Original Article
Uric acid levels are inversely correlated with endothelial function in type 2 diabetic patients

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Abstract: Introduction: Assessment of endothelial function in type 2 diabetic patients may be important in terms of reducing cardiovascular mortality. In this study, the relationship between hyperuricemia and endothelial dysfunction was investigated in type 2 diabetic patients. Method: The study consisted of type 2 diabetic patients with serum uric acid level greater or equal to 5.5 mg/dl as the experimental group and type 2 diabetic patients with serum uric acid level less than 5.5 mg/dl as the control group. Malondialdehyde (MDA) level as a marker of oxidative stress and superoxide dismutase (SOD), glutathione peroxidase (GPO), and catalase levels as markers of antioxidant system were analyzed. Endothelial function was assessed by measurement of flow-mediated dilatation (FMD) in forearm. Results: Demographic characteristics were similar in both groups. No significant difference was seen between the two groups in terms of MDA, SDO, GPO, or catalase levels. The study group's FMD was found to be significantly decreased compared to the control group (7 ± 4.5% versus 9.8 ± 5.1%, P = 0.02). Uric acid levels, body mass index, systolic blood pressure, diastolic blood pressure and microalbuminuria were negatively correlated with FMD in the one-way analysis. However, in the multivariate analysis, only uric acid was found to be negatively correlated with FMD significantly (OR 0.37, 95% CI 0.17 to 0.77, P = 0.008). Conclusion: Hyperuricemia in type 2 diabetic patients contributes to endothelial dysfunction by reducing FMD. This effect of uric acid cannot be explained by oxidative stress according to this study. Serum uric acid may be a new target for prevention of complications.

Keywords: Endothelial dysfunction, hyperuricemia, type 2 diabetes mellitus, uric acid, oxidative stress

Introduction

Endothelial dysfunction is associated with many diseases, such as hypertension, coronary artery disease, congestive heart failure, chronic renal failure, diabetes mellitus (DM), and obesity [1]. The first step in the development of cardiovascular disease in diabetic patients is thought to be endothelial dysfunction [2]. The pathophysiology of endothelial dysfunction is very complex and may occur through a variety of mechanisms. Perhaps the most important of these mechanisms is the reduction of nitric oxide (NO) release from endothelial cells [3].

Various studies have shown associations between hyperuricemia, cardiovascular disease, and death [4, 5]. Increases in serum uric acid levels in patients with type 2 diabetes are also commonly seen [6]. In vitro and in vivo studies have shown that high levels of uric acid contributes endothelial function disrupting NO mechanisms [5]. Free radicals and antioxidants are in equilibrium in normal, healthy people. This balance is disturbed in favor of free radicals in diabetic patients [7]. In addition, a correlation between serum uric acid levels and oxidative stress has been reported [8]. Oxidative stress or decreased NO production has been suggested to reduce endothelium-dependent vasodilation in diabetes; however, this idea is still controversial [9, 10].

Increased uric acid in diseases associated with oxidative stress may be the primary reason or protective response in the body [16]. Thus, this study examined the relationship between increased serum uric acid levels and endotheli-

al dysfunction in type 2 diabetic patients. A clear relationship would allow for uric acid levels to be used as a marker of cardiovascular damage in follow-up appointments for type 2 diabetic patients and uric acid could be a new target for treatment.

Materials and methods

Our study was approved by the Faculty of Medicine Ethics Committee of Suleyman Demirel University and all participants were informed about the study.

Study design and groups

This study was a cross-sectional. The cut-off level for uric acid was based on previous observational studies and accepted as 5.5 mg/dl [12, 13]. Type 2 diabetic patients admitted to Internal Medicine Department of Suleyman Demirel University were considered for this the study. Criteria for inclusion in the study group were type 2 DM diagnosis and a serum uric acid level greater than or equal to 5.5 mg/dl. Exclusion criteria for the study were serum creatinine more than 1.5 mg/dl; hyperuricemia due to tumor lysis syndrome; history of coronary artery disease, acute myocardial infarction, or cerebrovascular disease; peripheral vascular disease; or the use of diuretics.

The study group consisted of 40 patients with type 2 diabetes and a uric acid level greater than or equal to 5.5 mg/dl and the control group consisted of 40 patients with type 2 diabetes and uric acid level less than 5.5 mg/dl. All characteristics (e.g., age, sex, duration of diabetes, body mass index (BMI), and history of hypertension) of patients in the control group were similar to those in the study group except for uric acid levels.

