ABSTRACT

Aim: Evidence has emerged that glycosuria is associated with lowering of serum uric acid (UA) levels in patients with diabetes mellitus (DM). The present study investigated whether glycosuria, per se, is involved in the lowering of UA levels in type 2 diabetic patients without hypoglycemic agents with uricosuric property.

Subjects & Methods: Individuals who underwent an annual medical check-up and met the inclusion criteria were recruited for this cross-sectional analysis. Diabetic patients being treated with sodium glucose cotransporter 2 (SGLT2) inhibitors were excluded from the analysis. The final participants were a total of 11,649 males, which consisted of euglycemics, prediabetics, and diabetics. Multiple regression analysis was employed to estimate factors influencing serum UA level.

Results: The UA level in the overall diabetics (5.9 ± 1.4mg/dL, n=704) was comparable with that in euglycemics (6.0 ± 1.1mg/dL, n=9,871). Prediabetics had the highest UA level among the subgroups (6.6 ± 1.3mg/dL, n=1,074). The UA level in diabetics with glycosuria (5.5 ± 1.3mg/dL, n=197) was lower than that in diabetics without glycosuria (6.0 ± 1.2mg/dL, n=507, p<0.01). In addition, the severity of glycosuria had a negative correlation with the lowering of UA levels in diabetics. In addition, poor diabetic control was associated with the severity of glycosuria. Multiple regression analysis revealed that factors to predict the lowering of UA levels in diabetics were: age, estimated glomerular filtration rate (eGFR), and presence of glycosuria.

Conclusion: There is a close association between glycosuria and lowering of serum UA levels in patients with DM not being treated with SGLT2 inhibitors.

INTRODUCTION

In patients with diabetes mellitus (DM) at mild to moderate phases where glucose intolerance becomes apparent, the serum uric acid (UA) level increases due to the reduction of UA excretion through the kidney. This occurs in concert with increased insulin resistance and/or hyperinsulinemia, which act on the kidney to increase UA reabsorption, leading to an increase in the circulating serum UA level. A large number of studies have shown that hyperuricemia is closely associated with DM1-7). The prevalence of hyperuricemia was found to be 33% in Type 2 DM patients with central obesity in Asia8). Hyperuricemia, in addition, is
enhanced due to the reduced excretory capacity of the kidney when a patient’s renal function progresses into advanced stage chronic kidney disease (CKD).

Despite these solid associations between hyperuricemia and DM, increases in serum UA levels in relation to the stage or severity of DM are not always consistent. Indeed, some reports suggested that the serum UA level does not always increase in a stepwise fashion as the clinical course of DM progresses into a more advanced stage. A large-scale survey showed that the lowering of UA levels occurred in a subset of diabetic patients whose diabetic control was poor. Increased urinary excretion of UA in the presence of glycosuria may account for this UA-lowering.

Recently, evidence emerged that a novel hypoglycemic agent, sodium glucose co-transporter 2 (SGLT2) inhibitor, decreases serum UA levels via glucose/UA-coupled transporters in renal tubular cells. These findings disclosed that serum UA levels are variable depending on the clinical manipulations or diabetic severity where glycosuria plays a pivotal role.

The aim of the present study was to investigate a link between serum UA levels and diabetic stages. Comparison was made among three groups, euglycemics, prediabetics and diabetics, in the presence and absence of glycosuria by recruiting a subgroup of patients who developed overt glycosuria in the course of DM. Special attention was also paid to exclude patients with DM who had previously received SGLT2 inhibitors, which are known to elicit both glycosuric and uricosuric effects.

SUBJECTS & METHODS

Participants: The initial number of participants as 15,433, who were scheduled on an annual medical check-up every year at the health management center of the Tokyo Regional Taxation Bureau Clinic. They were all Japanese office workers aged 20 to 65 years old (average: 44 +/- 11). The exclusion criteria include individuals having insufficient data; those with past histories of incident major cardiovascular events such as cerebral apoplexy or myocardial infarction; those with any disease requiring hospitalization; those with current cancer or other life-threatening diseases; those who had ever been treated with SGLT2 inhibitors and those who were being treated with drugs such as diuretics or losartan that potentially influence serum UA levels. In addition, women were excluded from the analysis not only because of the apparent difference in the normal physiological UA range between the two genders but also the relatively small number of females (24%). After the application of these exclusion criteria, a total number of 11,649 men were eligible for a retrospective cross-sectional analysis of UA levels, which consisted of euglycemics (n=9,871), prediabetics (n=1,074) and a subset group of diabetics (n=704). Euglycemics were recruited as a reference to compare UA levels between dysglycemics and non-dysglycemics.

