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Journal

Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association, 129(1):50-55

Published

2018 Dec 12

URL

https://www.thieme-connect.com/products/ejournals/abstract/10.1055/a-0805-2197

Higher Serum Uric Acid Is a Risk Factor of Reduced Muscle Mass in Men with Type 2 Diabetes Mellitus

Short running title: UA and Muscle Mass in Patients with T2DM

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Abstract

Objective: Sarcopenia has been recognized as a diabetic complication, and hyperuricemia is often accompanied by type 2 diabetes mellitus (T2DM). However, it is unknown whether serum uric acid (UA) levels are associated with reduced muscle mass in T2DM.

Methods: We conducted a cross-sectional study to investigate the association of serum UA with muscle mass in 401 subjects with T2DM (209 men and 192 postmenopausal women). The relative skeletal muscle mass index (RSMI) was evaluated using whole-body dual-energy x-ray absorptiometry.

Results: Multiple regression analyses adjusted for body weight, age, serum creatinine, hemoglobin A1c (HbA1c), and duration of T2DM showed that serum UA was negatively associated with RSMI in all subjects and men with T2DM ($\beta = -0.13$, $p = 0.001$ and $\beta = -0.17$, $p = 0.003$, respectively). Moreover, logistic regression analyses adjusted for these confounding factors showed that a higher serum UA level was significantly associated with low RSMI in men with T2DM [odds ratio (OR) = 1.94, 95% confidence interval (CI) = 1.10–3.45 per SD increase, $p = 0.023$]. In addition, higher serum UA levels were significantly associated with low RSMI after additional adjustment for age, duration of T2DM, HbA1c level, serum creatinine level, and sex in all subjects with T2DM [OR = 1.80, 95% CI = 1.20–2.72 per SD increase, $p = 0.005$].

Conclusions: The present study showed for the first time that higher serum UA is an independent risk factor of reduced muscle mass in men with T2DM.

Quick Summary

We conducted a cross-sectional study to examine the association of serum uric acid (UA) with muscle mass in patients with type 2 diabetes mellitus (T2DM). We showed that serum UA is an independent risk factor of reduced muscle mass in men with T2DM.

Key words

uric acid, hyperuricemia, muscle mass, sarcopenia, diabetes mellitus

Introduction

Type 2 diabetes mellitus (T2DM) is characterized by chronic hyperglycemia because of the combination of resistance to insulin action and inadequate insulin secretion. The number of patients with T2DM is increasing rapidly all over the world along with the aging population, and it is estimated to double in the next three decades [1-6]. Various T2DM-induced complications, including diabetic neuropathy, retinopathy, nephropathy, and cardiovascular disease, can decrease the quality of life and increase the mortality of patients with T2DM. Moreover, previous studies have shown that patients with T2DM have an increased risk of sarcopenia [7-10], which is characterized by the progressive loss of skeletal muscle mass and function, resulting in frailty in elderly people. Therefore, sarcopenia has been recently recognized as a diabetic complication. Although several studies have shown that decreased insulin and insulin-like growth factor-I action as well as increased advanced glycation end products are involved in T2DM-related sarcopenia [11-15], the detailed mechanism of sarcopenia in T2DM is not fully understood.

Hyperuricemia is an abnormally high level of serum uric acid (UA) and is often accompanied by obesity and T2DM. Although UA acts as an antioxidant *in vivo* [16], we need to control the serum UA level to within the proper range with diet and anti-hyperuricemic drugs because hyperuricemia is

known to cause gout, cardiovascular disorders, hypertension, and progressive renal disease [17-19]. Several studies have reported that serum UA levels might be associated with sarcopenia. Beavers et al. conducted a cross-sectional study on 7,544 men and women at 40 years of age or older and reported that elevations in serum UA were significantly related to a reduced skeletal muscle mass index and that subjects with serum UA levels over 8 mg/dL had 2 times the risk of sarcopenia compared with those with UA levels below 6 mg/dL [20]. Garcia-Esquinas et al. showed that serum UA levels were positively associated with the risk of frailty, which is characterized by exhaustion, muscle weakness, low physical activity, and slow walking speed, in older adults aged over 60 years, independent of age, sex, and body mass index (BMI) [21]. In contrast, Beberashvili et al. conducted a prospective observational study showing that serum UA levels were positively associated with lean body mass and low inflammation in a hemodialysis population, which indicates that hyperuricemia, through its antioxidant action, might protect against loss of muscle mass [22]. The discordance among the previous studies might be due to the differences in background characteristics. Because patients with T2DM often experience loss of muscle mass and hyperuricemia, there is a possibility that hyperuricemia is involved in the incidence of muscle mass reduction in patients with T2DM. However, to our knowledge, no studies examining the association of serum UA levels with muscle mass in T2DM have

been reported. We thus conducted a cross-sectional study to clarify this issue in men aged 50 years and older and postmenopausal women with T2DM.