After taking the medical history and doing a physical examination, the age, duration of diabetes, type of treatment administered, and concomitant diseases of each patient were noted. Blood pressure was measured after a 10-minute rest. Weight and height were measured and the BMI was calculated according to weight (kg)/height^2 (m^2).

Collection and study of blood and urine samples

Serum uric acid, fasting blood glucose (FBG), hemoglobin Alc (HbA1c), lipids, blood urea nitrogen (BUN), creatinine, and morning spot urine creatinine levels of patients were analyzed through enzymatic methods with a Roche-Hitachi P800 autoanalyzer on the day of patient admission. Spot urine microalbumin level was analyzed with a BIO-DPC kit in the Immulite 2000 device on the same day. From the microalbumin and creatinine in the spot urine analyses, the albumin/creatinine ratio (ACR) was calculated (µg/mg). An ACR of less than 30 was considered normoalbuminuria, ACR of 30-299 as microalbuminuria, and ACR greater than or equal to 300 as macroalbuminuria (14). Creatinine clearance was calculated according to the Cockcroft-Gault formula: creatinine clearance (ml/min) = (140 - age) × (ideal weight)/ serum creatinine (mg/dl) × 72.

Blood samples were collected into tubes containing ethylenediamine tetraacetic acid (EDTA) and hemolysate and plasma were prepared for analysis of superoxide dismutase (SOD), catalase, glutathione peroxidase (GPO), and malondialdehyde (MDA). The prepared samples were stored at -80 °C and examined collectively. SOD, GPO, and catalase were examined in hemolysate and MDA level was examined in plasma. SOD was spectrophotometrically analyzed with an SOD assay kit (Catalog Number: 706002, Cayman Chemical Company, Michigan, USA). GPO was spectrophotometrically analyzed with a GPO assay kit (Catalog Number: 703102, Cayman Chemical Company, Michigan, USA). Catalase was spectrophotometrically analyzed with an catalase assay kit (Catalog Number: 707002, Cayman Chemical Company, Michigan, USA) according to the Aebi method (14). MDA was analyzed by high performance liquid chromatography (HPLC) with a serum MDA HPLC kit (Catalog Number: 67000, Chromsystems Instruments and Chemicals GmbH, Munich, Germany).

A non-invasive forearm test was used to assess endothelial function. In this test, an Shimadzu SDU 2200 machine (Shimadzu Corporation, Kyoto, Japan) was used to get an ultrasonic image of the FMD. A physiological unit was mounted in this device for internal electrocardiography (ECG) monitoring. Patients were asked to fast for at least 8-12 hours before the procedure, doing no exercise and using no caffeine, cigarettes, or vitamin C for at least 4-6 hours prior to the test.

Table 1. Demographic characteristics and biochemical parameters of study and control groups

	Study group (n = 40)	Control group (n = 40)	P
Uric acid (mg/dL)	6.7 ± 0.8	4.3 ± 0.7	< 0.0001
Gender (male/female)	24/16	23/17	NS
Age (years)	54.7 ± 8.5	52.9 ± 5.8	NS
Duration of diabetes (years)	5.3 ± 5.0	5.4 ± 4.8	NS
BMI (kg/m^2)	32 ± 4.3	30.9 ± 3.6	NS
Systolic BP (mmHg)	150.4 ± 23.5	140.5 ± 16.1	NS
Diastolic BP (mmHg)	91.4 ± 12.0	86.9 ± 10.4	NS
FBG (mg/dL)	169 ± 57.2	162.8 ± 47.7	NS
HbA1c (%)	7.5 ± 1.7	7.3 ± 1.3	NS
Total cholesterol (mg/dL)	201 ± 32.2	198.3 ± 41.7	NS
HDL-C (mg/dL)	54.4 ± 13.03	50.7 ± 10.5	NS
LDL-C (mg/dL)	116.5 ± 31.8	120.1 ± 35.2	NS
Triglycerides (mg/dL)	209.5 ± 100.1	165.2 ± 65.9	NS
BUN (mg/dL)	19.3 ± 6.0	17.8 ± 4.0	NS
Creatinine (mg/dL)	1.0 ± 0.1	0.9 ± 0.1	NS
Creatinine clearance (ml/min)	101.1 ± 31.1	101.8 ± 21.0	NS
Spot urine ACR (µg/mL)	105.3 ± 118.8	29.8 ± 27.6	< 0.0001

BMI, body mass index; BP, blood pressure; FBG, fasting blood glucose; HBA1c, glycosylated hemoglobin; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; BUN, blood urea nitrogen; ACR, albumin-creatinine ratio; NS, not significant.

