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ORIGINAL RESEARCH

Urine Glucose Excretion Attenuates the Association Between Lipid Accumulation Product and Serum Uric Acid in Subjects with Prediabetes

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Purpose: Obesity is known to be strongly associated with hyperuricemia. Moreover, the impact of urine glucose excretion (UGE) on serum uric acid (UA) levels has gained much more attention in recent years. Yet concern is raised about whether UGE influences the relationship between obesity and hyperuricemia. The aim of this study was to assess the effect of UGE on the association between lipid accumulation product (LAP), a novel marker of visceral adipose accumulation, and UA in subjects with prediabetes.

Materials and Methods: Data were obtained from a cross-sectional study. A total of 3645 subjects with prediabetes were included in the present study. The separate and joint associations of LAP and UGE with hyperuricemia were examined using logistic regression analyses.

Results: LAP was positively associated with UA in both genders. Subgroup analysis based on UGE revealed that the association was strongest in subjects with low UGE ($r = 0.328$, $p < 0.001$), whereas the positive association was weakened, but still remained significant in subjects with moderate and high UGE. High LAP was significantly associated with an increased odds ratio for hyperuricemia after adjustment for potential confounders in the overall population (OR = 2.07, 95% CI: 1.66–2.58, $p < 0.001$). However, a downward trend in odds ratios for hyperuricemia was observed across UGE categories. In addition, the joint association analysis confirmed that the relationship between LAP and hyperuricemia was attenuated by UGE.

Conclusion: The positive association between LAP and UA appears to be attenuated by UGE, indicating that promoting UGE may be an effective strategy for controlling UA levels, especially for people with obesity who are at increased risk for hyperuricemia.

Keywords: prediabetes, lipid accumulation product, uric acid, urine glucose excretion

Introduction

Hyperuricemia, mainly attributed to decreased excretion of uric acid (UA), has become a major health challenge worldwide due to its significant role in the development of hypertension, diabetes mellitus, and renal disease.[1,2] Moreover, elevated UA levels have been reported to be independently and significantly associated with the risk of cardiovascular diseases, nonalcoholic fatty liver disease, and metabolic syndrome.[3–7] Besides, a recent study suggested that UA may be a predictor of non-dipping pattern of blood pressure.[8] Therefore, further understanding of the detailed factors that contribute to increased serum UA levels is urgently needed for early prevention and improvement in health outcomes.

According to previous studies, obesity is strongly linked to hyperuricemia.[9,10] The levels of serum UA tend to rise with weight gain, while declining with weight

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reduction.[11,12] Our recent research also found that individuals with elevated body mass index (BMI) were at increased risk for hyperuricemia.[1] BMI is widely used to identify overweight or obesity, but it is unable to estimate body fat distribution. Current evidences have revealed that a variety of physiological aberrations caused by obesity depend not simply on overweight or obesity per se, but importantly, the distribution of body fat.[13–15] Lipid accumulation product (LAP), based on waist circumference (WC) and triglyceride (TG), has been recognized as a novel marker of visceral adipose accumulation. Although the measurement of visceral fat by computed tomography or magnetic resonance imaging is more accurate, they cannot be widely used in clinical practice, because of the relatively high cost. Studies have demonstrated that LAP is effective to predict visceral fat.[16–18] To date, a number of studies have been designed to focus on the association of LAP with hypertension, diabetes, non-alcoholic fatty liver disease, and cardiovascular disease.[19–22] But there is less evidence about the association between LAP and hyperuricemia.

Notably, our recent work found that urine glucose excretion (UGE) was an independent factor for hyperuricemia in individuals with newly diagnosed diabetes and further indicated that increased UGE was closely correlated with a reduced risk of hyperuricemia.[1] Moreover, other studies have confirmed a significant decrease in UA levels in subjects treated with sodium-glucose cotransporter 2 (SGLT2) inhibitors, a class of medications for the treatment of diabetes through increasing UGE.[23] Subsequently, the UA-lowering effect of SGLT2 inhibitors is attributed to increased glycosuria.[1,24] Of note, there is evidence that UA reabsorption is inhibited by increased glucose in the kidney tubule, eventually leading to a decrease in UA levels.[25] Therefore, based on the available data, UGE has a significant role in the regulation of UA levels. Until now, many studies have been performed to investigate the factors that affect UA levels, such as blood glucose, obesity, and lifestyle.[1,26] Nevertheless, these studies did not consider the impact of UGE on the associations.

