Journal of Diabetes and Its Complications 33 (2019) 511–515

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Differences in the association between glycemia and uric acid levels in diabetic and non-diabetic populations

Kuan-Ting Kuo [a,1], Yin-Fan Chang [a,b], I-Hsuan Wu [a], Feng-Hwa Lu [a,b], Yi-Ching Yang [a,b], Jin-Shang Wu [a,b], Chih-Jen Chang [a,b,*]

[a] Department of Family Medicine, National Cheng Kung University Hospital, Tainan, Taiwan
[b] Department of Family Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan

ARTICLE INFO

Article history:
Received 23 January 2019
Received in revised form 11 April 2019
Accepted 5 May 2019
Available online 11 May 2019

Keywords:
Glucose
Uric acid
Glucose tolerance
Diabetes mellitus
Oxidative stress

ABSTRACT

Aims: Our study aimed to investigate the influence of different glycemic statuses and their fasting plasma glucose/2-hour post-load glucose on uric acid level.
Methods: A total of 14,787 subjects were recruited after excluding subjects with medication for hyperuricemia or diabetes. Fasting plasma glucose (FPG), 2-hour post-load glucose (2hPG), and uric acid (UA) were measured. Then, subjects were divided into normal glucose tolerance (NGT), impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and diabetes.
Results: After adjustment for clinical variables, in NGT group, there was no significant relationship found between UA level and FPG. However, there was a positive association between UA level and 2hPG ($\beta = 0.003$, 95% CI: 0.002~0.004). A similar trend was also observed between UA level and 2hPG in IFG group ($\beta = 0.004$, 95% CI: 0.000~0.009) and IGT group ($\beta = 0.005$, 95% CI: 0.002~0.008), but relationship between UA level and FPG remained insignificant. In diabetes group, UA level was negatively associated with both FPG ($\beta = -0.008$, 95% CI: −0.010 ~ −0.007) and 2hPG ($\beta = -0.005$, 95% CI: −0.006 ~ −0.003).
Conclusions: In non-diabetic individuals, UA level increased with 2hPG, but not with FPG, and UA level was inversely associated with both FPG and 2hPG in diabetic population.

1. Introduction

Serum uric acid is the end product of purine metabolism. Elevated serum uric acid is considered to be associated with gout, cardiovascular disease, chronic kidney disease, and metabolic syndrome.[1–4] Patients with asymptomatic hyperuricemia are not aware of subsequent diseases and potential complications. In contrast, low levels of serum uric acid have been reported to be associated with neurological diseases, including Parkinson's disease[5] and Alzheimer's disease.[6] The above findings are not well understood, and they may be perceived to be related to uric acid as a double-edged sword due to its antioxidant[7] and pro-oxidant[8] roles in human metabolism.

The relationship between uric acid level and diabetes is still inconclusive.[9–12] A previous study indicated a positive association between serum uric acid and the incidence of diabetes.[9] In contrast, there have been studies showing that serum uric acid is not associated with an increased risk of diabetes.[10] Furthermore, some studies have found that serum uric acid is inversely associated with diabetes in a U.S. population[11] and in Japanese men.[12] Other studies have revealed a positive association between serum uric acid and the incidence of pre-diabetes.[13–15] Considering the correlation between uric acid and plasma glucose, one study indicated an inverted U-shape with a threshold of fasting plasma glucose for uric acid levels in non-diabetic subjects.[16] However, a U-shaped relationship between fasting and uric acid levels was also observed in individuals with normal glucose tolerance.[17] One study observed a decreasing trend of uric acid levels with increasing 2-h post-load glucose at concentrations over 144 mg/dL in a diabetic population.[18] Another study found uric acid to be positively associated with 2-hour post-load glucose in subjects with impaired glucose tolerance.[19] Due to the inconsistent results in the aforementioned studies,[16–19] our study was aimed toward an investigation of the association of different glycemic statuses, including normal glucose tolerance (NGT), impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and diabetes, with uric acid level. In addition, we also examined the influence of fasting plasma glucose and 2-hour post-load glucose on uric acid levels in individuals with different glycemic statuses.