Table 2. Ultrasonographic measurements of brachial artery in groups

	Study group	Control group	P
Basal brachial artery diameter (mm)	4.7 ± 0.6	4.6 ± 0.5	NS
Flow-mediated dilatation (%)	7.0 ± 4.5	9.8 ± 5.1	0.011
Dilatation with nitrate (%)	13.6 ± 5.3	15.5 ± 5.2	NS

NS, not significant.

For the test, the patients were asked to rest in the supine position in a 24°C room. After 10 minutes, blood pressure was measured in the right arm and patient was connected to an ECG monitoring device. Pulses of the brachial artery were palpated in the region of 2-5 cm proximal to the antecubital fossa, the brachial artery was visualized longitudinally by B-mode superficial probe, and the flow was observed with Doppler. Artery diameter was measured at the R-wave with concurrent ECG monitoring. This measurement was recorded as the basal artery diameter.

A sphygmomanometer cuff was then attached to the patient's wrist for a second measurement, inflated until the systolic blood pressure was greater than 50 mmHg, and kept 5 minutes at the same pressure. The patient's hand was observed for bruising, tingling, or reactive hyperemia. Then the cuff pressure was released.

From 45 to 60 seconds after releasing cuff pressure, artery diameter measurement was repeated as described above. The patient was then allowed to rest for 15 minutes. The basal artery diameter was measured again after the rest, and then the patients were given 5 mg sublingual nitrate. Measurements were repeated 3 minutes after sublingual nitrate [15].

FMD was determined from the measured artery diameters. The equation was calculated as FMD = % (basal diameter after hyperemic flow-basal diameter)/basal diameter. Endothelial dysfunction was defined as an FMD less than or equal to 4.90% [16].

Statistical analysis

Student's t-test was used to compare continuous variables between the two groups and the chi-square test was used to compare categorical variables. All the variables (age, sex, duration of diabetes, height, weight, BMI, systolic and diastolic blood pressure, uric acid, FBG, HbA1c, BUN, creatinine, triglyceride, total cholesterol, urine creatinine, urine microalbumin level, ACR, and creatinine clearance) were analyzed with one-way analysis (univariate) in terms of associations with FMD. Multivariate logistic regression analysis was performed to identify the possible factors associated with endothelial dysfunction. Data were evaluated as mean ± SD. P less than 0.05 was considered statistically significant. All analyzes were performed with SPSS 15.0 for Windows.

Results

Demographic characteristics and biochemical parameters of the study and control groups are presented in **Table 1**. No significant difference
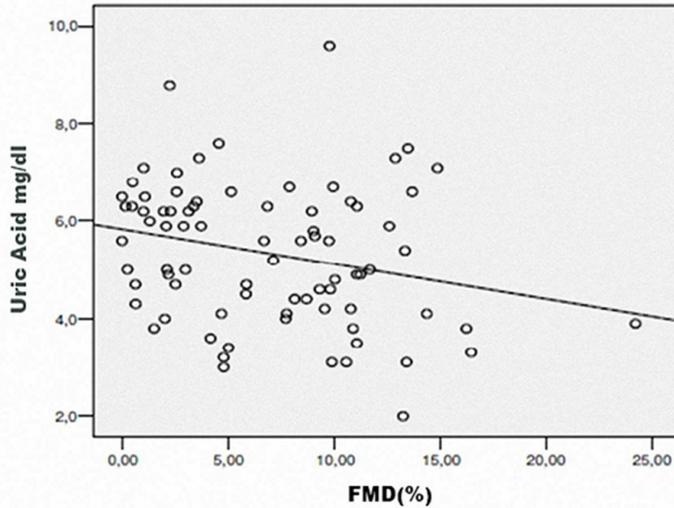
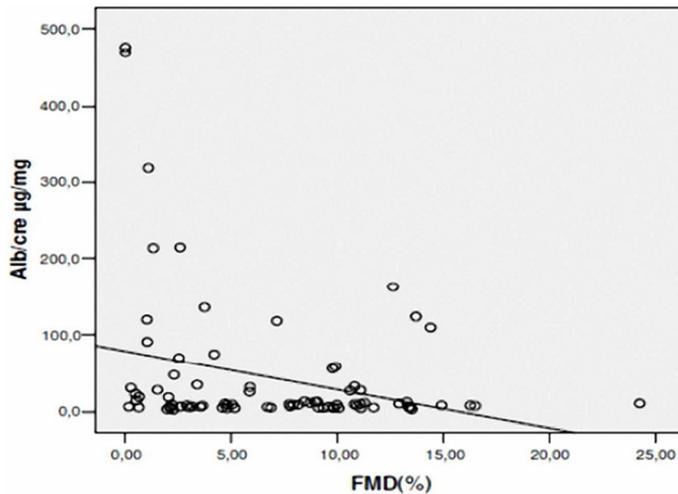**Figure 1.** Relationship between FMD-uric acid [r = -0.253, P = 0.028].