Together, since assessment of the clinical significance of UGE in hyperuricemia has gained much more attention,[1,24] UGE should be taken into account when LAP is used as a predictor of hyperuricemia. Therefore, in this study, we investigated the association between LAP and serum UA levels and further assessed the impact of UGE on this association.

Materials and Methods

Study Design and Subjects

This study is part of a population-based, cross-sectional study carried out in 6 cities in Jiangsu province, from November 12, 2015, to June 28, 2016. Individuals aged between 18 and 65 years old, without prior history of diabetes, were selected using a multistage stratified sampling method, as previously reported.[1,27] Subjects were excluded if they had been diagnosed with diabetes, severe psychiatric disturbance, pregnancy, or an unstable health condition. This study was approved by the ethical review committee of the Jiangsu Provincial Center for Disease Control and Prevention (JSJK2016-B003-03) and conducted in accordance with the Declaration of Helsinki. Each participant provided written informed consent. The diagnosis of prediabetes was according to the 2012 American Diabetes Association diagnostic criteria. As previously reported, of 7485 individuals, 3645 subjects were diagnosed as prediabetes after glucose tolerance test and included in the present study.[27]

Anthropometric and Laboratory Measurements

Information on demographic characteristics and medical histories was obtained using a structured questionnaire. Height, weight, WC, blood pressure (BP), and heart rate (HR) were measured according to standardized protocols. BMI was calculated as weight in kilograms divided by height in meters squared. After an overnight fast of at least 10 hours, blood samples were collected from each participant for the measurement of fasting plasma glucose (FPG), hemoglobin A1c (HbA1c), triglycerides (TG), total cholesterol (TC), alanine aminotransferase (ALT), aspartate transaminase (AST), blood urea nitrogen (BUN), creatinine, and UA. Second blood samples were collected 2 hours later for the measurement of plasma glucose (2h-PG). Two-hour period urine samples were collected after glucose loading for measuring UGE, as previously described.[1] LAP was calculated based on measured WC and TG, as previously described.[20]

Definitions

Prediabetes was defined as FPG $\geq$ 5.6 mmol/L and $\leq$ 6.9 mmol/L, 2h-PG $\geq$ 7.8 mmol/L and < 11.0 mmol/L, or 5.7% $\leq$ HbA1c $\leq$ 6.4%, according to the 2012 American Diabetes Association (ADA) criteria. Hyperuricemia was defined as UA greater than 416 umol/L in men and 357 umol/L in women.[1] UGE exceeding the 75th percentile (96 mg) of the study population was considered as high UGE, while UGE

less than the 25th percentile was considered as low UGE, and between 25th percentile and 75th percentile was considered as moderate UGE. LAP below the 50th percentile (29.9 mg) of the study population was considered as low LAP (L-LAP), while LAP above the 50th percentile was considered as high LAP (H-LAP).

Statistical Analysis

Continuous variables were described as means ± SD, or median (interquartile range) and categorical variables were described as numbers (percentages). Student's *t* test for continuous variables and χ^2 test for categorical variables were used to compare characteristics of subjects between two groups. Non-parametric Mann–Whitney *U*-test was used when the data distribution was skewed. Log-transformation was performed as necessary to approximate the normal distribution. Pearson's correlation was used to examine the relationship between UA and LAP. Logistic regression analyses with adjusted odds ratios (95% CI) were performed to determine the separate and joint association of UGE and LAP with hyperuricemia. The joint association of UGE and LAP was assessed by dividing the subjects into six groups: (1) L-LAP/low UGE, (2) L-LAP/moderate UGE, (3) L-LAP/high UGE, (4) H-LAP/low UGE, (5) H-LAP/moderate UGE and (6) H-LAP/high UGE. The L-LAP/low UGE group was used as a reference in the analysis. Potential confounders included in the multivariate analysis were age, genders, HR, BP, FPG, 2h-PG, HbA1c, ALT, AST, BUN, creatine, and BMI, which were chosen depend on reaching statistical significance in the comparative analysis and based on clinical judgment. Before multivariate analyses, multicollinearity detection was examined. A P value <0.05 was considered statistically significant. All statistical analyses were conducted using SPSS 22.0 (SPSS Inc, Chicago, IL, USA).