Declaration of Interest: All authors reported no conflicts of interest.
Funding information: This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

* Corresponding author at: Department of Family Medicine, National Cheng Kung University Hospital, No.138, Sheng Li Road, Tainan city 70403, Taiwan.
E-mail address: changcj.ncku@gmail.com (C.-J. Chang).
[1] Author address: Department of Family Medicine, National Cheng Kung University Hospital, No.138, Sheng Li Road, Tainan city 70403, Taiwan.

https://doi.org/10.1016/j.jdiacomp.2019.05.004
1056-8727/

2. Subjects and Methods

A total of 14,787 subjects who had received a health check-up were recruited from the Health Examination Center of National Cheng Kung University Hospital, Taiwan, between January 2000 and August 2009. We conducted a secondary data analysis without personal identification information, and informed consent was waived. This study was approved by the Institutional Review Board of National Cheng Kung University Hospital (approval number: B-ER-107-080). The exclusion criteria were hyperuricemia medication ($n = 459$) and antidiabetic agents ($n = 403$). A total of 14,787 subjects were included in the final analysis.

The demographic information was collected through a questionnaire and included medical history, medication use, and lifestyle habits. All the diabetic subjects were type 2 diabetes and none of them was type 1 diabetes based on medical history. Current smoking was defined as smoking at least 20 cigarettes per month for more than six months. Current alcohol consumption was defined as at least once drink per week for more than six months. Regular exercise was a minimum of 20 min of vigorous exercise at least three times per week.

Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters) squared (kg/m^2). Brachial systolic and diastolic blood pressure were measured with an automatic blood pressure monitor (DINAMAP SX1846, Critikon, California, USA) after at least 15 min of rest. Hypertension was defined as a positive self-reported history of hypertension, right brachial systolic blood pressure (SBP) of 140 mmHg or more or diastolic blood pressure (DBP) of 90 mmHg or more according to the Seventh Report of the Joint National Committee.[20] All subjects received blood tests after an overnight fast at least 10 hours. Laboratory data included uric acid (UA), fasting plasma glucose (FPG), creatinine, aspartate transaminase (AST), alanine transaminase (ALT), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and white blood cell (WBC) count. Two-hour post-load glucose (2hPG) was obtained using a 75-g oral glucose tolerance test in subjects without known diabetes history. FPG and 2hPG were measured using a hexokinase method (Roche Diagnostic, Mannheim, Germany). Uric acid was measured using enzymatic methods with an automated chemistry analyzer (7600–110; Hitachi, Tokyo, Japan). The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) equation.

According to the American Diabetes Association 2016 guidelines,[21] subjects were classified as having diabetes if they had a positive history of diabetes, FPG ≥ 126 mg/dL or 2hPG ≥ 200 mg/dL. NGT was defined as FPG < 100 mg/dL and 2hPG < 140 mg/dL without a history of diabetes. IFG was defined as a FPG of 100–125 mg/dL but 2hPG < 140 mg/dL without a history of diabetes. IGT was defined as having a 2hPG of 140–199 mg/dL and a FPG < 126 mg/dL without a history of diabetes.

We used SPSS version 17.0 (Chicago, IL, USA) for the statistical analyses. In the univariate analysis, we used a chi-square test and an ANOVA to compare categorical and continuous variables among subjects with different glycemic statuses, respectively. Multiple linear regression analyses were performed to test the independent association between UA level and different glycemic statuses. We also performed multiple linear regression analyses to evaluate the association of FPG and 2hPG with UA level based on adjustment for gender, age, BMI, eGFR, cholesterol/HDL-C ratio, triglyceride, hypertension, smoking, drinking, and exercise status. The results for the influence of glycemic status and glucose value on UA level were expressed as beta coefficient (β) and 95% confidence intervals (CI). A P-value <0.05 was considered to be statistically significant.

3. Results

The clinical characteristics of the 14,787 subjects are shown in Table 1 with NGT ($n = 9867$), IFG ($n = 809$), IGT ($n = 2785$), and diabetes ($n = 1326$). The level of uric acid ranged from 0.2 mg/dL to 14.9 mg/dL. A significant difference in UA level was observed among the different glycemic groups. There were also significant differences in gender, age, BMI, systolic blood pressure, diastolic blood pressure, creatinine, eGFR, AST, ALT, TC, TG, HDL-C, WBC count, and alcohol consumption among the groups.

A multiple lineal regression analysis was performed to test the independent association between different glycemic statuses and UA level with adjustment for gender, age, BMI, systolic blood pressure, eGFR, ALT, TC, TG, HDL-C, WBC count, smoking, drinking, and exercise statuses (Table 2). UA level was positively associated with IFG (β = 0.118, 95% CI: 0.033~0.204, $P = 0.007$) and IGT (β = 0.169, 95% CI: 0.116~0.221, $P < 0.001$). In contrast, we observed a non-significant relationship between UA level and diabetes (β = −0.029, 95% CI: −0.102~0.043, $P = 0.426$). In addition, UA level was positively associated with male gender, BMI, SBP, ALT, TC, TG, WBC count, and drinking status, but negatively correlated with eGFR, HDL-C, and smoking status.