Figure 2. Relationship between FMD-microalbuminuria [r = -0.271, P = 0.015].

was seen between the study group and control group in terms of gender, age, BMI, duration of diabetes, systolic blood pressure, diastolic blood pressure, FBG levels, HbA1c, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides, BUN, creatinine, or creatinine clearance (P > 0.05). Uric acid levels were 6.7 ± 0.8 mg/dl in the study group and 4.3 ± 0.7 mg/dl in the control group (P < 0.0001). Spot urine ACR was 105.3 ± 118.8 in the study group and 29.8 ± 27.6 in the control group (P < 0.0001). No difference was seen between the groups in terms of using drugs such as oral antidiabetic drugs, insulin, statins, acetylsali-

cylic acid, ACE inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, or other antihypertensive drugs (P > 0.05). As an oxidative marker, MDA levels were similar between the control and study groups and did not differ statistically (P > 0.05). For the antioxidant system, no significant difference between the study and control groups was seen in terms of SDO, GPO, or catalase levels (P > 0.05).

In the ultrasonographic measurements to assess endothelial function, no significant difference between the two groups was found in terms of basal diameter of the brachial artery or arterial dilatation with nitrates (P > 0.05). The calculated average FMD was 7 ± 4.5% in the study group and 9.8 ± 5.1% in the control group and this difference was statistically significant (P = 0.011) (**Table 2**).

Associations of FMD with all the variables were investigated in a one-way analysis. Uric acid, BMI, systolic blood pressure, diastolic blood pressure, and ACR were found to be negatively associated with FMD (P < 0.05) (**Figures 1-3**). Multiple logistic regression analysis revealed that serum uric acid level was significantly associated with endothelial dysfunction after adjustment for other risk factors, including age, FBG, HDL-C, LDL-C, systolic blood pressure, diastolic blood pressure, BMI, and creatinine clearance (OR 0.37; 95% CI 0.17 to 0.77; P = 0.008) (**Table 3**).

Discussion

In our study, FMD was found to be significantly decreased in the group with hyperuricemia, and uric acid was found to be an independent predictor of FMD (P = 0.011). This result suggests that an increase in uric acid in type 2 diabetic patients may be an independent risk factor for endothelial dysfunction. In addition, no significant difference in terms of MDA levels as a marker of oxidative stress was seen between the hyperuricemic and normouricemic groups,
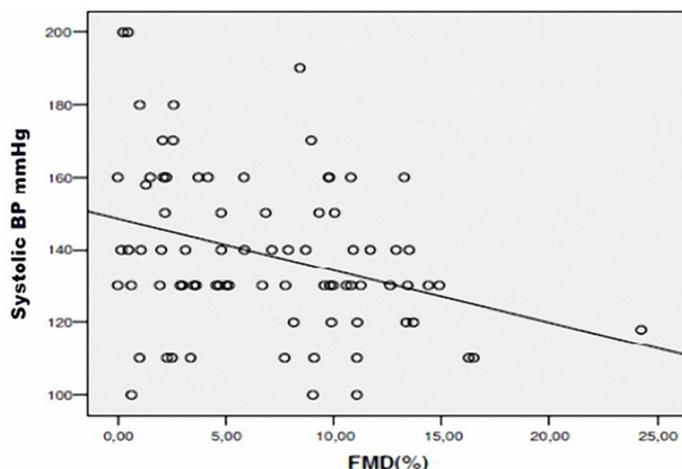
Figure 3. Relationship between FMD-systolic blood pressure [r = -0.303, P = 0.035].