Materials and Methods

Subjects

This was a cross-sectional study examining the association between serum UA level and muscle mass in patients with T2DM. Patients admitted to Shimane University Hospital for evaluation and treatment of T2DM, except for those having malignant diseases or infection, requiring surgery, and other special purposes, between 2006 and 2014 were screened. In our hospital, sarcopenia has been checked as a diabetic complication. According to the hospital records, 881 subjects (529 men and 352 women) were admitted. Among them, 652 subjects (418 men and 234 postmenopausal women) underwent serum UA level and body composition examination by whole-body dual-energy x-ray absorptiometry (DXA). We then excluded 1) men younger than 50 years of age, 2) premenopausal women who had spontaneous menses within 1 year, 3) patients who had renal dysfunction [estimated glomerular filtration rate <30 mL/min/1.73 m^2], 4) patients who had taken drugs for hyperuricemia, and 5) patients with nutritional derangements. Finally, 401 subjects with T2DM (209 men aged 50 years and older and 192 postmenopausal women) were included in this analysis. Patient demographic characteristics, biochemical parameters, and relative skeletal muscle mass index (RSMI) are shown in Table 1. This study was approved by the ethical review board of Shimane University Faculty of Medicine and

complied with the Helsinki Declaration. The requirement for informed patient consent was waived because no interventions or further examinations were performed.

Anthropometric and biochemical measurements

Body height (cm) was measured with a Martin metal anthropometer to the nearest 0.1 cm according to the standard technique, and body weight (kg) was measured using a medical electronic scale and recorded with 0.05 kg precision with the subject wearing light clothes. BMI was calculated as weight/height^2 (kg/m^2). On the second day after admission, blood and urine samples were collected after overnight fasting. Biochemical markers were measured using standard methods as previously described [23, 24]. Hemoglobin A1c (HbA1c) was determined with high-performance liquid chromatography. The value for HbA1c was estimated as the National Glycohemoglobin Standardization Program equivalent value calculated using the formula HbA1c (%) = HbA1c (Japan Diabetes Society) (%) + 0.4% [25].

Measurements of muscle mass according to whole-body dual-energy x-ray absorptiometry

Lean body mass of arms and legs, appendicular skeletal muscle mass (ASM), was evaluated by whole body DXA (QDR-4500, Hologic Co., Bedford, MA). RSMI was calculated as ASM/height^2, as

previously described [26]. We defined low RSMI as <7.0 kg/m^2 for men and <5.4 kg/m^2 for women, which are the values used for diagnosis of sarcopenia in Asians [27].

Statistical analysis

Data are expressed as mean ± standard deviation (SD). Because serum creatinine showed a skewed distribution, it was log-transformed before multiple regression and logistic analyses. All analyses were carried out using StatView (Abacus Concepts, Berkeley, CA, USA). A p value <0.05 was considered significant.

Results

Simple correlations of serum UA and RSMI with background characteristics

We examined simple correlations of serum UA and RSMI with various parameters (Table 2). Serum UA was significantly and positively correlated with body height, body weight, BMI and serum creatinine in all subjects and men, and with body weight, BMI and serum creatinine in postmenopausal women with T2DM. Moreover, serum UA was significantly and negatively correlated with age, duration of T2DM, and HbA1c in all subjects, with age and HbA1c in men, and with HbA1c in postmenopausal women with T2DM. RSMI was significantly and positively correlated with body height, body weight, BMI, serum creatinine, and serum UA in all subjects; with body height, body weight, BMI, and serum UA in men; and with body weight, BMI, and serum UA in postmenopausal women with T2DM. In addition, RSMI was significantly and negatively correlated with age and duration of T2DM in all subjects and with age in postmenopausal women with T2DM.

Association of serum UA with RSMI

Unadjusted correlation analysis showed a positive relationship between serum UA level and RSMI. However, serum UA and RSMI were correlated with various variables including age and body weight.

We thus performed multiple regression analyses (Table 3). After adjustment for body weight, age, serum creatinine level, HbA1c level, and duration of T2DM (model 5), the serum UA level was significantly and negatively associated with RSMI in all subjects (β = -0.13, $p = 0.001$) and men (β = -0.17, $p = 0.003$), whereas it was marginally, but not significantly, associated with RSMI in postmenopausal women with T2DM (β = -0.11, $p = 0.076$).