Then, we tested other models to determine the association of UA level with FPG and 2hPG in the NGT, IFG, IGT, and diabetes groups (Table 3). In the NGT group, there was no significant relationship between UA level and FPG, but there was a significantly positive association between UA level and 2hPG (β = 0.003, 95% CI: 0.002~0.004, $P < 0.001$). Similar results were also observed between the UA level and 2hPG in the IFG group (β = 0.004, 95% CI: 0.000~0.009, $P = 0.047$) and IGT group (β = 0.005, 95% CI: 0.002~0.008, $P = 0.002$), but the relationship between uric acid level and FPG was still insignificant. In diabetes group, UA level was negatively associated with both FPG (β = −0.008, 95% CI: −0.010 ~ −0.007, $P < 0.001$) and 2hPG (β = −0.005, 95% CI: −0.006 ~−0.003, $P < 0.001$).

4. Discussion

The association of glycemic status and glucose concentration with uric acid level is still inconsistent. For the NGT population, two studies indicated an inverse U-shaped relationship between FPG and uric acid level,[16,18] but one study observed a U-shaped relationship between them.[17] In a diabetic population, uric acid level was inversely correlated with FPG.[13,18] However, no study has examined the association between FPG and uric acid level in individuals with pre-diabetes. About the relationship between 2hPG and uric acid level, Fan et al. indicated a positive association between 2hPG and uric acid level in subjects with NGT, IGT, and diabetes, respectively.[19] However, they did not investigate the relationship between FPG and uric acid level. A decreasing trend of uric acid level with increasing 2hPG was observed in a mixed population with IFG and diabetes with 2hPG > 144 mg/dL.[18] Uric acid was also found to be negatively correlated with 2hPG in diabetic subjects.[22] Based on previous studies,[13,16–19,22] there were inconsistent findings for the association of FPG and 2hPG with uric acid level according to different glycemic statuses. In this study of a large population with carefully adjusting for confounders, we observed an insignificant relationship between FPG and uric acid level in subjects with NGT, IFG and IGT. However, a significantly positive relationship was found between 2hPG and uric acid level in subjects with NGT, IFG, and IGT. In the diabetic population, our results also showed that uric acid level decreased with elevation of both FPG and 2hPG. This is the first study to investigate the association of FPG and 2hPG with uric acid level in subjects with all spectrums of different glycemic statuses, from NGT, IFG, IGT, to diabetes. In summary, we found that the non-diabetic subjects exhibited an increasing trend of uric acid level with 2hPG but not with FPG. On the other hand, an inverse association of PFG and 2hPG with uric acid level was found in the diabetic subjects.

The possible mechanism for a positive relationship between glucose and uric acid level may be related to the antioxidant and pro-oxidant effects of uric acid[7,8] in non-diabetic subjects. Ames et al. proposed that uric acid is a powerful antioxidant, acting as a scavenger of singlet oxygen, peroxy radicals, and hydroxyl radicals.[7] Uric acid has a

Table 1
Characteristics of subjects by glycemic status.

