SERUM URIC ACID CONCENTRATIONS IN TYPE 2 DIABETES: ITS SIGNIFICANT RELATIONSHIP TO SERUM 1,5-ANHYDROGLUCITOL CONCENTRATIONS

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Objective. Serum uric acid concentrations in diabetics are well known to be significantly lower than those in non-diabetic subjects, due to increased its urinary clearance. Serum 1,5-anhydroglucitol concentrations are also specifically decreased in diabetics through the increased urinary excretion. To gain an insight into the idea that a common mechanism might be possible to work in reducing these serum substances, this study was conducted.

Methods. A total of 121 type 2 diabetic patients, 76 males and 45 females, were studied. Multiple regression analysis was performed to determine the independent association between potential predictor variables (mean blood pressure, body mass index, fasting plasma glucose, glycosylated hemoglobin A_{1c}, serum fructosamine, serum 1,5-anhydroglucitol, serum creatinine, serum total cholesterol, and serum triglycerides) and serum uric acid concentrations as the dependent variable.

Results. In the male subjects, serum 1,5-anhydroglucitol, serum creatinine and body mass index were the variables independently related to serum uric acid concentrations. In the female subjects, serum 1,5-anhydroglucitol and serum creatinine were the variables independently related to serum uric acid concentrations.

Conclusion. Considering the glucosuria-related urinary excretion of 1,5-anhydroglucitol, a close positive association between serum uric acid and 1,5-anhydroglucitol concentrations strongly supports the idea that the reduction in serum uric acid concentrations is mediated by urinary glucose excretion in diabetics.

Key Words: Diabetes mellitus type 2 – Uric acid – 1,5-anhydroglucitol – Glucosuria

Serum uric acid concentrations in diabetic patients have been well demonstrated to be significantly lower than those in non-diabetic subjects (HERMAN et al. 1967; YANO et al. 1977; TUOMILEHTO et al. 1988). Although this decrease in serum uric acid is due to increased renal uric acid clearance in diabetics, the underlying mechanism(s) remains unclear. Since both uric acid and glucose are filtered by the renal glomeruli and mainly reabsorbed in the renal proximal tubules, it has been postulated that the renal tubular reabsorption of uric acid is interfered by urinary glucose in type 1 diabetic patients (MAGOULA et al. 1991). However, there are few clinical data that positively support this idea (GOTFREDSEN et al. 1982; THALASSINOS et al. 1982).

Serum concentrations of 1,5-anhydroglucitol (1,5AG) have been indicated to decrease sensitively and specifically in diabetes mellitus (YAMANOUCHI et al. 1988), and to be useful as a clinical marker of glycemic control in diabetic patients (YAMANOUCHI et al. 1996). This reduction of serum 1,5AG in diabetic patients is associated with the urinary excretion of 1,5AG, which is coincident with the urinary excretion of glucose (AKANUMA et al. 1988). The competition between 1,5AG and glucose reabsorption at the renal tubules is thought to be a cause of the reduction of serum 1,5AG in dia-

betic patients (KAMETANI et al. 1987; YAMANOUCHI et al. 1990).

Both serum uric acid and 1,5AG concentrations are decreased in diabetic patients through the increase of their urinary excretion. A common mechanism might possibly participate in reducing the serum level of these substances. To gain an insight into this idea, this study was conducted. We demonstrate here that there is a significant positive relationship between serum uric acid and 1,5AG concentrations in type 2 diabetic patients.

Subjects and Methods

Subjects and sampling. We screened type 2 diabetic outpatients who regularly visit our hospital according to their medical records. The patients with overt proteinuria or concomitant diseases independent of diabetes were excluded from this study. The patients who showed overall stable glycemic control (that is, the variance of glycosylated hemoglobin A_{1c} (HbA_{1c}) level was within ±10 %) for at least last 3 consecutive months were invited to participate. During the following one month, a total of 121 type 2 diabetic patients, 76 males and 45 females, aged 39-74 years (58.4±7.7) were studied after giving an informed consent. None of the subjects were taking any medication except for the treatment of diabetes mellitus. All of the female subjects were post-menopausal.