Table 3. Multivariate analysis of the relation between endothelial dysfunction and variables

Variables	OR (% 95 CI)	P
Uric acid (mg/dL)	0.369 (0.17-0.77)	0.008
Age (years)	0.948 (0.88-1.02)	0.16
ACR (µg/mL)	0.99 (0.98-1.00)	0.24
Systolic BP (mmHg)	0.99 (0.94-1.04)	0.79
Diastolic BP (mmHg)	1.05 (0.99-1.11)	0.06
BMI (kg/m^2)	0.99 (0.84-1.17)	0.95
LDL-C (mg/dL)	1.00 (0.98-1.02)	0.80
HDL-C (mg/dL)	0.98 (0.94-1.03)	0.43
Creatinine clearance (ml/min)	1.01 (0.99-1.04)	0.13
FBG (mg/dL)	1.00 (0.99-1.01)	0.60

ACR, albumin-creatinine ratio; BP, blood pressure; BMI, body mass index; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; e-GFR, estimated-glomerular filtration rate; FBG, fasting blood glucose; NS, not significant.

and SOD, GPO, and catalase levels as a marker of antioxidant system were similar in both groups. This result suggests that the relationship between uric acid and endothelial dysfunction cannot be explained as just an imbalance between free radicals and antioxidants. Increased uric acid may cause endothelial dysfunction with a different mechanism independent of prooxidative or antioxidant effects. Another important finding from our study is that microalbuminuria is higher in type 2 diabetic patients with hyperuricemia than those without hyperuricemia. This result supports the association of increased uric acid level with microalbuminuria. In addition, we demonstrated that

ACR was inversely associated with FMD in our study. This result indicates a significant relationship between microalbuminuria and endothelial dysfunction (P = 0.015).

In Feig et al.'s study, 89% of pediatric patients with primary hypertension uric acid level was found to be over 5.5 mg/dl. Their study suggested that the increase of uric acid plays a significant role in the pathogenesis of primary hypertension [12]. A National Health and Nutrition Examination Survey study conducted over healthy adolescents in the United States between 1996 and 2006 revealed a significant relation between serum uric acid levels and blood pressure [13]. However, we could not find such a relation between serum uric and levels and systolic and diastolic blood pressures in our study.

Increased uric acid concentration has been shown to have an association with metabolic syndrome symptoms, such as hypertension [16, 17], obesity, insulin resistance [13] and dyslipidemia [19]. Association of high serum uric acid levels with metabolic syndrome has been reported in previous studies. Sui X and his colleagues followed 8429 male and 1260 female patients between the years of 1977 and 2003 and reported that serum uric acid levels greater than or equal to 6.5 mg/dl in males and greater than or equal to 4.6 mg/dl in females increased the risk of metabolic syndrome 1.6- and 2-fold, respectively [20]. In addition, Nakagawa T reported in his study that decreasing the levels of uric acid in fructose-fed rats corrects the components of metabolic syndrome, such as lowering blood pressure, serum triglycerides, insulin levels, and preventing weight gain [21]. In our study, the study and control groups did not differ in terms of blood pressure, BMI, or lipid parameters. This result cannot be interpreted as the absence of any association of variables with hyperuricemia, because the control group in our study was selected from individuals as similar to patients

in the study group as possible to assess the net effect of uric acid in type 2 diabetic patients on the endothelium.

A clear mechanism has not been revealed for the pathogenesis of endothelial dysfunction caused by uric acid. Oxidative stress is known to be important in the pathogenesis of endothelial dysfunction [3, 18]. Uric acid was thought to increase as a compensatory mechanism to increased oxidative stress because uric acid, along with vitamin C, was considered a major antioxidant in plasma [18]. In vitro and in vivo studies showed that high levels of uric acid contributes to endothelial dysfunction by disrupting NO extraction [5]. On the other hand, uric acid has antioxidant activity in vitro [22].

In our study, no significant difference was seen in terms of MDA levels as a marker of oxidative stress between the hyperuricemic group and normouricemic group. SOD, GPO, and catalase levels as a marker of antioxidant system were also similar in both groups. Therefore, the relationship between uric acid and endothelial dysfunction cannot be explained as just an imbalance between free radicals and antioxidants.

In many studies, associations of hyperuricemia with coronary heart disease, cardiovascular disease, and death have been reported [23]. An increase in the level of uric acid was known to be associated with hypertension, insulin resistance, diabetes, obesity, and metabolic syndrome [18]. However, the strength of this relationship and its pathogenesis could not be explained. Was the increase of uric acid in these diseases a factor, compensatory increase, or coincidental situation? Uric acid could not be proven as an independent cardiovascular risk factor [24].