Association between serum UA and low RSMI

Next, we compared demographic and biochemical parameters as well as RSMI between subjects with and without low RSMI. As shown in Table 4, all subjects with low RSMI were significantly older and had shorter body height and lower body weight and BMI than those without it ($p < 0.05$ for all). Men with low RSMI were significantly older and had shorter body height, lower body weight and BMI, and higher HbA1c level than those without it ($p < 0.05$ for all). Women with low RSMI had significantly lower body weight and BMI than those without it ($p < 0.001$ for both). Serum UA was not different between subjects with and without low RSMI in men and women ($p = 0.064$ and $p = 0.143$, respectively).

Finally, we performed logistic regression analyses (Table 5). Although there was no association

between the serum UA level and low RSMI adjusted for body weight, a higher serum UA level was significantly associated with low RSMI after additional adjustment for age, duration of T2DM, HbA1c, and serum creatinine in men with T2DM [odds ratio (OR) = 1.94, 95% confidence interval (CI) = 1.10–3.45 per SD increase, $p = 0.023$]. On the other hand, serum UA was marginally, but not significantly, associated with low RSMI in postmenopausal women with T2DM (OR = 1.95, 95% CI = 0.97–3.91 per SD increase, $p = 0.061$). In contrast, a higher serum UA level was significantly associated with low RSMI after additional adjustment for age, duration of T2DM, HbA1c, serum creatinine, and sex in all subjects with T2DM [odds ratio (OR) = 1.80, 95% confidence interval (CI) = 1.20–2.72 per SD increase, $p = 0.005$].

Discussion

This is the first study to examine the association between serum UA concentration and muscle mass in patients with T2DM. Hyperuricemia is often accompanied by obesity. Indeed, serum UA was positively correlated with body weight and BMI in this study. Of interest, serum UA was positively correlated with RSMI; however, when adjusted for body weight, the association became negative. Previous studies have shown a body weight-independent negative association between serum UA and muscle mass [20, 21]. Moreover, the adjusted analysis of the present study showed that higher serum UA was significantly associated with lower RSMI. In contrast, a prospective observational study reported that serum UA levels were positively associated with lean body mass [22]; however, the association was not adjusted for body weight or BMI. These findings suggest that when the analysis was adjusted for the effect of body weight on muscle mass, serum UA may negatively affect muscle mass.

UA has an antioxidant effect. A previous study showed that very low levels of serum UA were associated with reduced muscle mass [22]. In contrast, the present and previous studies have shown that higher serum UA is associated with lower muscle mass [20, 21]. The underlying mechanism of the negative effect of higher serum UA levels on muscle mass remains unclear. Visser et al. showed

that high levels of serum UA induce inflammatory molecules, such as interleukin-6 and tumor necrosis factor-α [28]. In addition, intracellular UA is known to produce oxidative stress and worse muscle performance [29]. It has been shown that 1α,25-dihydroxyvitamin D enhanced myoblastic differentiation through modulating growth factors and fast-myosin heavy chain expression in mouse myoblastic C2C12 cells [15, 30, 31], suggesting that vitamin D may have a beneficial effect on muscle mass. Previous epidemiological and intervention studies have shown that serum UA negatively affects the production of vitamin D [32, 33]. It is known that patients with T2DM frequently have vitamin D insufficiency and deficiency [34, 35], although the vitamin D concentration was not measured in this study. Thus, the UA-associated reduction in muscle mass might easily occur in patients with T2DM with hyperuricemia.

Interestingly, higher serum UA was negatively associated with muscle mass in men rather than women, although a marginal association was found in women. There is a possibility that the differences in background characteristics such as age and serum UA might contribute to the sex difference. Physiologically, the serum UA concentration increases with age and is higher in men than age-matched women. Thus, the effects of high UA on muscle mass might be more potent in men than women. However, the finding that higher serum UA levels were associated with low RSMI after additional

adjustment for sex in all subjects with T2DM indicates that there is no sex difference in the association between higher serum UA level and low RSMI. We need a larger sample size to examine whether serum UA is associated with muscle mass independent of sex.