Blood and urine samplings were performed between 8:30 and 10:30 a.m. after an overnight fast during a visit of our outpatient clinic. Urine was collected and re-confirmed negative dipstic test for albuminuria. Blood was drawn from an antecubital vein. Blood pressure (mm Hg) was measured in the sitting position with a mercury sphygmomanometer after a 5-min rest. The mean blood pressure was calculated as diastolic pressure + (systolic pressure - diastolic pressure)/3. Measurements of body weight and height were taken in the patients with light clothing and without shoes. The body mass index (BMI) was calculated as weight (kg)/height squared (m^2).

Biochemical determination. Fasting plasma glucose (FPG) concentrations were measured by a glucose oxidase method. HbA_{1c} level was assayed by high-performance liquid chromatography (Auto A_{1c}, Kyoto Daiichi Kagaku, Kyoto, Japan). Serum 1,5AG concentrations were determined by a commercial kit using the enzymatic method (Lana-AG kit, Nippon Kayaku, Tokyo, Japan). Serum fructosamine (FRA) concentrations were measured by the fructosamine test (Roche, Nutley, NJ, USA). Serum uric acid, creatinine, total cholesterol, and triglycerides concentrations were measured by enzymatic method using a Hitachi 7350 autoanalyzer (Tokyo. Japan).

Statistical evaluation. Data are reported as the mean±S.D., except for serum 1,5AG concentrations, for which median (range) is indicated. Comparison between the male and female subjects was made by unpaired Student's t-test. For this analysis serum 1,5AG concentrations were log-transformed to eliminate skewness and kurtosis of the distribution. Least-squares linear regression analyses were used to study the relationship between the variables. Variables were likely to interacting so that each variable might be influenced by others. Multiple linear regression analysis with a forward stepwise procedure was performed to determine the more important independent variable in association with serum uric acid concentrations (dependent variable). Statistical significance was set at a p value of less than 0.05. These analyses were carried out using the StatView (Abacus Concepts, Berkely, CA, USA) statistical package.

Results

Characteristics of the subjects. Table 1 summarized basal information of the subjects. Serum uric acid and creatinine concentrations were significantly lower in the female than in the male subjects, while serum total cholesterol concentrations were significantly higher in the female than in the male subjects. Thus, the male and female subjects were analyzed separately.

Correlation coefficients matrix. Linear regression analyses between two variables are shown in Table 2. There were significant relationships between some variables. In the male subjects, serum uric acid concentrations significantly correlated with BMI (r=0.265, p=0.0204), serum creatinine (r=0.392, p=0.0004), FPG (r=-0.249, p=0.0297), serum FRA (r=0.298, p=0.0087), serum 1,5AG (r=0.364, p=0.0011) and serum triglycerides (r=0.269, p=0.0183). In the female subjects, serum uric acid concentrations significantly correlated with serum creatinine (r=0.423, p=0.0048) and serum 1,5AG (r=0.431, p=0.0040). In both genders, the clinical markers of glycemic control, that is FPG, HbA_{1c}, FRA and 1,5AG, significantly correlated to each other.

Multiple regression analysis. A forward stepwise multiple regression analysis was performed to determine the independent association between potential predictor variables (mean blood pressure, BMI, serum