Results

General Characteristics of the Study Subjects

A total of 3645 subjects with prediabetes were included in this study. Of those, 2995 subjects exhibited normal UA and 650 showed hyperuricemia. The baseline characteristics of the study population, according to the levels of UA, are summarized in Table 1. Individuals with hyperuricemia were more likely to have significantly higher HR, blood pressure, 2h-PG, TC, TG, ALT, AST, BUN, creatinine, WC, LAP and BMI than those with normal UA (all P < 0.05).

Table 1 Characteristics of the Study Subjects According to the Levels of UA

	Normal UA	Hyperuricemia	P value
Number	2995	650	
Male	1204 (40.2%)	440 (67.7%)	<0.001
Age (years)	47.43 ± 10.76	45.12 ± 12.39	<0.001
HR (beats/min)	77.10 ± 11.35	78.36± 11.96	0.01
HbA1c (%)	5.75 ± 0.29	5.75 ± 0.30	0.92
Blood pressure (mmHg)			
Systolic	130.63 ± 19.16	132.34 ± 17.47	0.04
Diastolic	79.75 ± 11.81	83.08 ± 11.87	<0.001
Plasma glucose (mmol/l)			
FPG	5.54 ± 0.53	5.56 ± 0.54	0.32
2h-PG	6.57 ± 1.58	6.72 ± 1.75	0.03
TC (mmol /L)	4.71 ± 0.94	4.99 ± 0.92	<0.001
TG (mmol /L)	1.21 (0.86–1.76)	1.66 (1.16–2.58)	<0.001
ALT (U/L)	18.00 (13.90–24.25)	25.00 (18.00–35.80)	<0.001
AST (U/L)	20.00 (16.50–24.50)	24.00 (19.00–32.08)	<0.001
BUN (mmol /L)	5.07 ± 1.46	5.62 ± 1.97	<0.001
Creatinine (umol/L)	72.13 ± 17.86	79.85 ± 28.14	<0.001
WC (cm)	83.86 ± 9.75	89.64 ± 9.15	<0.001
LAP	27.54 (15.51–46.82)	44.12 (27.19–75.98)	<0.001
BMI (kg/m^2)	25.40 ± 3.83	27.03 ± 3.74	<0.001
BMI ≥ 24 kg/m^2 (%)	1889 (63.1%)	519 (79.8%)	<0.001
UGE (mg)	30.00 (10.50–93.03)	35.00 (12.50–107.25)	0.06

Note: Data are presented as n (%), mean ± SD, or median (interquartile range) as appropriate.

Abbreviations: UA, uric acid; HR, heart rate; FPG, fasting plasma glucose; 2h-PG, 2 h plasma glucose; TC, total cholesterol; TG, triglycerides; ALT, alanine aminotransferase; AST, aspartate transaminase; BUN, blood urea nitrogen; WC, waist circumference; LAP, lipid accumulation product; BMI, body mass index; UGE, urine glucose excretion.

However, age was lower in hyperuricemia group. In addition, hyperuricemia was more common in men than in women since the proportion of men in hyperuricemia group was 67.7%.

Correlations of LAP with UA Grouped by UGE and Genders

Log-transformation of LAP was performed to normalize its distribution before Pearson's correlation analyses. The data showed that LAP was positively associated with UA levels in both genders (all P < 0.05) (Figure 1A). Moreover, subgroup analyses based on UGE revealed that the association was strongest in subjects with low UGE (r = 0.328, p < 0.001), whereas the positive