In a study by Matheus ASM and his colleagues, type 1 diabetic patients and healthy individuals were compared and uric acid levels were found higher in the diabetic patients. In addition, microvascular vasodilator response to acetylcholine was significantly lower in type 1 diabetic patients than in the healthy individuals [25]. Erdogan D et al. demonstrated that an increase in serum uric acid levels in healthy adults is directly proportional to the intima-media thickness of the carotid artery and inversely related to endothelial-mediated vasodilatation in the brachial arteries [19]. In a study by Masahiko K et al., increased serum uric acid levels were reported to have an association with endothelial dysfunction in individuals without any cardiovascular disease [22]. In addition, Maruhashi T et al. demonstrated that uric acid was a significant independent risk factor for endothelial dysfunction in postmenopausal women [16]. However, in a study by Waring and his colleagues, a high-dose infusion of uric acid did not impair endothelium-dependent dilatation in healthy individuals [26]. The same researchers showed that intravenous administration of uric acid in type 1 diabetic patients and smokers improved endothelial function, and this situation was attributed to antioxidant effect of uric acid [24].

Allopurinol treatment to decrease uric acid levels in patients with hyperuricemia and congestive heart failure was shown to improve FMD [27]. However, this situation was attributed more to reduced hydrogen peroxide production and decreased oxidative stress through the inhibition of xanthine oxidase than to allopurinol decreasing uric acid levels [24]. Hyperuricemia in patients at high risk for cardiovascular disease is associated with endothelial dysfunction and endothelial function was reported to be improved by infusion of allopurinol [28]. Bayram et al. reported that decreasing uric acid levels with allopurinol treatment seemed to have beneficial effects on endothelial functions in moderate chronic kidney disease patients [29]. Finally, in a study by Melendez- Ramirez G et al., allopurinol improved FMD in hyperuricemic patients without any other risk factors [30]. In our study, FMD significantly decreased in the hyperuricemic group. This result suggests the increase in uric acid in type 2 diabetic patients may be an independent risk factor for endothelial dysfunction.

In the one-way analysis, microalbuminuria was seen to have an association with endothelial dysfunction. Microalbuminuria is a risk factor for renal insufficiency, as well as cardiovascular disease [31]. In addition, endothelial dysfunction in type 1 and type 2 diabetics has been associated with microalbuminuria [32]. Microalbuminuria is known to be an important risk factor for cardiovascular disorders in hypertensive and healthy populations. Microalbuminuria was also shown to have an association with endothelial dysfunction in both diabetics and healthy adults in a study by Hoorn [33].

Endothelial dysfunction is thought to be a precursor of progression to microalbuminuria;

however, the mechanism of pathogenesis is not clearly understood [34]. Hyperuricemia produced by administering oxalic acid in rats whose kidneys were partly removed was reported to increase proteinuria significantly, and proteinuria was preserved in rats given allopurinol to prevent hyperuricemia. Hyperuricemic rats developed severe periglomerular vasculopathy and glomerulosclerosis, and these changes were attributed to the effects of hyperuricemia, such as the increased proliferation of vascular smooth muscle cells and the chemotactic effect on macrophages [28]. A strong association was also found between serum uric acid levels and microalbuminuria in patients with prehypertension [35]. A study of 343 Taiwanese patients with type 2 diabetes showed that serum uric acid level and microalbuminuria has an association [36]. In our study, increased microalbuminuria and impaired endothelial function was detected in type 2 diabetic patients with high uric acid levels. These results may suggest uric acid increases microalbuminuria by disrupting glomerular endothelial function, as in the mentioned rat experiments, but this is not sufficient to prove the pathogenetic mechanism.

Many studies in the literature have reported impaired endothelial functions in hypertensive individuals [16, 17, 37]. In a study by Sundström J et al., serum uric acid levels were reported to have an positively associated with changes in systolic and diastolic blood pressure in 3329 Framingham Study participants [38]. Similarly, impaired endothelial function in hypertensive individuals was found in our study.

The study and control groups in this paper were similar in terms of endothelial dysfunction risk factors other than uric acid. The analysis of oxidative stress and antioxidant markers showed that the relationship between uric acid and endothelial dysfunction is independent of oxidative stress or antioxidant effect. However, our study lacked a healthy control group and patients with microalbuminuria were not excluded. Thus, the effect of uric acid on endothelial function could not be assessed independently of microalbuminuria.

In conclusion, hyperuricemia in patients with type 2 diabetes was associated with endothelial dysfunction in our study. This relationship cannot be explained as simply an imbalance between free radicals and antioxidants. With further study, uric acid may become a new therapeutic target in the prevention of vascular complications. We suggest that follow-up appointments to check uric acid levels and FMD measurements will be useful in the early detection of cardiovascular disease in diabetic patients.

Disclosure of conflict of interest

None.