Table 1

Characteristics of the subjects

	male	female
Number	76	45
Age (years)	57.6±7.4	59.8±8.0
Diabetes duration (years)	8.9±8.5	9.3±5.5
Body mass index (kg/m^2)	22.9±2.5	23.0±2.6
Mean blood pressure (mmHg)	92.8±10.6	93.9±14.0
Serum creatinine (μmol/l)	81.9±10.4	66.8±11.7**
Serum uric acid (μmol/l)	297.0±62.2	251.8±55.5**
Serum total cholesterol (mmol/l)	4.92±0.90	5.65±0.96**
Serum triglycerides (mmol/l)	1.47±0.81	1.69±0.89
Fasting plasma glucose (mmol/l)	8.9±2.2	8.5±2.1
Glycosylated hemoglobin A_{1c} (%)	8.1±1.4	8.2±1.4
Serum fructosamine (μmol/l)	356.5±64.4	375.4±57.7
Serum 1,5-anhydroglucitol (μmol/l)	328.5 (24.4—1353.7)	273.7 (12.2—853.7)
Log_{10}(1,5-anhydroglucitol)	2.34±0.40	2.23±0.49

Values are the mean ± S.D., except for serum 1,5AG concentrations, for which median (range) is indicated. **, $p < 0.01$ vs. male subjects (two-tailed unpaired t-test).

creatinine, FPG, HbA_{1c}, serum FRA, serum 1,5AG, serum total cholesterol, and serum triglycerides) and serum uric acid concentrations as the dependent variable. The results are summarized in Table 3. In the male subjects, serum 1,5AG, serum creatinine and BMI were the variables independently related to serum uric acid concentrations. In the female subjects, serum 1,5AG and serum creatinine were the variables independently related to serum uric acid concentrations.

Discussion

In diabetic patients, serum uric acid concentrations are low due to its increased renal clearance. However, underlying mechanism(s) is still unclear. Some investigators have reported that the reduction of uric acid concentrations is attributed to the renal tubular abnormality in diabetes (Hisatome et al. 1992). Although these cases seem likely to be specific, it may be possible that diabetic nephropathy affects the renal handling of uric acid. In the present study, therefore, the patients with overt proteinuria were excluded.

The polyol 1,5AG is a reduced form of glucopyranose lacking a hydroxyl at the C-1 position. 1,5AG mainly originates from orally ingested food and exists in a large body pool, being little degraded and metabolised. 1,5AG is filtered out by the glomeruli and largely reabsorbed by the renal tubules. In healthy subjects, the oral intake and urinary excretion of 1,5AG are almost balanced (Yamanouchi et al. 1992). The reduction of serum (or plasma) 1,5AG in diabetic subjects is associated with accelerated urinary excretion of 1,5AG, which occurs concomitantly with the excretion of glucose (Akanuma et al. 1988; Yamanouchi et al. 1989, 1996). Because 1,5AG has a structure similar to that of glucose, its reabsorption is thought to be competitively interfered with glucose in the renal tubles (Yamanouchi et al. 1990). When the blood glucose concentrations exceed the renal threshold for glucose, the reabsorption of 1,5AG is reduced resulting in the decrease of serum 1,5AG concentrations (Kametani et al. 1987).

In the male diabetic subjects of this study, although the clinical markers of glycemic control correlated to each other, linear regression analyses revealed serum uric acid concentrations were associated with FPG, serum FRA, and serum 1,5AG concentrations, but not with HbA_{1c} level. HbA_{1c} level gives an estimation of the average glucose level during the 6 to 8 weeks preceding the test, and does not reflect the current glycemic status. This could be the reason why serum uric acid concentrations had no correlation with HbA_{1c} level. Our finding that there was a negative relationship between serum uric acid and FRA concentrations is comparable to the observation of Golik et al. (1993) in 18 type 2 diabetic patients with elevated glomerular filtration rates. In the female diabetic subjects, serum

Table 2

Correlation coefficients matrix showing relationships between mean blood pressure (MBP), body mass index (BMI), serum uric acid (UA), serum creatinine (Cr), fasting plasma glucose (FPG), glycosylated hemoglobin A_{1c} (HbA_{1c}), serum fructosamine (FRA), serum 1,5-anhydroglucitol (1,5AG), serum total cholesterol (Tcho), and serum triglycerides (TG) in the (a) male and (b) female diabetic subjects.

