine medical examination was enrolled between January 2009 and December 2013. The relationships of lipid concentrations and eGFR to HUA were analyzed using multivariate logistic regression analyses. Results: The prevalence of HUA was 22.80% in 11,501 participants aged 18-96 years. It was higher among men than among women (32.03% vs. 11.96%, $P < 0.01$). Men aged < 30 years had a greater HUA burden ($P < 0.05$), and the prevalence of HUA increased significantly in women after the age of 50 years ($P < 0.01$). In multivariate logistic regression analysis, the odds ratios (ORs) of HUA in the high triglyceride (TG), high low-density lipoprotein cholesterol (LDL-c), and low high-density lipoprotein cholesterol (HDL-c) groups were 2.66, 1.82, and 1.17 times higher, respectively, than those of normal TG, LDL-c, and HDL-c groups. The ORs of HUA among participants with mild and moderate eGFR decline were 1.29 and 2.29 times those of the normal eGFR group, respectively ($P < 0.01$). Conclusion: HUA is prevalent in Guangzhou City, southern China. Treatment to improve renal function and target hyperlipidemia, particularly hypertriglyceridemia, may have beneficial effects on lowering serum uric acid levels.

Keywords: Prevalence, hyperuricemia, lipid profile, renal function, southern China

Introduction

The prevalence of hyperuricemia (HUA) has increased in recent decades. HUA is well established as the most important risk factor for the onset and development of gout. Numerous studies have associated HUA with metabolic syndrome, [1] a risk factor for cardiovascular diseases, including hypertension, coronary artery disease, and ischemic heart disease, [2-5] and identified it as an independent risk factor for chronic kidney disease (CKD) [6].

Although the pathophysiology of HUA is not fully understood, accumulation of serum uric acid (SUA) may be due to increased production or decreased elimination. Previous studies demonstrated that HUA is closely correlated with

dyslipidemia, hyperglycemia, hypertension, and low glomerular filtration rate (GFR) [7, 8]. In addition, the prevalence of HUA is associated with sex, age, geographic region, and ethnicity. Wang *et al.* [9] reported that the prevalence of HUA was 32.6% in patients with type 2 diabetes mellitus in Guangdong Province, southern China, and that HUA was positively associated with central obesity, hypertension, dyslipidemia, and low GFR. However, reports on the prevalence of HUA in the general population of Guangdong Province have been scarce, and the relationship between HUA and relevant risk factors in this area is not clear. In the current study, we calculated the prevalence of HUA in the past 5 years in Guangzhou City and analyzed the associations of this condition with estimated

glomerular filtration rate (eGFR) and serum lipids, including total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-c), and high-density lipoprotein cholesterol (HDL-c). The discriminatory value of risk factors for the prediction of HUA was also determined.

Materials and methods

Study population

This retrospective study included adults aged over 18 years who visited the Third Affiliated Hospital of Sun Yat-sen University for routine medical examination and health counseling between January 2009 and December 2013. Recruited individuals were Han origin and have lived in the urban area of Guangzhou City for more than 1 year. Individuals with suspicious or known chronic renal diseases, self-reported or definite diagnosis of gout were excluded. Totally, 11,501 participants (6229 men, 5272 women) were selected and the study was based on the analysis of data from examinations of this general population. The study was approved by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University. All patients provided written informed consent according to the Declaration of Helsinki.

SUA measurement

SUA levels were measured using a Hitachi 7180 automatic biochemical analyzer (Tokyo, Japan) and reagents from Roche Diagnostics (Mannheim, Germany). Hyperuricemia was defined as SUA > 420 $\mu\text{mol/L}$ (7 mg/dL) in men and > 357 $\mu\text{mol/L}$ (6 mg/dL) in women.