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References

[1] Hartge M, Pharm B, Kintscher U, Unger T. Endothelial dysfunction and its role in diabetic vascular disease. Endocrinol Metab Clin North Am 2006; 35: 551-560.

[2] Schalkwijk CG, Stehouwer CD. Vascular complications in diabetes mellitus: the role of endothelial dysfunction. Clin Sci (Lond) 2005; 109: 143-159.

[3] Endemenn DH, Schriffrin EL. Endothelial dysfunction. J Am Soc Nephrol 2004; 15: 1983-1992.

[4] Freedman DS, Williamson DF, Gunter EW, Byers T. Relation of uric acid to mortality and ischemic heart disease. The NHANES 1 epidemiologic Follow-up study. Am J Epidemiol 1995; 141: 637-644.

[5] Zoppini G, Targher G, Negri C, Stoico V, Perrone F, Muggeo M, Bonora E. Elevated serum uric acid concentrations independently predict cardiovascular mortality in type 2 diabetic patients. Diabetes Care 2009; 32: 1716-1720.

[6] Saggiani F, Pilati S, Targher G, Branzi P, Muggeo M, Bonora E. Serum uric acid related factors in 500 hospitalized subjects. Metabolism 1996; 45: 1557-1561.

[7] Memisogullari R, Taysi S, Bakan E, Capoglu I. Antioxidant Status and Lipid Peroxidation in Type II Diabetes Mellitus. Cell Biochem Func 2003; 21: 291-296.

[8]   Madero M, Sarnak MJ, Wang X, Greene T, Beck GJ, Kusek JW, Collins AJ, Levey AS, Menon V. Uric acid and longterm outcomes in CKD. Am J Kidney Dis 2009; 53: 796-803.

[9]   Praticò D. Antioxidants and endothelium protection. Atherosclerosis 2005; 181: 215-224.

[10]   Ostenson CG. The pathophysiology of type 2 diabetes mellitus: an overview. Acta Physiologica Scandinavica 2001; 171: 241-247.

[11]   Koenig W, Meisinger C. Uric acid, type 2 diabetes, and cardiovascular diseases: fueling the common soil hypothesis? Clin Chem 2008; 54: 231-233.

[12]   Feig DI, Johnson RJ. Hyperuricemia in childhood primary hypertension. Hypertension 2003; 42: 247-252.

[13]   Loeffler LF, Navas-Acien A, Brady TM, Miller ER 3rd, Fadrowski JJ. Uric acid level and elevated blood pressure in US adolescents: National Health and Nutrition Examination Survey, 1999-2006. Hypertension 2012; 59: 811-817.

[14]   Aebi H. Catalase in vitro. Methods Enzymol 1984; 105: 121-126.

[15]   Corretti MC, Anderson TJ, Benjamin EJ, Celermajer D, Charbonneau F, Creager MA, Deanfield J, Drexler H, Gerhard-Herman M, Herrington D, Vallance P, Vita J, Vogel R. International Brachial Artery Reactivity Task Force. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. J Am Coll Cardiol 2002; 39: 257-265.

[16]   Maruhashi T, Nakashima A, Soga J, Fujimura N, Idei N, Mikami S, Iwamoto Y, Kajikawa M, Matsumoto T, Hidaka T, Kihara Y, Chayama K, Goto C, Noma K, Tomiyama H, Takase B, Yamashina A, Higashi Y. Hyperuricemia is independently associated with endothelial dysfunction in postmenopausal women but not in premenopausal women. BMJ Open 2013; 3: e003659.

[17]   Johnson RJ, Segal MS, Srinivas T, Ejaz A, Mu W, Roncal C, Sánchez-Lozada LG, Gersch M, Rodriguez-Iturbe B, Kang DH, Acosta JH. Essential hypertension, progressive renal disease, and uric acid: a pathogenetic link? J Am Soc Nephrol 2005; 16: 1909-1919.

[18]   Yoo TW, Sung KC, Shin HS, Kim BJ, Kim BS, Kang JH, Lee MH, Park JR, Kim H, Rhee EJ, Lee WY, Kim SW, Ryu SH, Keum DG. Relationship between serum uric acid concentration and insulin resistance and metabolic syndrome. Circ J 2005; 69: 928-933.

[19]   Erdogan D, Gullu H, Calıskan M, Yildirim E, Bilgi M, Ulus T, Sezgin N, Muderrisoglu H. Relationship of serum uric acid to measures of endothelial function and atherosclerosis in heal-

thy adults. Int J Clin Pract 2005; 59: 1276-1282.