(a) male

	MBP (mmHg)	BMI (kg/m²)	UA (μmol/l)	Cr (μmol/l)	FPG (mmol/l)	HbA_{1c} (%)	FRA (μmol/l)	1,5AG (μmol/l)	Tcho (mmol/l)
BMI (kg/m²)	0.290*								
UA (μmol/l)	0.217	0.265*							
Cr (μmol/l)	-0.017	0.152	0.392**						
FPG (mmol/l)	-0.152	-0.027	-0.249*	-0.188					
HbA_{1c} (%)	-0.088	-0.154	-0.215	-0.119	0.522**				
FRA (μmol/l)	-0.020	-0.225	-0.298**	-0.103	0.416**	0.745**			
1,5AG (μmol/l)	0.045	-0.101	0.364**	0.156	-0.385**	-0.574**	-0.533**		
Tcho (mmol/l)	0.178	0.158	-0.056	-0.023	-0.031	-0.064	-0.153	0.090	
TG (mmol/l)	0.082	0.420**	0.269*	0.226*	-0.090	-0.199	-0.319**	0.100	0.050

(b) female

	MBP (mmHg)	BMI (kg/m²)	UA (μmol/l)	Cr (μmol/l)	FPG (mmol/l)	HbA_{1c} (%)	FRA (μmol/l)	1,5AG (μmol/l)	Tcho (mmol/l)
BMI (kg/m²)	0.362*								
UA (μmol/l)	0.045	-0.057							
Cr (μmol/l)	-0.227	-0.098	0.449**						
FPG (mmol/l)	-0.236	-0.355*	-0.192	-0.157					
HbA_{1c} (%)	-0.268	-0.187	-0.220	-0.075	0.679**				
FRA (μmol/l)	-0.148	-0.025	-0.091	-0.095	0.625**	0.768**			
1,5AG (μmol/l)	-0.199	-0.186	0.445**	0.219	-0.523**	-0.645**	-0.640**		
Tcho (mmol/l)	0.102	0.118	0.072	-0.065	-0.180	-0.093	-0.216	0.199	
TG (mmol/l)	0.033	0.202	0.139	0.106	-0.152	-0.144	-0.117	0.221	0.436**

*, $p<0.05$. **, $p<0.01$.

uric acid concentrations were not associated with FPG or serum FRA concentrations. This could be due to an insufficient number of the female subjects.

Among the clinical markers of glycemic control, multiple regression analysis indicated that serum 1,5AG concentrations, but not FPG and serum FRA, were independently associated with serum uric acid concentrations in the both genders. Serum 1,5AG concentrations fall immediately after urinary excretion of glucose. The correlation between this reduction and the amount of urinary glucose is very high (YAMANOUCHI et al. 1989). Therefore, we suppose the close association between serum 1,5AG and uric acid concentrations in the diabetic subjects could be explained by the mediation of urinary glucose excretion.

Experimental studies have demonstrated the effect of glucose on renal uric acid excretion in non-diabetic subjects. BONSNES and DANA (1946) reported an increase in renal uric acid excretion with the intravenous infusion of hypertonic glucose, and suggested that the tubular reabsorption of the uric acid was competitively interfered with glucose only when the tubules were saturated with glucose. HERMAN and KEYNAN (1969) examined the effect of glucose or saline infusion on the uric acid clearance in seven volunteers. Six of seven subjects showed higher uric acid clearance during the glucose infusion than during the saline infusion. These six cases with increased uric acid clearance also showed glucosuria. In that one exceptional case, glucosuria did not occur and uric acid clearance did not increase. Similar uricosuric effect of glucose was also reported by BONER and RIESELBACH (1974). In addition, they examined the subjects with renal glucosuria, and found that uricosuric response to glucose was related to the urinary glucose concentra-

Table 3

Multiple regression analysis of the association between serum uric acid concentrations (as the dependent variable) and potential predictor variables (mean blood pressure, body mass index, serum creatinine, fasting plasma glucose, glycosylated hemoglobin A_{1c}, serum fructosamine, serum 1,5-anhydroglucitol, serum total cholesterol, and serum triglycerides) with a forward stepwise procedure.