Assessment of renal function

Renal function was assessed using eGFRs, calculated using the abbreviated Modification of Diet in Renal Disease equation [10]: $\text{eGFR (mL/min per } 1.73 \text{ m}^2) = 186.3 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203} \times 0.742$ (if female). Normal renal function was defined as $\text{eGFR} \geq 90 \text{ mL/min/1.73 m}^2$. CKD was classified as mild ($\text{eGFR} = 60\text{-}90 \text{ mL/min/1.73 m}^2$), moderate ($\text{eGFR} = 30\text{-}59 \text{ mL/min/1.73 m}^2$), or severe ($\text{eGFR} < 30 \text{ mL/min/1.73 m}^2$).

Lipid measurement

All procedures were performed following a 10-12-hour overnight fast. Before the fasting

period, all subjects were asked to follow a bland diet prior to blood testing. Blood was drawn from the antecubital vein. TC, TG, HDL-c, and LDL-c levels were measured using a Hitachi 7180 automatic biochemical analyzer. Dyslipidemia was classified according to the 2007 Chinese guidelines for the prevention and treatment of dyslipidemia in adults [11] [TG: normal (< 1.76 mmol/L), borderline high (1.76-2.26 mmol/L), high (≥ 2.27 mmol/L); TC: normal (< 5.18 mmol/L), borderline high (5.18-6.18 mmol/L), high (≥ 6.19 mmol/L); HDL-c: high (≥ 1.55 mmol/L), normal (1.04-1.54 mmol/L), low (< 1.04 mmol/L); LDL-c: normal (< 3.37 mmol/L), borderline high (3.37-4.13 mmol/L), high (≥ 4.14 mmol/L)].

Statistical analysis

SPSS statistical software (version 17.0; SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. Continuous variables are presented as means \pm standard deviations and categorical variables are presented as percentages per group. Comparisons of numerical data between groups were performed by independent-sample *t*-tests. Factors that influenced rates of HUA were screened by univariate analysis, and the chi-squared test was used for the unordered categorical variable (sex), and the Kruskal-Wallis test was used for ordinal categorical variables (age; TC, TG, LDL-c, and HDL-c levels; eGFR). Independent factors (sex; TC, TG, LDL-c, and HDL-c levels; eGFR) identified potentially affecting HUA in univariate analysis were examined using multivariate logistic regression analysis, with calculation of odds ratios (ORs) and 95% confidence intervals (CIs). Receiver operating characteristic (ROC) curves were utilized to assess the ability of TG, LDL-c, and HDL-c levels and eGFR to predict HUA. *P* values < 0.05 were considered statistically significant.

Results

Baseline characteristics and distribution of SUA levels

This study included a total of 11,501 participants [6229 (54.16%) men, 5272 (45.84%) women] with a mean age of 42.99 ± 12.76 (range, 18-96) years. Baseline characteristics of the study population are shown in **Table 1**. SUA levels in all age groups were significantly

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Table 1. Baseline characteristics of the study population

Characteristic	Mean	SD
Age (years)	42.99	12.76
SUA ($\mu\text{mol/L}$)	333.61	101.98
TC (mmol/L)	5.03	0.99
TG (mmol/L)	1.64	1.48
LDL-c (mmol/L)	3.01	0.89
HDL-c (mmol/L)	1.32	0.33
sCr ($\mu\text{mol/L}$)	74.71	18.95
eGFR (mL/min/1.73 m ²)	98.07	21.71

SD, standard deviation; SUA, serum uric acid; TC, total cholesterol; TG, triglycerides; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; sCr, serum creatinine; eGFR, estimated glomerular filtration rate.

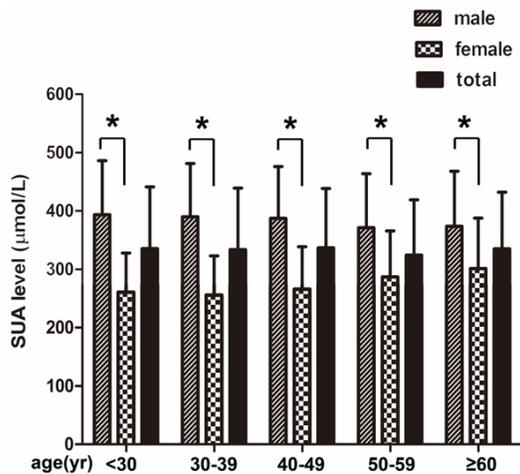


Figure 1. Distribution of serum uric acid (SUA) levels by age and sex. * $P < 0.05$.