	Normal glucose tolerance (n = 9867)	Impaired fasting glucose (n = 809)	Impaired glucose tolerance (n = 2785)	Diabetes (n = 1326)	P value
Male gender (%)	5545 (56.2%)	526 (64.6%)	1740 (62.5%)	838 (63.2%)	$P < 0.001$
Age (years)	45.94 ± 12.24	52.18 ± 11.65	52.80 ± 11.76	56.48 ± 11.00	$P < 0.001$
BMI (kg/m^2)	23.69 ± 3.35	25.43 ± 3.33	25.33 ± 3.55	25.87 ± 3.70	$P < 0.001$
SBP (mmHg)	114.69 ± 15.88	123.32 ± 18.00	122.93 ± 24.76	128.50 ± 25.58	$P < 0.001$
DBP (mmHg)	67.84 ± 10.48	72.82 ± 10.91	72.64 ± 19.40	74.87 ± 11.09	$P < 0.001$
Creatinine (mg/dL)	0.87 ± 0.29	0.90 ± 0.25	0.90 ± 0.49	0.94 ± 0.87	$P < 0.001$
eGFR (mL/min/1.73 m^2)	93.85 ± 17.84	89.58 ± 17.86	90.35 ± 18.69	89.78 ± 20.65	$P < 0.001$
Uric acid (mg/dL)	5.84 ± 1.49	6.39 ± 1.56	6.36 ± 1.54	6.26 ± 1.63	$P < 0.001$
ALT (U/L)	28.96 ± 30.16	33.72 ± 44.73	38.44 ± 38.26	46.21 ± 46.52	$P < 0.001$
AST (U/L)	24.93 ± 14.49	27.32 ± 36.61	28.89 ± 18.59	34.51 ± 31.74	$P < 0.001$
FPG (mg/dL)	85.97 ± 6.69	104.49 ± 4.59	92.14 ± 11.13	127.73 ± 49.04	$P < 0.001$
2hPG (mg/dL)	99.41 ± 20.92	109.29 ± 20.61	162.16 ± 16.43	254.35 ± 76.79	$P < 0.001$
TC (mg/dL)	193.45 ± 36.16	202.31 ± 37.08	202.26 ± 36.77	205.79 ± 42.80	$P < 0.001$
Triglyceride (mg/dL)	116.19 ± 72.75	148.71 ± 113.14	150.89 ± 95.82	177.45 ± 149.08	$P < 0.001$
HDL-C (mg/dL)	50.95 ± 13.91	47.39 ± 13.10	46.11 ± 12.69	43.85 ± 12.57	$P < 0.001$
WBC count (10^3/uL)	5.97 ± 1.61	6.24 ± 1.68	6.39 ± 1.76	6.58 ± 1.81	$P < 0.001$
Smoking	1681 (17.0%)	145 (17.9%)	527 (18.9%)	289 (21.8%)	$P = 0.167$
Alcohol use	1345 (13.6%)	125 (15.5%)	489 (17.6%)	254 (19.2%)	$P < 0.001$
Regular exercise	823 (8.3%)	61 (7.5%)	216 (7.8)	83 (6.3%)	$P = 0.058$

Data were presented as mean (±SD) or number (%).
Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; e-GFR, estimated glomerular filtration rate; AST, Aspartate transaminase; ALT, alanine transaminase; FPG, fasting plasma glucose; 2hPG, 2-hour post-load glucose; TC, Total cholesterol; HDL-C, high density lipoprotein cholesterol; WBC, white blood cell.

concentration-dependent effect on scavenging hydroxyl radicals and superoxide and slows the accumulation of reactive species-mediated markers of tissue injury.[23] Oxidative stress, also known as the production of reactive oxygen species (ROS), is linked to insulin resistance, β-cell dysfunction, and impaired glucose tolerance.[24,25] Previous studies on the relationship between oxidative stress and glucose level have indicated that hyperglycemia leads to overproduction of free radicals through glucose autoxidation and protein glycation and reduced production/bioavailability of nitric oxide (NO).[26–28] As for the contribution of fasting and postprandial blood glucose increments on level of inflammation and oxidative stress biomarkers, postprandial blood glucose increment significantly contributes to increased levels of lipid peroxidation and the expression of cell adhesion molecules, as compared to fasting plasma glucose.[29] Many studies have found that postprandial hyperglycemia is associated with an increase in the levels of reactive species of oxygen and the activation of oxidative stress.[30,31] Therefore, we may assume that elevated 2hPG is associated with increased oxidative stress in non-diabetic subjects, including NGT, IFG, and IGT. With this increase in 2hPG-induced oxidative stress, uric acid might become elevated and act as an antioxidant. Another possible reason for the positive association of 2hPG with uric acid level may be the pro-oxidant effect of uric acid. Acting as pro-oxidant in human metabolism, hyperuricemia may induce insulin resistance by increasing ROS production.[32] An elevation of uric acid level has been proven to disturb glucose metabolism in muscle tissue and in the liver by inhibiting insulin signaling and increasing insulin resistance.[33] The insulin sensitivity of skeletal muscles is known to be the primary determinant of the whole body and the predominant factor related to insulin-mediated glucose uptake in the postprandial state.[34] Previous research has shown that insulin resistance is associated with significant increases in postprandial glycemia.[35] We therefore hypothesized that elevated uric acid concentration, as a pro-oxidant, leads to increased insulin resistance, mainly in skeletal muscle, resulting in a decreased glucose uptake and further contributing to the elevation of 2hPG. However, the causal relationship between hyperuricemia and 2-h PG needs more investigation in non-diabetic population.

Table 2
Adjusted beta coefficient and 95% confidence interval of clinical variables for uric acid levels in all subjects.