Definition of type 2 DM, prediabetic and euglycemic:
As per the guidelines of the Japanese Society of Diabetes Association, type 2 DM was defined as having a fasting plasma glucose (FPG) ≥ 126mg/dL, plasma glucose of OGTT 2 hours ≥ 200mg/dL, or casual plasma glucose level ≥ 200mg/dL, and/or 2) HbA1c ≥ 6.5%. The “normal or euglycemic type” was defined as having a FPG < 110mg/dL and 2 hour postprandial plasma glucose level <140mg/dL. Accordingly, the “prediabetic type” was defined as those who do not meet the criteria of either the DM type or normal type described above.

Other variables: Body mass index (BMI) was calculated based on the equation: BMI = Body weight (BW) X 1/ (Body Height) squared. Laboratory tests were carried out after an 8- to 12-hour fasting. Measurements were made on serum creatinine (Cr) concentration, serum UA concentration, and lipid profiles including total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDLC),
SBP-DBP performed for these parameters. The renal function tests in all participants.

Because the histograms of TG distributed in a non-parametric fashion, logarithmic transformation was performed for these parameters. The renal function expressed as eGFR for Japanese was calculated based on the equation: eGFR = 194 x Cr⁻¹.044 x Age⁻⁰.287 (if women x 0.739), reported elsewhere.[1]

Glycosuria was evaluated by the qualitative measurement of urinary glucose excretion in all participants using Ames urinalysis test paper, Hema Combi Sticks (glucose oxidase method). These results were classified into 5 different grades: (-), (1+), (2+), (3+), and (4+). Quantitatively, the estimated amount of qualitatively measured urinary glucose (UG) was approximately as follows; UG (1+); 100mg, (2+); 250mg, (3+); 500mg and (4+); 1000mg.

Laboratory tests were performed using the BioMajesty™ auto-analyzer Series JCA-9130 (JOEL, Tokyo, Japan). The value of HbA1c was measured as a unit of NGSP (National glycohemoglobin standardization program) based on the equation; NGSP (%) = JSD x 1.02 + 0.25 (%).

Blood pressure (BP) was measured in a sitting position during a morning visit (fasting, 9 to 11AM), after 5 minutes of rest in a supine position using an automatic self-measuring device equipped with a 47 x 13 cm cuff and 24 x 13 cm bladder to avoid so-called “white coat hypertension” and/or “cuff hypertension”. Mean blood pressure (MBP) was calculated from systolic blood pressure (SBP) and diastolic blood pressure (DBP) based on the equation: MBP = DBP + (SBP–DBP) / 3.

Ethical considerations: The study was conducted in accordance with “Recommendations on the Establishment of Animal Experimental Guidelines” approved at the 80th General Assembly of the Japanese Science Council in 1980, and the principles set out in the Declaration of Helsinki 1964 as modified by subsequent version revisions. The study protocol design was a retrospective screened cohort. This epidemiological survey was submitted to the Institutional Review Board (IRB)/Ethics Committee of the Jikei University School of Medicine. After the deliberation the protocol was approved by the ethics committee of the university with the clinical trial number 25–203 (7338).

Statistical analysis: The database and all statistical outputs were retained by the University. The access to the database was limited as deemed necessary. The authors assume full responsibility for the completeness and accuracy of the content of the manuscript. Multiple regression analysis was used to estimate factors affecting serum UA levels. The final variables were chosen on the basis of clinical importance and biological plausibility at the investigators’ discretion. Results of the different subgroups were examined by one-way analysis of variance (ANOVA) with further multiple comparison between the two respective groups using Tukey’s test.