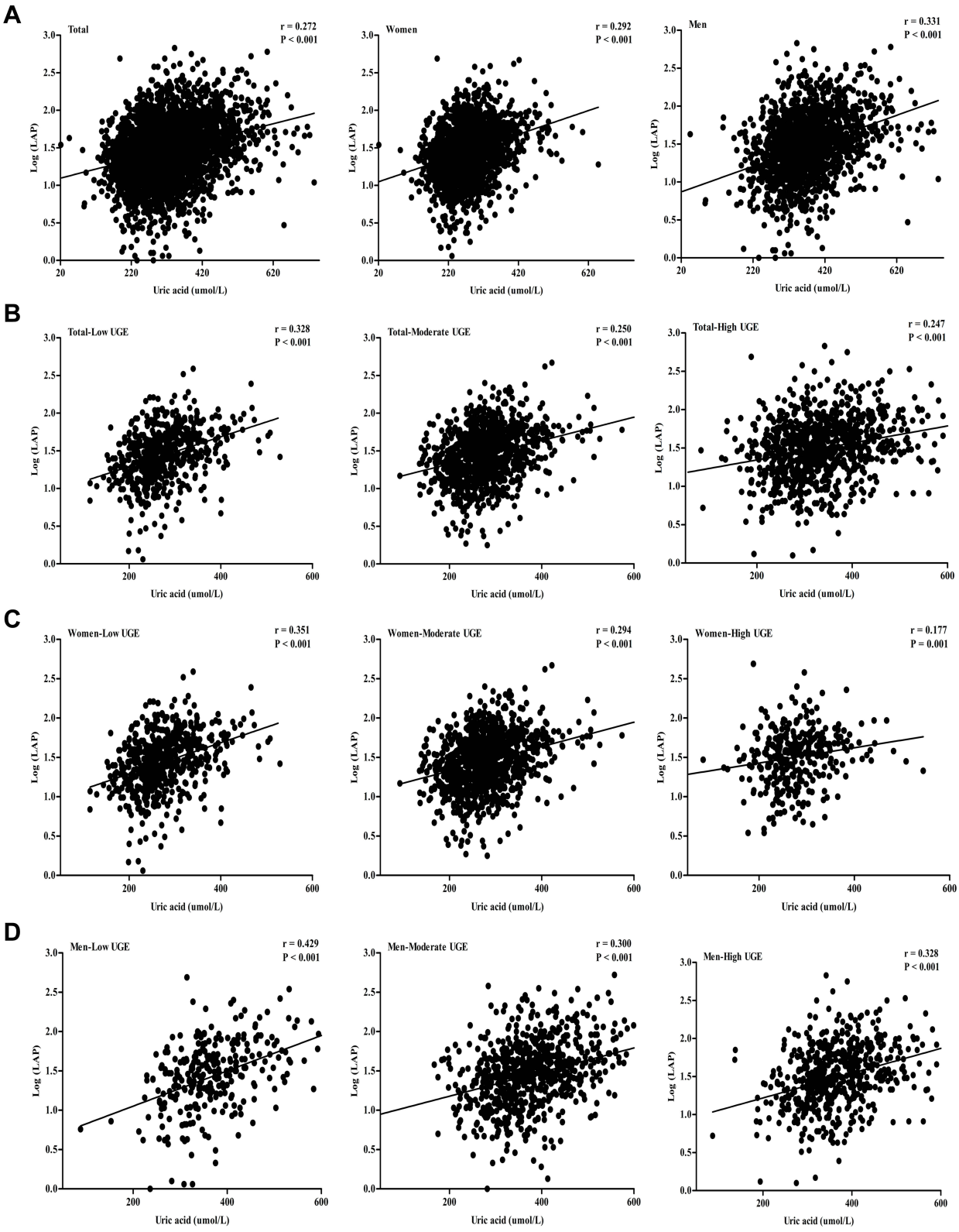

Figure 1 Association between LAP and UA. Log-transformation of LAP was performed to normalize its distribution before Pearson's correlation analyses. (**A**) Association of LAP with UA in the overall population and grouped by genders, (**B**) subgroup analyses based on UGE in the overall population, (**C**) subgroup analyses based on UGE in women, and (**D**) subgroup analyses based on UGE in men.

Abbreviations: LAP, lipid accumulation product; UA, uric acid; UGE, urine glucose excretion.

association was weakened, but still remained significant in subjects with moderate and high UGE (Figure 1B). Further subgroup analyses based on UGE and genders also showed the correlation coefficients tended to be lower with an increase in UGE in women (Figure 1C). Furthermore, in men, the correlation coefficient was 0.429 in low UGE group, while decreased by 30% in moderate UGE group and 23.5% in high UGE group, respectively (Figure 1D).

Logistic Regression Analyses of Odds Ratios for Hyperuricemia

As shown in Table 2, logistic regression analyses were performed to identify the association between LAP and the risk of hyperuricemia. The results showed that H-LAP was significantly associated with an increased odds ratio for hyperuricemia after adjustment for potential confounders, including age, gender, HR, systolic and diastolic blood pressure, FPG, 2h-PG, BUN, creatinine, AST, ALT, and BMI in the overall population (OR = 2.07, 95% CI: 1.66–2.58, $p < 0.001$). Besides, subgroup analysis stratified by UGE was performed for more detailed information. In low UGE group, individuals with H-LAP displayed 2.52-fold increased odds ratio for hyperuricemia compared with individuals with L-LAP, whereas the odds ratio was reduced to 2.03 and 1.89 in moderate UGE group and high UGE group, respectively. A downward trend in odds ratios for hyperuricemia was observed across UGE categories.