(a) male

variable	regression coefficeient	standard error of regression coefficeient	p
Serum 1,5-anhydroglucitol (μmol/l)	0.068	0.020	0.00098
Serum creatinine (μmol/l)	1.782	0.599	0.00398
Body mass index (kg/m^2)	6.202	2.437	0.01307

F=10.769, R-square=0.310

(b) female

variable	regression coefficeient	standard error of regression coefficeient	p
Serum creatinine (μmol/l)	1.751	0.615	0.00680
Serum 1,5-anhydroglucitol (μmol/l)	0.086	0.031	0.00749

F=10.241, R-square=0.328

tions rather than those of plasma. It is possible that the hypertonic glucose might produce an osmotic diuresis that could affect renal uric acid excretion. However, SKEITH et al. (1967) reported that the uric acid clearance per unit osmolar load increased three times more during intravenous glucose infusion than during mannitol infusion, and concluded that the effect of glucose resulted from the factors other than the osmotic diuresis it produces. Also in diabetic patients, uricosuric effect of glucose was reported by PADOVA et al. (1964) who found that uric acid clearance was increased in 5 diabetic subjects following administration of oral glucose load. Although ERDBERG et al. (1992) found no correlation between urinary uric acid excretion and the degree of glucosuria in type 1 diabetic patients, THALASSINOS et al. (1982) and GOTFREDSEN et al. (1982) demonstrated a significant relationship between these two variables in diabetic patients. These findings suggest the mediating effect of urinary glucose excretion in the reduction of serum uric acid.

It has been demonstrated that extracellular fluid expansion causes an increase in uric acid clearance without an increase in urine volume, and such a mechanism is responsible for hypouricaemia in the syndrome of inappropriate secretion of antidiuretic hormone (SHICHIRI et al. 1985) and liver cirrhosis (DECAUX et al. 1982). ISHIHARA et al. (1988) reported that serum uric acid concentrations in type 2 diabetic patients were significantly lower than those in control subjects. Since the degree of glucosuria did not correlate with serum uric acid concentrations, they interpreted their data as the result of elevated extracellular fluid volume. However, it could not be plausible that extracellular fluid expansion caused the decrease in serum 1,5AG concentrations in diabetic subjects. Thus, the close association between serum uric acid and 1,5AG concentrations in the diabetic subjects of this study could not be explained by an extracellular fluid expansion.

In the present study, serum creatinine concentrations were independently associated with serum uric acid concentrations in the male and female diabetic subjects. This finding is compatible with that of ISHIHARA et al. (1988) who showed a similar relationship between serum creatinine and uric acid concentrations in non-nephrotic type 2 diabetic patients. At the same time, they found no correlation between serum urea nitrogen and uric acid concentrations. Thus, it is likely that this association is independent on the renal function. Creatinine, the metabolic product of skeletal muscle creatine, is produced in an amount directly proportional to skeletal muscle mass. On the other hand, uric acid is the final breakdown product of purine degradation. Although purine nucleotides are degraded in all tissues, skeletal muscle constitutes a large part of body tissues. This seems likely to be the reason for the relationship between serum creatinine and uric acid concentrations. Also, the same reason appears

likely to be responsible for the association between serum uric acid concentrations and BMI in the male diabetic subjects. The absence of this association in the female diabetic subjects might be due to an insufficient number of the subjects or gender difference in the constitution of BMI. These considerations argue with the findings reported by TUOMILEHTO et al. (1988) who found that plasma uric acid concentrations were significantly correlated with plasma creatinine concentrations and BMI in non-diabetic population of Fiji.

In summary, the present study is the first to indicate the close association between serum uric acid and 1,5AG concentrations in diabetic subjects. Considering the glucosuria-related decrease of serum 1,5AG concentrations in diabetic patients, our finding strongly supports the idea that the decrease in serum uric acid concentrations is mediated by urinary glucose excretion in diabetic patients.

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