Statistical analyses were carried out with Stat Flex version 6.0 (Artec Ltd. Co., Osaka, Japan) and STATA version 11.1 (STATA Cooperation, College Station, TX, USA). Data are presented as the mean +/- standard deviation (SD), unless otherwise indicated. P ≤ 0.05 was considered statistically significant, and 95% confidence intervals (CI) are expressed as 95% CI.

RESULTS

Table 1 shows the baseline characteristics of enrolled subjects. Since this study primarily focuses on serum UA levels in diabetics with or without glycosuria, the euglycemics and prediabetics were recruited as references for comparison of a UA levels in diabetics. Subjects who met the criteria for a
A definite diagnosis of DM accounted for 6.0% (n=704) of the overall participants (n=11,649), and those with prediabetics 9.1% (n=1,074). Each parameter showed variability among the three subgroups (ANOVA).

Note that the value of HbA1c was significantly higher in diabetics (7.3 ± 1.2% (n=704)), than in the other groups (euglycemics: 5.3 ± 0.3% (n=9,871), prediabetics: 5.7 ± 0.4% (n=1,074), p<0.01 for each).

Table 2 shows the results of multiple regression analysis to estimate factors affecting the serum UA level. Factors predicting an increase in serum

| Table 1: Baseline characteristics of participants |
|------------------------------------------------|
| (n) | Euglycemics | Prediabetes | Diabetics | P |
|-----|-------------|-------------|-----------|---|
| Age (y) | 42±11 | 48±9 | 52±8 | <0.01 |
| BMI (Kg/m²) | 23±3 | 27±3 | 27±5 | <0.01 |
| SBP (mmHg) | 119±14 | 133±13 | 128±15 | <0.01 |
| DBP (mmHg) | 76±11 | 87±10 | 81±10 | <0.01 |
| Mean BP (mmHg) | 90±11 | 102±10 | 97±11 | <0.01 |
| Cr (mg/dL) | 0.84±0.12 | 0.86±0.14 | 0.86±0.51 | <0.01 |
| eGFR (mL/min/1.73m²) | 82.6±14.0 | 77.8±13.1 | 79.5±16.4 | <0.01 |
| UA (mg/dL) | 6.0±1.2 | 6.6±1.4 | 5.9±1.2 | <0.01 |
| TC (mg/dL) | 199±32 | 214±34 | 202±34 | <0.01 |
| TG (mg/dL) | 87 (31) | 177 (50) | 128 (51) | <0.01 |
| HDLC (mg/dL) | 60±15 | 51±12 | 54±14 | <0.01 |
| LDLC (mg/dL) | 121±30 | 132±31 | 123±31 | <0.01 |
| PG (mg/dL) | 93±9 | 104±13 | 147±42 | <0.01 |
| HbA1c (NGSP) (%) | 5.3±0.3 | 5.7±0.4 | 7.3±1.2 | <0.01 |

BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, Cr: serum creatinine concentration, eGFR: estimated glomerular filtration rate, UA: serum uric acid concentration, TC: total cholesterol, TG: triglycerides, HDLC: HDL cholesterol, LDLC: LDL cholesterol, PG: plasma glucose concentration, HbA1c: glycated hemoglobin.

As the histograms of TG distributes in a non-parametric fashion, logarithmic transformation was performed, and TG is expressed as the median and quartiles (in parenthesis).

Statistical significance was verified by ANOVA.

Table 2: Multiple regression analysis to predict factors influencing serum UA levels in diabetics

| Variable | R Coefficient | SE | t value | P |
|----------|---------------|----|---------|---|
| Age      | -0.017        | 0.006 | -15.59 | <0.001 |
| BMI      | 0.080         | 0.003 | 25.77   | <0.001 |
| MBP      | 0.011         | 0.001 | 11.08   | <0.001 |
| eGFR     | -0.021        | 0.001 | -24.74  | <0.001 |
| UG (−) Reference | 1 | | | |
| UG (1+)  | 0.229         | 0.125 | 1.833   | 0.068 |
| UG (2+)  | 0.018         | 0.154 | 0.12    | 0.906 |
| UG (3+)  | -0.298        | 0.140 | -2.13   | 0.003 |
| UG (4+)  | -0.584        | 0.137 | -4.27   | <0.001 |

BMI: body mass index, MBP: mean blood pressure, eGFR: estimated glomerular filtration rate, UG: urinary glucose. R coefficient: regression coefficient, SE: standard error.
UA levels were BMI and MBP. In contrast, those predicting a decrease in serum UA levels were age, eGFR and urinary glucose. Note that the t-value became more significant with worsening glycosuria in UG-positive groups (UG (3+) and (4+)).