Table 2 Odds Ratios for Hyperuricemia According to LAP Stratified by Categories of UGE

Category	β	SE of β	OR	95% CI	P value
Low UGE					
L-LAP	1 (Ref.)				
H-LAP	0.92	0.25	2.52	1.53–4.13	<0.001
Moderate UGE					
L-LAP	1 (Ref.)				
H-LAP	0.71	0.16	2.03	1.49–2.78	<0.001
High UGE					
L-LAP	1 (Ref.)				
H-LAP	0.63	0.22	1.89	1.22–2.92	0.004
Total					
L-LAP	1 (Ref.)				
H-LAP	0.73	0.11	2.07	1.66–2.58	<0.001

Notes: All models were adjusted for age, gender, heart rate, blood pressure, fasting plasma glucose, 2h plasma glucose, HbA1c, total cholesterol, creatinine, blood urea nitrogen, alanine aminotransferase, aspartate transaminase, body mass index.
Abbreviations: SE, standard error; OR, odds ratio; CI, confidence interval; UGE, urine glucose excretion; LAP, lipid accumulation product.

Joint Association of UGE and LAP with Hyperuricemia

As shown in Figure 2, we evaluated the effect of UGE on the association between LAP and hyperuricemia in the overall population and in both genders. The results showed that subjects with H-LAP were more likely to have hyperuricemia, regardless of UGE, in the overall population. Subjects with H-LAP/low UGE displayed the highest risk for hyperuricemia (OR = 2.61, 95% CI: 1.68–4.04, $p < 0.001$). However, the odds ratio was slightly decreased in individuals with H-LAP/moderate UGE (OR = 2.51, 95% CI: 1.68–3.75, $p < 0.001$) and reduced to 1.65 in individuals with H-LAP/high UGE. UGE attenuated the relationship of LAP and hyperuricemia. Similar results were also observed in men. Moreover, in women, individuals with H-LAP/moderate UGE showed 1.85-fold increased odds ratio for hyperuricemia compared with those with L-LAP/low UGE. However, the significantly increased risk of hyperuricemia was not observed in women with H-LAP/high UGE. The association between LAP and hyperuricemia appeared to be completely attenuated by UGE in women with H-LAP/high UGE.

Discussion

In this study of Chinese subjects with prediabetes, we found that LAP was positively correlated with UA levels. Further subgroup analyses based on UGE showed that the positive association tended to be weaker with an increase in UGE. Moreover, the result obtained from multivariable logistic regression analyses showed that LAP was an independent factor for hyperuricemia. Individuals with H-LAP were at an increased risk of hyperuricemia, no matter in low UGE group, moderate UGE group, or high UGE group. However, a downward trend in odds ratios for hyperuricemia was observed across UGE categories. The joint association analyses further confirmed that the relationship between LAP and hyperuricemia was attenuated by UGE. The results suggest that promoting UGE may be an effective strategy for controlling UA levels, especially for people with obesity who are at increased risk for hyperuricemia.

Several risk factors of hyperuricemia have been reported, ranging from lifestyle behaviors to biological factors such as body weight status and age. Of these risk factors, obesity has a clear effect on UA levels.[11,12] However, in recent years, the distribution of fat accumulation in the body, rather than overweight or obesity per se,