	β	95% CI	P value
Male vs. Female	1.136	1.090 ~ 1.182	$P < 0.001$
Age (years)	−0.012	−0.014 ~ −0.010	$P < 0.001$
BMI (kg/m^2)	0.078	0.072 ~ 0.084	$P < 0.001$
SBP (mmHg)	0.002	0.001 ~ 0.003	$P < 0.001$
ALT (U/L)	0.002	0.001 ~ 0.003	$P < 0.001$
eGFR (mL/min/1.73 m^2)	−0.019	−0.020 ~ −0.018	$P < 0.001$
TC (mg/dL)	0.003	0.002 ~ 0.003	$P < 0.001$
Triglyceride (mg/dL)	0.001	0.000 ~ 0.001	$P < 0.001$
HDL-C (mg/dL)	−0.011	−0.012 ~ −0.009	$P < 0.001$
WBC count (10^3/uL)	0.048	0.036 ~ 0.061	$P < 0.001$
Smoking (yes vs. no)	−0.128	−0.187 ~ −0.069	$P < 0.001$
Alcohol use (yes vs. no)	0.156	0.095 ~ 0.218	$P < 0.001$
Regular exercise (yes vs. no)	−0.032	−0.102 ~ 0.039	$P = 0.381$
IFG	0.118	0.033 ~ 0.204	$P = 0.007$
IGT	0.169	0.116 ~ 0.221	$P < 0.001$
Diabetes	−0.029	−0.102 ~ 0.043	$P = 0.426$

Abbreviations: CI, confidence interval; BMI, body mass index; SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate; ALT, alanine transaminase; TC, Total cholesterol; HDL-C, high density lipoprotein cholesterol; WBC, white blood cell; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

Table 3
Adjusted beta coefficient and 95% confidence interval of fasting plasma glucose and 2-hour post-load glucose on uric acid level by different glycemic statuses.

NGT subgroup			
	β (95% CI)		β (95% CI)
FPG (mg/dL)	0.003 (0.000 ~ 0.006)	2hPG (mg/dL)	0.003 (0.002 ~ 0.004)***
IFG subgroup			
	β (95% CI)		β (95% CI)
FPG (mg/dL)	0.000 (-0.019 ~ 0.020)	2hPG (mg/dL)	0.004 (0.000 ~ 0.009)*
IGT subgroup			
	β (95% CI)		β (95% CI)
FPG (mg/dL)	0.000 (-0.005 ~ 0.004)	2hPG (mg/dL)	0.005 (0.002 ~ 0.008)**
Diabetes subgroup			
	β (95% CI)		β (95% CI)
FPG (mg/dL)	-0.008 (-0.010 ~ -0.007)***	2hPG (mg/dL)	-0.005 (-0.006 ~ -0.003)***

Adjustment for gender, age, BMI, eGFR, TC/HDL-C ratio, triglyceride, hypertension, smoking, alcohol use, and exercise status.
* $P < 0.05$
** $P < 0.01$
*** $P < 0.001$

In the diabetic population, we observed an inverse association of FPG and 2hPG with uric acid level. The results were consistent with those of other studies.[18,22] Previous studies have indicated that diabetic patients with glycosuria have a null prevalence of hyperuricemia and a higher urine excretion of uric acid than that observed in those without glycosuria.[36] The renal system plays an important role in the excretion and reabsorption of serum uric acid. Approximately 70% of uric acid is filtered in renal glomeruli and then almost completely reabsorbed in the proximal tubule via glucose transporter 9 (GLUT9) isoform 2. A recent study showed a lowering effect on uric acid due to glycosuria induced by sodium-glucose cotransporter 2 (SGLT2) inhibitors.[37] In addition, this study revealed that there was a significantly negative association between uric acid level and urine glucose ($\beta = -0.672$, 95% CI: $-0.854 \sim -0.490$, $P < 0.001$) in the diabetic subjects, based on multiple linear regression. This could help to explain that glycosuria causes increased UA excretion in diabetic population. Thus, in diabetic subjects, glycosuria resulting from elevated glucose levels will competitively inhibit uric acid reabsorption and lead to excessive uric acid excretion, resulting in a lower serum uric acid level. This may be an explanation for the negative relationship between plasma glucose and uric acid level in the diabetic population.