Table 3 shows the relationship between serum UA levels and HbA1c with respect to the degree of glycosuria stratified by the qualitatively measured urinary glucose. The upper table shows a trend whereby the greater the glycosuria, the higher the HbA1c. Similarly, the lower table indicates a trend whereby the greater the glycosuria, the lower the serum UA levels.

Figure 1 shows UA levels in the different subgroups

| Table 3: Serum UA levels and HbA1c classified by glycosuria in diabetic patients |
|--------------------------|----------------|----------|----------|----------|
| UG | n  | HbA1c (%) mean | SD | Max | Min |
| --- | --- | --------------- | --- | ---- | ---- |
| −  | 507 | 6.9             | 0.8 | 4.9  | 11.0 |
| 1+ | 63  | 7.4             | 1.0 | 5.8  | 10.3 |
| 2+ | 37  | 8.0             | 1.3 | 6.3  | 11.1 |
| 3+ | 47  | 8.5             | 1.4 | 6.2  | 12.5 |
| 4+ | 50  | 9.5             | 1.5 | 7.1  | 12.9 |

| UG | n  | UA (mg/dL) mean | SD | Max | Min |
| --- | --- | ----------------- | --- | ---- | ---- |
| −  | 507 | 6.0              | 1.2 | 3.0  | 9.5  |
| 1+ | 63  | 5.9              | 1.3 | 3.4  | 9.2  |
| 2+ | 37  | 5.6              | 1.2 | 3.1  | 8.1  |
| 3+ | 47  | 5.4              | 1.2 | 2.8  | 8.2  |
| 4+ | 50  | 5.0              | 1.2 | 1.9  | 7.5  |

UG: urinary glycosuria, Max: maximum value, Min: minimum value.

Figure 1: Serum UA levels among subgroups with difference in glycemic control with or without glycosuria

Group1 (G1): euglycemics, G2: prediabetics, G3: diabetics without glycosuria, G4: those with glycosuria 1+, G5: those with 2+, G6: those with 3+ and G7: those with 4+.

UG: urinary glucose, Pre-DM: prediabetics.

ANOVA shows the differences among subgroups (p<0.01) with further comparison using Tukey’s test, indicating statistical significance between two respective groups at p<0.01. ns: not significant.
of participants: euglycemics (Group 1: G1), prediabetics (G2) and diabetics (G3–G7). Serum UA levels in diabetics with glycosuria (G4–G7; 5.5 ± 1.3mg/dL, n=197) were significantly lower than in diabetics without glycosuria (G3; 6.0 ± 1.2mg/dL, n=507). Serum UA levels in diabetics without glycemia (G3) were comparable to those in euglycemics (G1: 6.0 ± 1.1mg/dL, n=9,871). Prediabetics (G2) had the highest serum UA level among the groups (6.6 ± 1.3mg/dL, n=1,074). Moreover, serum UA levels in prediabetics (G2) were significantly higher than that in diabetics with glycosuria (G4–G7; p<0.01). The serum UA value of the latter (G4–G7) was comparable with that in euglycemics (G1).

Figure 2 shows PG and HbA1c in all subgroups (G1 to G7) with different level of glycemic control. These parameters of glycemic control (PG and HbA1c) increased in a stepwise fashion as glycemic control worsened: euglycemics (G1), prediabetics (G2), diabetics without glycosuria (G3), and diabetics with glycosuria (G4–G7), in this order (ANOVA, p<0.01).

**DISCUSSION**

The present study investigated whether glycosuria itself has an influence on serum UA levels without interference with SGLT2 inhibitors. By recruiting three groups with a different glycemic control status, normoglycemic, prediabetic, and diabetic, our study clearly demonstrates that there is a reciprocal relationship between serum UA levels and the degree of glycosuria in diabetics. In addition, the serum UA level in prediabetics without glycosuria was the highest among the groups. Based on the approximate conversion from the qualitatively measured to quantitatively estimated UG to influence serum UA, glycosuria of 0.5 g (UG 3+) to 1.0 g (UG 4+) or more can lower the serum UA level (Table 2).