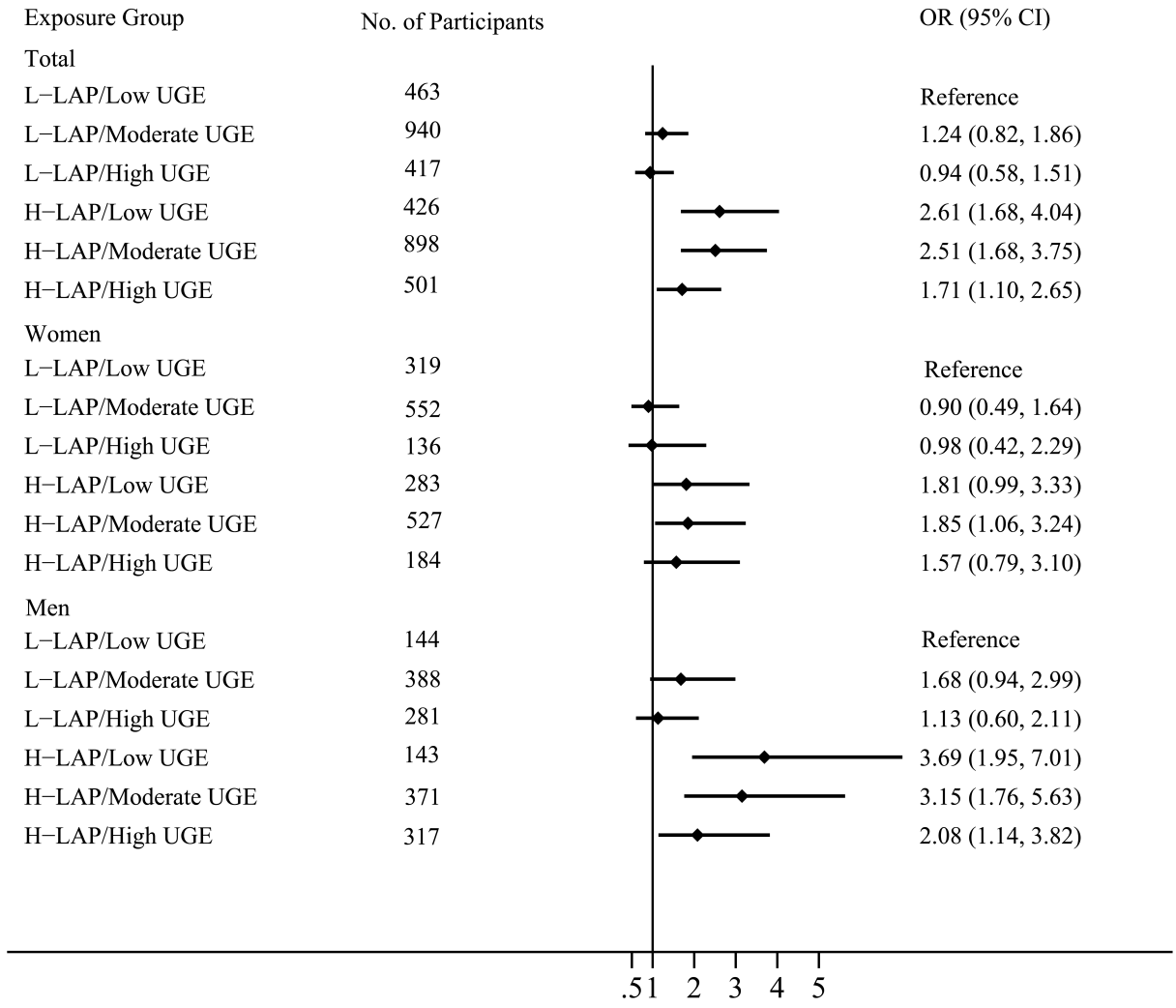

Figure 2 Joint association of UGE and LAP with hyperuricemia in overall sample and in subgroups stratified by genders. The joint association of UGE and LAP was assessed by dividing the subjects into six groups: (1) L-LAP/low UGE, (2) L-LAP/moderate UGE, (3) L-LAP/high UGE, (4) H-LAP/low UGE, (5) H-LAP/moderate UGE and (6) H-LAP/high UGE. The L-LAP/low UGE group was used as a reference in the analysis. All models were adjusted for age, genders, heart rate, blood pressure, fasting plasma glucose, 2h plasma glucose, HbA1c, total cholesterol, creatinine, blood urea nitrogen, alanine aminotransferase, aspartate transaminase, body mass index.
Abbreviations: LAP, lipid accumulation product; UGE, urine glucose excretion; OR, odds ratio; CI, confidence interval.

is becoming increasingly important for a variety of physiological aberrations.[13–15] Many studies did not consider the impact of fat distribution on UA levels. Therefore, we conducted the present study to investigate the association of LAP, characterized as an index of visceral adiposity distribution, with the levels of UA. Until now, studies on the correlation between LAP and UA are relatively scarce. Our study confirmed a positive correlation between LAP and UA, which was consistent with prior study.[28] However, our study population was consisted of subjects with prediabetes. In addition, after adjustment for potential confounders, including age, gender, HR, blood pressure, FPG, 2h-PG, creatinine, and BMI, individuals with H-LAP were more likely to have hyperuricemia. According to prior reports, fat accumulation plays an important role in the production and excretion of UA.[26,29] Noteworthy, visceral fat, but not subcutaneous fat, has been found to be significantly associated with the prevalence of hyperuricemia.[30] Serum UA levels are determined by the interplay between the rates of its production and excretion. Therefore, the finding can be attributed to decreased UA clearance and increased UA production in individuals with H-LAP.[26,29] Moreover, our findings support previous evidence that visceral adipose tissue is strongly associated with metabolic risk factors.[17,31]