Table 2. Prevalence of hyperuricemia by age and sex

Age (years)	Male		Female		Total	
	n	%	n	%	n	%
< 30	310	35.11	52	7.62	362	23.13
30-39	711	33.60	108	7.07	819	22.47
40-49	564	32.96	122	10.00	686	23.40
50-59	232	26.76	180	16.36	412	20.95
≥ 60	178	27.30	167	22.51	345	24.75

higher in men than in women ($P < 0.01$), and the mean SUA level in the total sample was higher in men than in women ($385.5 \pm 91.5 \mu\text{mol/L}$ vs. $271.8 \pm 75.5 \mu\text{mol/L}$, $P < 0.01$; **Figure 1**). In men, the average SUA level was

Table 3. Univariate analysis of variables associated with hyperuricemia

Variable	χ^2/H	P
Age	7.762 ^b	0.101
Sex	654.858 ^a	< 0.001
TC	127.962 ^b	< 0.001
TG	727.526 ^b	< 0.001
LDL-c	172.796 ^b	< 0.001
HDL-c	388.549 ^b	< 0.001
eGFR	87.437 ^b	< 0.001

TC, total cholesterol; TG, triglycerides; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate. ^a: calculated by chi-squared test, ^b: calculated by Kruskal-Wallis test.

highest in subjects aged < 30 years and lowest in the 50-59-year age group. In women, the mean SUA level was highest among participants aged > 60 years (**Figure 1**), with a gradual increase from the age of 40 years.

Prevalence of HUA

The overall prevalence of HUA was 22.80%; annual prevalences from 2009 to 2013 were 21.86%, 20.75%, 18.97%, 23.93%, and 32.14%, respectively. HUA prevalence was thus highest in 2013 and lowest in 2011 in the last 5 years. In general, HUA was more prevalent in men than in women (32.03% vs. 11.96%, $P < 0.01$). It was more prevalent among men aged < 30 years than among those aged 50-59 and ≥ 60 years ($P < 0.01$), and the prevalence decreased with increasing age. In contrast, HUA was less prevalent among women aged 30-39 years than among those in other age groups, and the prevalence increased significantly with age after 50 years ($P < 0.01$). HUA was more prevalent in men than in women in all age groups ($P < 0.05$; **Table 2**).

Risk factors for HUA

In univariate analysis, HUA was significantly associated with sex, all lipid profiles, and eGFR, but not age (**Table 3**). Multivariate analysis included six variables: sex; TC, TG, LDL-c, and HDL-c levels; and eGFR. Stepwise logistic regression screening resulted in the retention of sex, TG, LDL-c, HDL-c and eGFR in the model. The OR of HUA in women was 0.39 (95% CI, 0.35-0.43) times that of HUA in men.

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Table 4. Multivariate regression analysis of variables associated with hyperuricemia

	β	OR (95% CI)	P
Sex			
Male		1	
Female	-0.95	0.39 (0.35-0.43)	< 0.05
TC			
Normal TC			NS
Borderline high TC			NS
High TC			NS
TG			
Normal TG		1	
Borderline high TG	0.57	1.77 (1.54-2.02)	< 0.001
High TG	0.98	2.66 (2.36-2.99)	< 0.001
LDL-c			
Normal LDL-c		1	
Borderline high LDL-c	0.37	1.45 (1.29-1.62)	< 0.001
High LDL-c	0.60	1.82 (1.53-2.10)	< 0.001
HDL-c			
Normal HDL-c		1	
High HDL-c	-0.40	0.67 (0.58-0.77)	< 0.001
Low HDL-c	0.158	1.17 (1.04-1.32)	0.008
eGFR			
Normal eGFR		1	
Mild eGFR decline	0.26	1.29 (1.18-1.42)	< 0.001
Moderate eGFR decline	0.83	2.29 (1.65-3.18)	< 0.001
Severe eGFR decline	0.95	2.58 (0.93-7.21)	0.069