There are several limitations in our study. First, the sample size was not large enough to make definite conclusions. Second, we analyzed only subjects who visited our hospital, a tertiary center, for treatment of diabetes mellitus. Therefore, the participants enrolled in this study might have a relatively severe state of the disorder and might not be representative of Japanese patients in general. Third, non-diabetic control subjects were not examined in this study. Therefore, we cannot compare the contribution of serum UA to muscle mass between patients with T2DM and patients who are not diabetics. Finally, we need to conduct not only cross-sectional studies but also longitudinal ones to understand the causal relationship between serum UA level and muscle mass in T2DM.

In conclusion, this study for the first time showed that a high serum UA level might be involved in muscle mass reduction in men with T2DM. Therefore, it is suggested that the levels of serum UA should be controlled within the proper range in order to prevent loss of muscle mass in patients with T2DM.

Conflict of Interest

Ken-ichiro Tanaka, Ippei Kanazawa, Masakazu Notsu, and Toshitsugu Sugimoto declare that they have no conflicts of interest.

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Table 1 Baseline characteristics of subjects

	Total	Male	Female
Number of patients	401	209	192
Age (years)	63.7 ± 11.7	61.0 ± 12.6	66.6 ± 9.9
Duration of T2DM (years)	11.3 ± 9.8	10.4 ± 8.9	12.3 ± 10.6
Body height (cm)	158.3 ± 10.2	165.6 ± 7.6	150.4 ± 6.0
Body weight (kg)	60.3 ± 14.0	65.8 ± 13.8	54.5 ± 11.6
Body mass index (kg/m^2)	23.9 ± 4.3	23.9 ± 4.0	24.0 ± 4.7
Number of insulin	79	30	49
Number of sulfonylurea	130	71	59
Number of metformin	61	27	34
Number of pioglitazone	29	16	13
Number of αGI	61	33	28
Number of DPP-4 inhibitor	40	21	19
Serum creatinine (mg/dL)	0.70 ± 0.18	0.78 ± 0.16	0.62 ± 0.16
HbA1c (%)	8.6 ± 2.3	8.6 ± 2.2	8.6 ± 2.4
Serum UA (mg/dL)	5.1 ± 1.4	5.5 ± 1.4	4.6 ± 1.3
RSMI (kg/m^2)	6.89 ± 1.19	7.43 ± 1.11	6.31 ± 0.99

T2DM, type 2 diabetes mellitus; HbA1c, hemoglobin A1c; UA, uric acid; RSMI, relative skeletal muscle mass index; αGI, alpha-glucosidase; DPP-4, dipeptidyl peptidase-4

Table 2 Correlations of serum UA and RSMI with various parameters

	Total				Male				Female			
	Serum UA		RSMI		Serum UA		RSMI		Serum UA		RSMI	
	r	p	r	p	r	p	r	p	r	p	r	p
Age	-0.21	<0.001	-0.40	<0.001	-0.26	<0.001	-0.46	<0.001	0.02	0.816	-0.15	0.036
Duration of T2DM	-0.11	0.032	-0.16	0.003	-0.12	0.087	-0.18	0.012	-0.05	0.510	-0.07	0.363
Body height	0.37	<0.001	0.48	<0.001	0.29	<0.001	0.32	<0.001	0.11	0.117	0.07	0.315
Body weight	0.46	<0.001	0.81	<0.001	0.43	<0.001	0.76	<0.001	0.33	<0.001	0.77	<0.001
Body mass index	0.32	<0.001	0.67	<0.001	0.37	<0.001	0.76	<0.001	0.31	<0.001	0.79	<0.001
Serum creatinine	0.51	<0.001	0.23	<0.001	0.38	<0.001	-0.02	0.762	0.50	<0.001	0.10	0.165
HbA1c	-0.23	<0.001	-0.08	0.133	-0.28	<0.001	-0.13	0.063	-0.21	0.003	-0.04	0.613
Serum UA			0.34	<0.001			0.25	<0.001			0.22	0.002

UA, uric acid; RSMI, relative skeletal muscle mass index; T2DM, type 2 diabetes mellitus

Table 3 Association between RSMI and serum UA

	Total		Male		Female	
	β	p	β	p	β	p
Crude	0.34	<0.001	0.25	<0.001	0.22	0.002
Model 1	-0.04	0.300	-0.09	0.064	-0.04	0.486
Model 2	-0.03	0.303	-0.10	0.049	-0.06	0.268
Model 3	-0.12	0.001	-0.15	0.008	-0.10	0.090
Model 4	-0.13	<0.001	-0.18	0.002	-0.09	0.112
Model 5	-0.13	0.001	-0.17	0.003	-0.11	0.076