We divided subjects into normal UA group (UA < 6.0 mg/dL, $n = 7473$) and elevated UA group (UA ≥ 6.0 mg/dL, $n = 7314$) by uric acid status. Based on multiple lineal regression, in both normal UA and elevated UA groups, the association between FPG and UA level was significant in diabetic subjects, but not in NGT, IFG, and IGT subjects. The relationship between FPG and UA level held in both normal UA and elevated UA groups. As for the relationship between 2hPG and UA level, the association of 2hPG with UA level still held in NGT and diabetic subjects of normal UA group and in NGT and IGT subjects of elevated UA group. Although the association did not reach statistical significance in IFG and IGT subjects of normal UA group and in IFG and diabetic subjects of elevated UA group, the directions of beta coefficients were the same. The statistical insignificance might be due to relatively small sample size of sub-group analysis. Based on the results of sub-group analysis, we further confirmed that the independent association between FPG and UA level in diabetes subjects, but not in NGT, IFG, and IGT subjects. However, the relationship between 2hPG and UA level needs more studies in subjects with different glycemic statuses.

Previous studies have yielded inconsistent results for age-related distribution of uric acid levels.[38–41] However, we observed a significantly negative association between age and uric acid level in the subjects for all glycemic statuses. A previous study proposed that oxygen-derived free radicals are responsible for the aging process.[42] Uric acid levels have been found to correlate with the life span of mammals, despite the potential risk of developing gout, renal stones, and cardiovascular disease.[7,43] Uric acid has also been confirmed to reduce intracellular ROS accumulation and protect against DNA damage and cell death.[44] When humans grow older, uric acid may be consumed to decreased age-associated oxidative stress. These might provide a partial explanation for an inverse relationship between age and uric acid levels. These inconsistent age-related distributions of uric acid levels in different population-based studies may result from the fact that uric acid levels are also influenced by genetic, physiological, and environmental factors.

We observed a significantly negative correlation between uric acid level and smoking. Smoking is thought to be a significant source of oxidative stress.[45] Acting as an antioxidant, uric acid administration has been found to improved endothelial function among smokers, suggesting that high uric acid concentrations in vivo might serve a protective role.[46] Studies have indicated that uric acid levels in smokers are significantly lower than in nonsmokers as a result of the chronic exposure to cigarette smoke, which is a significant source of oxidative stress.[47,48] Our study indicated a similar relationship between uric acid level and smoking status in the total and IGT groups. We assumed glucose-induced oxidative stress to be higher in IGT group than in NGT and IFG groups due to higher average plasma glucose levels.[24] Therefore, it was expected that uric acid as an antioxidant would be consumed more in IGT group. On the other hand, there are multiple factors that interfere with uric acid levels among the diabetic population, including systemic inflammation,[49] glucose levels,[50] and renal secretion.[36] This may be an explanation for the insignificant relationship between smoking and uric acid level in diabetes group.

There are some limitations in our study. Since our study was a cross-sectional design, it is difficult to prove a definitive causal relationship between uric acid level and glucose concentration, including both FPG and 2hPG. Subjects with medication for either hyperuricemia or diabetes were excluded. However, medications that would interfere with uric acid level, such as diuretics, could not be addressed since this information was not available in our study although we took history of hypertension into consideration in the multivariate analysis. Additionally, uric acid level is also affected by other factors, including ethnicity, diet (such as organ meats, seafood, sugary foods, beverages, etc.), and environment. However, the record of dietary uric acid intake was not available in this study. Our study was conducted in a Taiwanese population, so further investigations in other populations are needed.

In conclusion, uric acid level increased with 2hPG, but not with FPG in the non-diabetic individuals. Uric acid level decreased with both FPG and 2hPG in the diabetic population. This study provides a direction for further studying the impact of different glycemic statuses and glucose concentrations on uric acid level.

Acknowledgement

We thank Savana Moore, proofreader at the Foreign Language Center of National Cheng Kung University, for assistance with proof reading the article.