Multivariate logistic regression analysis included sex, TC, TG, LDL-c, HDL-c, and eGFR as variables. OR, odds ratio; CI, confidence interval; TC, total cholesterol; TG, triglycerides; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate.

TC level did not significantly affect the prevalence of HUA. Compared with the normal TG group, the ORs of HUA in the borderline high and high TG groups were nearly two and three times higher, respectively (**Table 4**). Similarly, the ORs of HUA among participants with borderline high and high LDL-c levels were higher than those in the normal LDL-c group (**Table 4**). In contrast, the OR of HUA was lower in the high HDL-c group than in the normal HDL-c group (**Table 4**).

The ORs of HUA among participants with mild and moderate eGFR declines were 1.29 and 2.29 times that of the normal eGFR group, respectively ($P < 0.01$). Although the OR of HUA in the severe eGFR decline group was 2.58 times that of the normal eGFR group, this difference was not significant.

ROC curve analysis of risk factors associated with HUA

ROC curve analysis demonstrated that TG, LDL-c, and HDL-c levels and eGFR were significant predictors of HUA in the subjects studied (**Figure 2**). The areas under the curve (AUCs) for risk factors were: TG, 0.69 (95% CI, 0.68-0.70); LDL-c, 0.59 (95% CI, 0.58-0.60); HDL-c, 0.65 (95% CI, 0.63-0.66), and eGFR, 0.57 (95% CI, 0.56-0.58). The AUC was largest for TG level, suggesting that this variable had the highest discriminatory value related to HUA. The total discriminatory value of identified risk factors (TG, LDL-c, and HDL-c levels; eGFR) was 0.73 (95% CI, 0.72-0.74).

Discussion

The prevalence of HUA has increased recently with improvements in economic status and lifestyle changes in many cities in China. Liu et al. [12] reported a total HUA prevalence of 8.40% (9.90% in men, 7.00% in women), based on a national cross-sectional survey conducted in 2009 and 2010. Previously reported HUA prevalences have differed among regions; for example, 17.70% in men and 5.20% in women in Inner Mongolia, [13] 14.70% among people of Han ethnicity in northwestern China, [14] and 18.32-25.30% in coastal regions of China [15, 16]. We found that

the prevalence of HUA in Guangzhou was 22.80%, higher than that in inland China. This high prevalence may be related to the high degree of regional economic development in Guangdong Province [7]. In addition, most study participants lived in the coastal urban area of Guangzhou City; intakes of purine-rich meat and seafood may be responsible for the high prevalence of HUA in this population.

The prevalence of HUA in this population was particularly high in 2012 and 2013 (23.97% and 32.14%, respectively). Xiong et al. [17] reported an HUA prevalence of 12.01% among participants receiving health examinations in the same hospital (Third Affiliated Hospital, Sun Yat-sen University) in 2002. Thus, the prevalence of HUA has increased dramatically over the past decade in this area.