In addition, promoting UGE has become an attractive approach for the treatment of diabetes. Our recent study pointed out that UGE has an independent role in regulation

of UA levels and promoting UGE may be an effective approach to reduce the levels of UA.[1] Obviously, UGE plays an important role in UA levels that cannot be ignored. With regards to UGE categories, we found that the positive association between LAP and UA tended to be weaker with an increase in UGE. Additionally, a downward trend in odds ratios for hyperuricemia was observed across UGE categories. The joint association analyses further confirmed that the relationship between LAP and hyperuricemia was attenuated by UGE.

There is evidence that increased glucose in the lumen of the proximal convoluted tubule inhibits UA reabsorption, thereby leading to decreased UA levels.[32] There seems to be some interaction between the transport of glucose and UA in the kidney. Furthermore, studies have demonstrated that glycosuria is responsible for increased UA excretion.[25] Obviously, UGE should be taken into account when LAP is used as a predictor of hyperuricemia. Based on the available data, both LAP and UGE have an independent role in the regulation of UA levels.[1] In addition, since glucose is the major energy source for human body, increased UGE results in excess energy excretion, finally leading to weight loss.[33,34] However, weight reduction was shown to be associated with a significant decrease in UA levels.[11,12] In this study, we confirmed the possible interdependent relationship between UGE and LAP in predicting hyperuricemia.

Besides, subgroup analysis based on genders revealed that similar results were also observed in men. But a significantly increased risk of hyperuricemia was not observed in women with H-LAP/high UGE. It seems like that high UGE eliminate the positive influence of LAP on hyperuricemia in women. This finding can partly be explained by the differences in UGE that exist between men and women.[27] Another explanation may be that hyperuricemia is more common in men.[1] Also, it is possible that there are other novel factors that may differentially influence hyperuricemia risk between genders. Nevertheless, UGE has a negative impact on UA levels and increasing UGE may be an important strategy for controlling obesity and hyperuricemia.

Until now, few studies have been designed to focus on the association of LAP and UA levels and the effect of UGE on this relationship. Three thousand six hundred and forty-five subjects were included in our study. The large sample size may give high statistical power for current data analysis. However, several limitations should be considered in interpreting the current results. First, LAP has been considered as an index for visceral fat and study has demonstrated that LAP is effective to predict visceral fat.[16] However, we did not assess visceral fat by computed tomography or magnetic resonance imaging, which are more accurate. Second, the influence of lifestyle factors on UA levels was not taken into consideration in the current study, which should be considered in the future researches. Third, our study only involved subjects with prediabetes. Therefore, the results may not generalize to subjects with normal glucose tolerance. Finally, since the present study was cross-sectional in design, the causal relationship could not be determined.

Conclusion

The positive association between LAP and UA appears to be attenuated by UGE, indicating that promoting UGE may be an effective strategy for controlling UA levels, especially for people with obesity who are at increased risk for hyperuricemia.

Abbreviations

UA, uric acid; LAP, lipid accumulation product; BMI, body mass index; UGE, urine glucose excretion; WC, waist circumference; HR, heart rate; FPG, fasting plasma glucose; 2h-PG, 2 h plasma glucose; HbA1c, hemoglobin A1c; TC, total cholesterol; TG, triglyceride; ALT, alanine aminotransferase; AST, aspartate transaminase; BUN, blood urea nitrogen; SGLT2, sodium-glucose cotransporter 2; L-LAP, low LAP; H-LAP, high LAP; OR, odds ratio; CI, confidence interval.

Ethics Approval and Informed Consent

This study was approved by the ethical review committee of the Jiangsu Provincial Center for Disease Control and Prevention (JSJK2016-B003-03). Informed consent was obtained from all subjects included in the study.

Data Sharing Statement

The data used to support the findings of this study are available from the corresponding author upon request.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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