References

1. Choi HK, Mount DB, Reginato AM. Pathogenesis of gout. Ann Intern Med 2005;143:499-516.
2. Gerber Y, Tanne D, Medalie JH, Goldbourt U. Serum uric acid and long-term mortality from stroke, coronary heart disease and all causes. Eur J Cardiovasc Prev Rehabil 2006;13:193-8.
3. Chou YC, Kuan JC, Yang T, et al. Elevated uric acid level as a significant predictor of chronic kidney disease: a cohort study with repeated measurements. J Nephrol 2015;28:457-62.
4. Cicero AF, Rosticci M, Bove M, et al. Serum uric acid change and modification of blood pressure and fasting plasma glucose in an overall healthy population sample: data from the Brisighella heart study. Ann Med 2017;49:275-82.
5. Wen M, Zhou B, Chen YH, et al. Serum uric acid levels in patients with Parkinson's disease: A meta-analysis. PLoS One 2017;12, e0173731.
6. Kim TS, Pae CU, Yoon SJ, et al. Decreased plasma antioxidants in patients with Alzheimer's disease. Int J Geriatr Psychiatry 2006;21:344-8.
7. Ames BN, Cathcart R, Schwiers E, Hochstein P. Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: a hypothesis. Proc Natl Acad Sci U S A 1981;78:6858-62.
8. Sautin YY, Johnson RJ. Uric acid: the oxidant-antioxidant paradox. Nucleosides Nucleotides Nucleic Acids 2008;27:608-19.
9. Chien KL, Chen MF, Hsu HC, et al. Plasma uric acid and the risk of type 2 diabetes in a Chinese community. Clin Chem 2008;54:310-6.
10. Taniguchi Y, Hayashi T, Tsumura K, Endo G, Fujii S, Okada K. Serum uric acid and the risk for hypertension and Type 2 diabetes in Japanese men: The Osaka Health Survey. J Hypertens 2001;19:1209-15.
11. Bandaru P, Shankar A. Association between Serum Uric Acid Levels and Diabetes Mellitus. Int J Endocrinol 2011;2011, 604715.
12. Oda E, Kawai R, Sukumaran V, Watanabe K. Uric acid is positively associated with metabolic syndrome but negatively associated with diabetes in Japanese men. Intern Med 2009;48:1785-91.
13. Nakanishi N, Okamoto M, Yoshida H, Matsuo Y, Suzuki K, Tatara K. Serum uric acid and risk for development of hypertension and impaired fasting glucose or Type II diabetes in Japanese male office workers. Eur J Epidemiol 2003;18:523-30.
14. Zhang Q, Bao X, Meng G, et al. The predictive value of mean serum uric acid levels for developing prediabetes. Diabetes Res Clin Pract 2016;118:79-89.
15. van der Schaft N, Brahimaj A, Wen KX, Franco OH, Dehghan A. The association between serum uric acid and the incidence of prediabetes and type 2 diabetes mellitus: The Rotterdam Study. PLoS One 2017;12, e0179482.
16. Li H, Zha X, Zhu Y, Liu M, Guo R, Wen Y. An Invert U-Shaped Curve: Relationship Between Fasting Plasma Glucose and Serum Uric Acid Concentration in a Large Health Check-Up Population in China. Medicine 2016;95, e3456.