[20]   Sui X, Church TS, Meriwether RA, Lobelo F, Blair SN. Uric acid and the development of metabolik syndrome in woman and men. Metabolism 2008; 57: 845-852.

[21]   Nakagawa T, Hu H, Zharikov S, Tuttle KR, Short RA, Glushakova O, Ouyang X, Feig DI, Block ER, Herrera-Acosta J, Patel JM, Johnson RJ. A causal role for uric acid in fructose induced metabolic syndrome. Am J Physiol Renal Physiol 2006; 290: 625-631.

[22]   Kato M, Hisatome I, Tomikura Y, Kotani K, Kinugawa T, Ogino K, Ishida K, Igawa O, Shigemasa C, Somers VK. Status of endothelial dependent vasodilation in patients with hyperuricemia. Am J Cardiol 2005; 96: 1576-1578.

[23]   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.

[24]   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: 3127-3132.

[25]   Matheus AS, Tibirica E, da Silva PB, de Fatima Bevilacqua da Matta M, Gomes MB. Uric acid levels are associated with microvascular endothelial dysfunction in patients with type 1 diabetes. Diabet Med 2011; 28: 1188-1193.

[26]   Waring WS, Adwani SH, Breukels O, Webb DJ, Maxwell SR. Hyperuricaemia does not impair cardiovascular function in healthy adults. Heart 2004; 90: 155-159.

[27]   Doehner W, Schone N, Rauchhaus M, Leyva-Leon F, Pavitt DV, Reaveley DA, Schuler G, Coats AJ, Anker SD, Hambrecht R. Effects of xanthine oxidase inhibition with allopurinol on endothelial function and peripheral blood flow in hyperuricemic patients with chronic heart failure: results from 2 placebo controlled studies. Circulation 2002; 105: 2619-2624.

[28]   Kang DH, Nakagawa T, Feng L, Watanabe S, Han L, Mazzali M, Truong L, Harris R, Johnson RJ. A role for uric acid in the progression of renal disease. J Am Soc Nephrol 2002; 13: 2888-2897.

[29]   Bayram D, Tuğrul Sezer M, İnal S, Altuntaş A, Kıdır V, Orhan H. The effects of allopurinol on metabolic acidosis and endothelial functions in chronic kidney disease patients. Clin Exp Nephrol 2015; 19: 443-449.

[30]   Melendez-Ramirez G, Perez-Mendez O, Lopez-Osorio C, Kuri-Alfaro J, Espinola-Zavaleta N. Effect of the treatment with allopurinol on the endothelial function in patients with hyperuricemia. Endocr Res 2012; 37: 1-6.

[31] Garber AJ. Vascular disease and lipids in diabetes. Med Clin North Am 1998; 82: 931-948.

[32] Laedia AM, Ladeia-Frota C, Pinho L, Stefanelli E, Adan L. Endothelial dysfunction is correlated with microalbuminuria in children with short-duration type 1 diabetes. Diabetes Care 2005; 28: 2048-2050.

[33] Jager A, Kostense PJ, Ruhé HG, Heine RJ, Nijpels G, Dekker JM, Bouter LM, Stehouwer CD. Microalbuminuria and peripheral arterial disease are independent predictors of cardiovascular and all-cause mortality, especially among hypertensive subjects: five-year follow-up of the Hoorn Study. Arterioscler Thromb Vasc Biol 1999; 19: 617-624.

[34] Steuhower CD, Henry RM, Dekker JM, Nijpels G, Heine RJ, Bouter LM. Microalbuminuria is associated with impaired brachial artery, flow-mediated vasodilation in elderly individuals without and with diabetes: further evidence for a link between microalbuminuria and endothelial dysfunction--the Hoorn Study. Kidney Int Suppl 2004; 92: 42-44.

[35] Lee Je, Kim YG, Choi YH, Huh W, Kim DJ, Oh HY. Serum uric acid is associated with microalbuminuria in prehypertension. Hypertension 2006; 47: 962-967.

[36] Tseng CH. Correlation of uric acid and urinary albumin excretion rate in patients with type 2 diabetes mellitus in Taiwan. Kidney Int 2005; 68: 796-801.

[37] Toda N, Arakawa K. Salt-induced hemodynamic regulation mediated by nitric oxide. J Hypertens 2011; 29: 415-424.

[38] Sundstrom J, Sullıvan L, D'agostino RB, Levy D, Kannel WB, Vasan RS. Relations of serum uric acid to longitudinal blood pressure tracking and hypertension incidence. Hypertension 2005; 45: 28-33.