Multiple regression analyses were adjusted as follows:
Crude: no adjustment;
Model 1 adjusted for body weight
Model 2 adjusted as for model 1 + age
Model 3 adjusted as for model 2 + serum creatinine
Model 4 adjusted as for model 3 + HbA1c
Model 5 adjusted as for model 4 + duration of T2DM
RSMI, relative skeletal muscle mass index; HbA1c, hemoglobin A1c; T2DM, type 2 diabetes mellitus

Table 4 Comparison of demographic and biochemical parameters between subjects stratified by RSMI

Total

	low	high	*P*
Number of patients	99	302	
Age (years)	66.3 ± 10.0	62.8 ± 12.1	0.011
Duration of T2DM (years)	11.4 ± 10.1	11.2 ± 9.7	0.869
Body height (cm)	160.1 ± 9.4	157.7 ± 10.5	0.049
Body weight (kg)	52.4 ± 9.0	63.0 ± 14.3	<0.001
Body mass index (kg/m^2)	20.4 ± 2.5	25.1 ± 4.1	<0.001
Serum creatinine (mg/dL)	0.73 ± 0.19	0.70 ± 0.17	0.070
HbA1c (NGSP) (%)	9.0 ± 2.5	8.5 ± 2.2	0.062
Serum uric acid (mg/dL)	5.0 ± 1.5	5.1 ± 1.4	0.454
RSMI (kg/m^2)	5.94 ± 0.89	7.21 ± 1.10	<0.001

Male

	low	high	*P*
Number of patients	72	137	
Age (years)	65.9 ± 10.3	58.4 ± 13.0	<0.001
Duration of T2DM (years)	11.0 ± 9.3	10.0 ± 8.7	0.457
Body height (cm)	163.5 ± 7.8	166.7 ± 7.4	0.005
Body weight (kg)	55.9 ± 7.4	71.0 ± 13.6	<0.001
Body mass index (kg/m^2)	20.9 ± 2.4	25.5 ± 3.7	<0.001
Serum creatinine (mg/dL)	0.79 ± 0.18	0.78 ± 0.15	0.648
HbA1c (NGSP) (%)	9.0 ± 2.4	8.4 ± 2.1	0.033
Serum uric acid (mg/dL)	5.2 ± 1.4	5.6 ± 1.4	0.064
RSMI (kg/m^2)	6.35 ± 0.58	8.00 ± 0.87	<0.001

Female

	low	high	*P*
Number of patients	27	165	
Age (years)	67.3 ± 9.4	66.5 ± 10.0	0.675
Duration of T2DM (years)	12.6 ± 12.2	12.3 ± 10.4	0.886
Body height (cm)	150.8 ± 6.7	150.4 ± 0.5	0.722
Body weight (kg)	43.0 ± 5.8	56.3 ± 11.2	<0.001
Body mass index (kg/m^2)	19.0 ± 2.5	24.9 ± 4.4	<0.001
Serum creatinine (mg/dL)	0.59 ± 0.15	0.63 ± 0.16	0.213
HbA1c (NGSP) (%)	8.7 ± 2.7	8.6 ± 2.4	0.680
Serum uric acid (mg/dL)	4.2 ± 1.5	4.6 ± 1.3	0.143
RSMI (kg/m^2)	4.84 ± 0.58	6.56 ± 0.81	<0.001

Data are means ± SD. *P* values were calculated using Student's t-test or χ^2 tests.

RSMI, relative skeletal muscle mass index; T2DM, type 2 diabetes mellitus; HbA1c, hemoglobin A1c

Low or high RSMI was determined by 7.0 kg/m^2 in men and 5.4 kg/m^2 in women.

Table 5 The association of serum UA with the presence of low RSMI

	Total		Male		Female	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Crude	0.92 (0.74-1.15)	0.453	0.74 (0.54-1.02)	0.066	0.71 (0.44-1.12)	0.142
Model 1	1.49 (1.07-2.08)	0.020	1.35 (1.00-1.83)	0.053	1.43 (0.83-2.46)	0.199
Model 2	1.80 (1.20-2.72)	0.005	1.94 (1.10-3.45)	0.023	1.95 (0.97-3.91)	0.061

Logistic regression analyses were adjusted as follows:
Crude: no adjustment
Model 1: adjusted for body weight (plus sex for total subjects)
Model 2: adjusted for body weight, age, duration of T2DM, HbA1c and serum creatinine (plus sex for total subjects)
Unit of change; Standard deviation per increase
OR, odds ratio; CI, confidence interval; RSMI, relative skeletal muscle mass index; T2DM, type 2 diabetes mellitus; HbA1c, hemoglobin A1c