17. Wang Y, Chi J, Che K, et al. Fasting plasma glucose and serum uric acid levels in a general Chinese population with normal glucose tolerance: A U-shaped curve. PLoS One 2017;12, e0180111.
18. Nan H, Dong Y, Gao W, Tuomilehto J, Qiao Q. Diabetes associated with a low serum uric acid level in a general Chinese population. Diabetes Res Clin Pract 2007;76: 68-74.
19. Fan HQ, Tang W, Wang ZX, et al. Association of serum uric acid with 2-hour postload glucose in Chinese with impaired fasting plasma glucose and/or HbA1c. PLoS One 2013;8, e67759.
20. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003;42:1206-52.
21. Standards of medical care in diabetes-2016 abridged for primary care providersClin Diab 2016;34:3-21.
22. Wei F, Chang B, Yang X, Wang Y, Chen L, Li WD. Serum Uric Acid Levels were Dynamically Coupled with Hemoglobin A1c in the Development of Type 2 Diabetes. Sci Rep 2016;6, 28549.
23. Stinefelt B, Leonard SS, Blemings KP, Shi X, Klandorf H. Free radical scavenging, DNA protection, and inhibition of lipid peroxidation mediated by uric acid. Ann Clin Lab Sci 2005;35:37-45.
24. Wright Jr E, Scism-Bacon JL, Glass LC. Oxidative stress in type 2 diabetes: the role of fasting and postprandial glycaemia. Int J Clin Pract 2006;60:308-14.
25. Meigs JB, Larson MG, Fox CS, Keaney Jr JF, Vasan RS, Benjamin EJ. Association of oxidative stress, insulin resistance, and diabetes risk phenotypes: the Framingham Offspring Study. Diabetes Care 2007;30:2529-35.
26. Hunt JV, Smith CC, Wolff SP. Autoxidative glycosylation and possible involvement of peroxides and free radicals in LDL modification by glucose. Diabetes 1990;39:1420-4.
27. Lamers ML, Almeida ME, Vicente-Manzanares M, Horwitz AF, Santos MF. High glucose-mediated oxidative stress impairs cell migration. PLoS One 2011;6, e22865.
28. Russell JW, Golovoy D, Vincent AM, et al. High glucose-induced oxidative stress and mitochondrial dysfunction in neurons. FASEB J 2002;16:1738-48.
29. Djindjic B, Kostic T, Radovanovic Z, et al. The contributions of fasting and postprandial blood glucose increments to oxidative stress and inflammation in dyslipidemic type 2 diabetic patients with stable ischemic heart disease. Int J Cardiol 2017;227:611-6.
30. Neri S, Calvagno S, Mauceri B, et al. Effects of antioxidants on postprandial oxidative stress and endothelial dysfunction in subjects with impaired glucose tolerance and type 2 diabetes. Eur J Nutr 2010;49:409-16.
31. Zheng F, Lu W, Jia C, Li H, Wang Z, Jia W. Relationships between glucose excursion and the activation of oxidative stress in patients with newly diagnosed type 2 diabetes or impaired glucose regulation. Endocrine 2010;37:201-8.
32. Wan X, Xu C, Lin Y, et al. Uric acid regulates hepatic steatosis and insulin resistance through the NLRP3 inflammasome-dependent mechanism. J Hepatol 2016;64:925-32.
33. Zhu Y, Hu Y, Huang T, et al. High uric acid directly inhibits insulin signalling and induces insulin resistance. Biochem Biophys Res Commun 2014;447:707-14.
34. DeFronzo RA, Tripathy D. Skeletal muscle insulin resistance is the primary defect in type 2 diabetes. Diabetes Care 2009;32:S157-63.
35. Dickinson S, Colagiuri S, Faramus E, Petocz P, Brand-Miller JC. Postprandial hyperglycemia and insulin sensitivity differ among lean young adults of different ethnicities. J Nutr 2002;132:2574-9.
36. Andrade JA, Kang HC, Greffin S, Garcia Rosa ML, Lugon JR. Serum uric acid and disorders of glucose metabolism: the role of glycosuria. Braz J Med Biol Res Rev Bras Pesqui Med Biol 2014;47:917-23.
37. Chino Y, Samukawa Y, Sakai S, et al. SGLT2 inhibitor lowers serum uric acid through alteration of uric acid transport activity in renal tubule by increased glycosuria. Biopharm Drug Dispos 2014;35:391-404.
38. Liese AD, Hense HW, Lowel H, Doring A, Tietze M, Keil U. Association of serum uric acid with all-cause and cardiovascular disease mortality and incident myocardial infarction in the MONICA Augsburg cohort. World Health Organization Monitoring Trends and Determinants in Cardiovascular Diseases. Epidimiology 1999;10:391-7.
39. Fang J, Alderman MH. Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study, 1971-1992. National Health and Nutrition Examination Survey. Jama 2000;283:2404-10.
40. Kuzuya M, Ando F, Iguchi A, Shimokata H. Effect of aging on serum uric acid levels: longitudinal changes in a large Japanese population group. J Gerontol A Biol Sci Med Sci 2002;57:M660-4.
41. Culleton BF, Larson MG, Kannel WB, Levy D. Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study. Ann Intern Med 1999;131:7-13.
42. De la Fuente M. Effects of antioxidants on immune system ageing. Eur J Clin Nutr 2002;56:S5-8.
43. Cutler RG. Antioxidants and aging. Am J Clin Nutr 1991;53:373s-9s. Suppl.
44. Itahana Y, Han R, Barbier S, Lei Z, Rozen S, Itahana K. The uric acid transporter SLC2A9 is a direct target gene of the tumor suppressor p53 contributing to antioxidant defense. Oncogene 2015;34:1799-810.
45. Mallampalli A, Guntupalli KK. Smoking and systemic disease. Clin Occup Environ Med 2006;5:173-92. x.
46. Waring WS, McKnight JA, Webb DJ, Maxwell SR. Uric acid restores endothelial function in patients with type 1 diabetes and regular smokers. Diabetes 2006;55:3127-32.
47. Hanna BE, Hamed JM, Touhala LM. Serum uric Acid in smokers. Oman Med J 2008;23: 269-74.
48. Haj Mouhamed D, Ezzaher A, Neffati F, Douki W, Gaha L, Najjar MF. Effect of cigarette smoking on plasma uric acid concentrations. Environ Health Prev Med 2011;16: 307-12.
49. Duncan BB, Schmidt MI, Pankow JS, et al. Low-grade systemic inflammation and the development of type 2 diabetes: the atherosclerosis risk in communities study. Diabetes 2003;52:1799-805.
50. Amaro S, Llull L, Renu A, et al. Uric acid improves glucose-driven oxidative stress in human ischemic stroke. Ann Neurol 2015;77:775-83.