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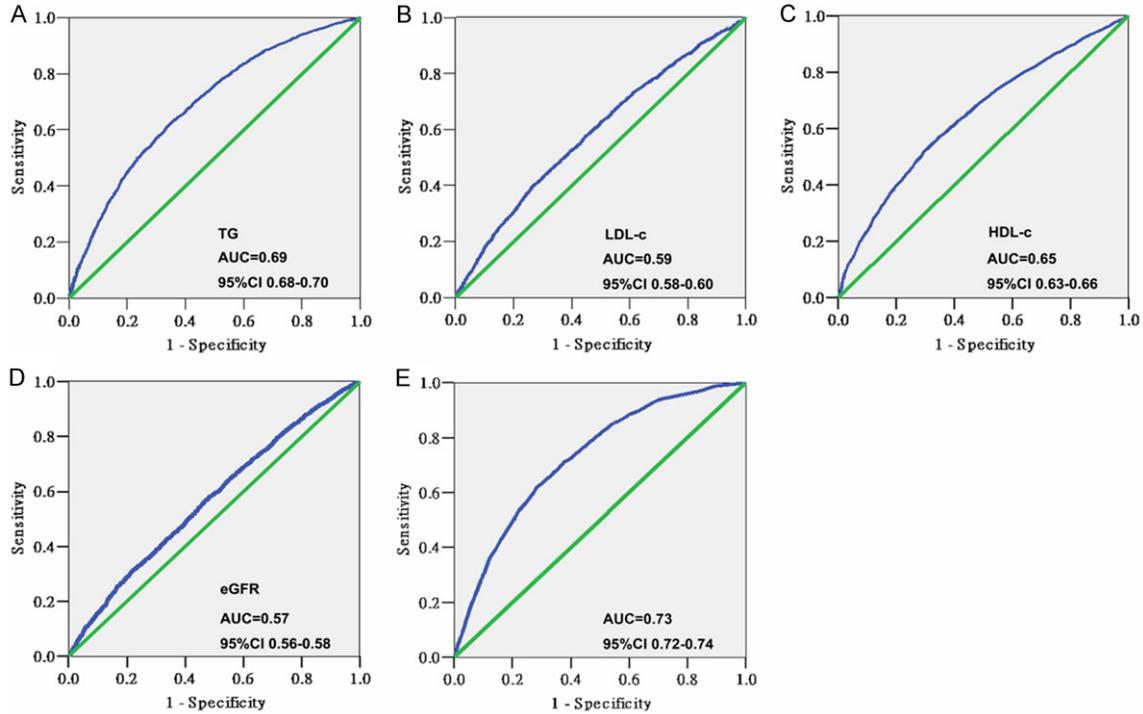


Figure 2. Receiver operating characteristic curves showing the discriminatory powers of risk factors for hyperuricemia. A. Triglyceride (TG) level. B. Low-density lipoprotein cholesterol (LDL-c) level. C. High-density lipoprotein cholesterol (HDL-c) level. D. Estimated glomerular filtration rate (eGFR). E. All risk factors (TG, LDL-c, and HDL-c levels; eGFR). The cut off value was determined at the point on ROC curve when the value of (sensitivity + specificity -1) was maximized. Optimal cut off value of TG was 1.45 mmol/L with sensitivity and specificity were 0.63 and 0.65, respectively. Optimal cut off value of LDL-c was 3.41 mmol/L with sensitivity and specificity were 0.40 and 0.74, respectively. Optimal cut off value of HDL-c was 1.31 mmol/L with sensitivity and specificity were 0.53 and 0.70, respectively. Optimal cut off value of eGFR was 93.79 mL/min/1.73 m² with sensitivity and specificity were 0.56 and 0.54, respectively. Optimal cut off value of all risk factors was 0.23 with sensitivity and specificity were 0.68 and 0.66, respectively. AUC, area under the curve; CI, confidence interval.

In agreement with the established pattern, SUA levels were higher in men than in women in our study population. Sex differences were evident in all age groups, with men showing a higher prevalence of HUA than women. Previous studies have reported that the prevalence of HUA increases after the ages of 30 years in men and 50 years in women in the Chinese population, [18] whereas Qiu and colleagues [7] documented high SUA levels in men aged 25-34 years in northern and northeastern Chinese provinces. In our sample, the burden of HUA was concentrated among men aged < 30 years. We also found that women aged > 50 years showed a higher prevalence of HUA, and this increased risk may be related to menopause.