Up to now, a large body of evidence has shown that hyperuricemia is associated with abnormality in glucose metabolism such as obesity, and DM and/or metabolic syndrome. One of the common mechanisms to account for this link can be explained by hyperinsulinemia or insulin resistance. These conditions are known to act on the glucose/UA coupled transporter in the renal tubules to inhibit UA transport,
decreasing UA excretion through the kidney, resulting in hyperuricemia. In contrast, paradoxical evidence has accumulated that serum UA may be lowered in some patient populations when glycosuria becomes obvious. In this patient population, hyperinsulinemia increases UA clearance in the hyperfiltrable diabetic kidney, possibly leading to lowering of the serum UA level. Mild to moderate hyperglycemia is normally associated with hyperuricemia, whereas a high degree of hyperglycemia or poor glycemic control is associated with the lowering of UA levels\(^7\). These conflicting findings were not clearly understood until recently when newly-developed hypoglycemic agents, SGLT2 inhibitors, which have a unique uricosuric pharmacological property, came into clinical use.

A decrease in serum UA levels has been almost universally reported in patients treated with SGLT2 inhibitors\(^12-15\). SGLT2 inhibitors decrease serum UA levels through a uricosuric effect\(^13,14\). Using SGLT2 inhibitors and glucose clamped euglycemia method, Lytvyn et al suggested the mechanism of glycosuria-mediated accelerated excretion of UA through the kidney in patients with type 1 DM\(^16\). Increased urinary excretion of UA in the presence of glycosuria accounts for this lowering of UA. The mechanism may presumably be mediated either by blocking SGLT2-mediated glucose reabsorption in renal tubules or an enhanced osmotic effect in the kidney. This study also suggests that glycosuria rather than hyperglycemia increases uricosuria in type 1 DM patients.

It is beyond the scope of the present study to speculate on the molecular details of the glycosuria-induced UA-lowering effect in diabetic patients. However, speculating on its pathogenesis may be of interest. Vitart et al. reported that the glucose transporter GLUT9 plays the role of a UA transporter at the same time in renal tubular cells\(^17\). By further analyzing the role of GLUT9, Anzai et al. found that the GLUT9 transporter is voltage-driven urate transporter1 (URATv1)\(^18\). This evidence helps to explain how the lowering of serum UA levels in the presence of glycosuria may be related to glucose-UA interaction through the GLUT9 transporter. Glycosuria in diabetic patients is responsible for the observed uricosuria via the activation of GLUT9 isoform2 located on the proximal tubules. To explain the UA-lowering effect of SGLT2 inhibitors, Chino et al. suggested that the massive glucose burden inhibits URATv1-driven glucose-UA exchange in the proximal tubular cells and URATv1-driven reabsorption of UA in the collecting tubules\(^10\). In the presence of SGLT2 inhibitors, the enhanced excretion of UA in response to glucose exposure results in lowering serum UA levels. Since hyperuricemia is regarded as a risk factor for cardiovascular events such as hypertension and CKD, the decrease in serum UA levels might have contributed to the beneficial effect on diabetes associated cardiovascular complications.

Recently, the benefits of lowering the serum UA level in conjunction with improving the primary outcomes have been comprehensively supported by two SGLT2 inhibitors, empagliflozin and canagliflozin, in the EMPA-REG OUTCOME trial and the CANVAS Program\(^19,20\). The clinical implication of glycosuria-induced serum UA lowering without SGLT2 inhibitors will, however, be a subject for future study.

The present study has several limitations. First, it is an epidemiological survey in which “the Cause and Effect Scenario” is not always inferred. Second, the population distribution among subgroups, especially the groups with negative and positive UG, was very biased. Third, the amount of urinary glucose was measured qualitatively, not quantitively. Lastly, the molecular details on the UG-induced lowering of UA have never been addressed with this study design.

In conclusion, the present study provides evidence that glycosuria lowers the serum UA level, probably via the stimulation of glucose-mediated uricosuric transporters in the kidney.
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CONFLICT OF INTEREST

No conflict of interest is declared.

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