In the current study, we found that TG and LDL-c levels were positively associated with HUA. The OR of HUA was nearly three-fold greater in the high TG group than in the normal TG group, suggesting that TG was a more sig-

nificant contributing factor than were other lipid profiles. Therefore, more attention should be paid to subjects with hypertriglyceridemia, as they have an increased risk of HUA development. Similar to other studies, our results showed that high HDL-c level was negatively related to the prevalence of HUA. However, TC level did not contribute significantly to HUA prevalence. In contrast to our findings, Qiu et al. [7] reported that an abnormal TC level resulted in a small increase in the odds of HUA development. However, they also demonstrated that LDL-c and TG levels contributed to the OR of HUA prevalence and that TG was the most significant contributing factor, in accordance with our results. Geographic and ethnic differences may be responsible for the variability in findings.

SUA is eliminated mainly through the kidney and SUA level is closely related to renal function. The prevalence of HUA and gout has been

found to be increased in patients with CKD and reduced eGFR (< 60 mL/min/1.73 m²), independent of other factors [19]. Similarly, we showed that eGFR < 60 mL/min per 1.73 m² was associated with an increased OR of HUA, suggesting that SUA elimination is affected by eGFR decline in patients with CKD. However, the OR of HUA in subjects with severe eGFR decline was not significantly higher than that of the normal eGFR group. As only 16 participants were included in the severe eGFR decline group, the small sample and limited data may have affected the results. Furthermore, other research has demonstrated that HUA contributes to eGFR decline as an independent risk factor [20, 21] and is associated with a shorter time until the start of dialysis [22]. Thus, the relationship between HUA and renal function is complex.

Nevertheless, the significant association between HUA and CKD progression has been well established, and improvement of HUA by non-pharmacologic or pharmacologic therapies in patients with CKD is important. Currently, pharmacotherapy with urate-lowering drugs is recommended for asymptomatic HUA with CKD in patients with SUA levels of 416-535 μ mol/L that are insufficiently controlled through diet and lifestyle measures for 3-6 months and those with SUA levels ≥ 535 μ mol/L in mainland China. Urate-lowering drugs such as febuxostat may thus be a good choice to reduce SUA level and prevent further eGFR reduction in patients with CKD.

ROC curve analysis to identify the discriminatory value of risk factors associated with HUA showed that TG level is closely related to HUA, consistent with previous reports [8]. Milionis HJ [23] reported that fenofibrate administration was associated with a uric acid-lowering effect. Thus, lipid lowering therapy for patients with dyslipidemia, particularly those with hypertriglyceridemia, may have beneficial effects for lowering SUA. We also found that risk factors including LDL-c, and HDL-c levels, and eGFR were significant predictors of HUA and that the total discriminatory value was high. Given the high prevalence of HUA in Guangzhou City, clinicians in this area should conduct frequent SUA screening of subjects with high levels of TG and LDL-c, low levels of HDL-c, and/or eGFR decline to ensure the early identification of HUA.

This study has several limitations. It was retrospective and the prevalence of HUA was not adjusted. Furthermore, limited clinical data were collected. We recommend the use of stratified sampling to calculate the adjusted prevalence of HUA in Guangzhou City and the collection of menopausal age data from women to investigate their relationship to HUA prevalence. Other factors, including alcohol consumption, physical activity, obesity, lifestyle, fasting glucose level, hypertension, other metabolic abnormalities, and administration of drugs such as thiazide and loop diuretics, should be added as covariates to multivariate logistic regression analyses to further investigate relevant risk factors of HUA.

Conclusions

In the current study, we demonstrated that HUA is more prevalent in Guangzhou City than in other inland areas of China. The risk factors for HUA include male sex, hypertriglyceridemia, high LDL-c level, low HDL-c level, and eGFR decline. These findings indicate that treatments targeting risk factors, such as compromised renal function and hyperlipidemia, particularly hypertriglyceridemia, may have beneficial effects by lowering SUA levels and reducing the prevalence of HUA and, ultimately, gout.

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Disclosure of conflict of interest

None.

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