Effect of Visceral Fat Accumulation on Uric Acid Metabolism in Male Obese Subjects: Visceral Fat Obesity Is Linked More Closely to Overproduction of Uric Acid Than Subcutaneous Fat Obesity

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We investigated the relationship between uric acid (UA) metabolism and fat distribution in 36 obese men with a mean ± SD age of 38 ± 16 years and mean body-mass index (BMI) of 34 ± 4 kg/m^2. Subjects were divided into two groups: subcutaneous fat obesity (SFO) and visceral fat obesity (VFO), according to their abdominal fat distribution based on the results of computed tomography (CT). SFO was defined as having a ratio of visceral fat area (VFA) to subcutaneous fat area (V/S) of less than 0.4, and VFO was defined as having a V/S ratio ≥ 0.4. The levels of serum total cholesterol (T-Chol), triglyceride (TG), and fasting plasma glucose (FPG), and the diastolic blood pressure (dBP) were significantly higher in the VFO group than in the SFO group. Serum UA levels were much higher in both the SFO and VFO groups than in the non-obese control group (492 ± 107 and 474 ± 90 *v* 309 ± 48 μmol/L, respectively). The 24-hour urinary urate excretion (u-UA24h) and the UA clearance (Cua) to creatinine clearance (Ccr) ratio were significantly higher in the VFO group than in the SFO group (3.75 ± 1.43 *v* 2.69 ± 1.12 mmol/d, $P < .05$; and 5.9% ± 2.0% *v* 3.6% ± 1.7%, $P < .001$, respectively). The frequency of hyperuricemia was markedly higher in both the SFO and VFO groups compared with the control group (71% and 73% *v* 0%, respectively). Although the high serum UA level seemed to be related to low u-UA24h in 80% of SFO subjects with hyperuricemia, this was the case in only 10% of VFO subjects. While 44% of VFO subjects with hyperuricemia were designated as an overproduction type. These results suggest that the mechanism of hyperuricemia in obesity may be affected by the difference in body fat distribution and that the assessment of body fat distribution and types of hyperuricemia is crucial for the treatment of obese patients with hyperuricemia.

OBESE SUBJECTS frequently have hyperuricemia, as well as other metabolic and circulatory disorders, such as glucose intolerance, hyperlipidemia, and hypertension. A number of epidemiological and clinical studies have confirmed a positive correlation between body weight and serum uric acid (UA) level.[1,2] Weight reduction was shown to be associated with a significant decrease in serum UA level in obese subjects.[3-5] In our previous study, we clarified that hyperuricemia in obesity is mainly attributed to an impaired renal clearance of UA.[5]

Recent studies have shown that the complications of obesity are affected by the profile of body fat distribution. We established a method for estimating body fat distribution using a computed tomographic (CT) scan and proposed two types of obesity: visceral fat obesity (VFO), characterized by a marked accumulation of fat in the abdominal cavity, and subcutaneous fat obesity (SFO), characterized by fat accumulation mainly in the subcutis.[6,7] We showed that abnormalities of glucose and lipid metabolism, hypertension, and cardiac dysfunction are more frequently observed in patients with VFO than in those with SFO.[7-9] It is possible that VFO may have a different association with UA metabolism compared with SFO.

In the current study, we examined UA metabolism and fat distribution in obese subjects to evaluate the influence of visceral fat accumulation on hyperuricemia in obesity.

MATERIALS AND METHODS

Subjects

We studied 36 obese Japanese men aged 38 ± 16 (mean ± SD) years, ranging from 14 to 67 years, who were admitted for the purpose of weight reduction to the Second Department of Internal Medicine at the Osaka University Hospital. The obese subjects were designated as having a body-mass index (BMI) ≥ 26.4. The mean BMI of these obese subjects was 34 ± 4 kg/m^2 (range, 27 to 45). Fifteen non-obese male subjects with a BMI value of 21 ± 1 kg/m^2 and aged 44 ± 13 years, who had no metabolic or endocrine disorders, were selected from healthy volunteers and served as controls. Body weight was stable for at least 1 month before admission and the study was performed within 1 week after admission, during which time the subjects were given a weight-maintaining diet of 2,000 to 2,400 kcal (daily purine intake from 150 to 250 mg) with 60% of the calories provided as carbohydrate, 20% as fat, and 20% as protein. No subject received any medications for hyperuricemia, hyperlipidemia, or hypertension before or during the study. None had renal dysfunction, hepatic disease other than fatty liver, or atherosclerotic disease. All subjects gave informed consent to participate in the study.

Procedure

A blood sample was drawn after an overnight fast and a 24-hour urine sample was also collected at 9 AM. UA in serum and urine was measured by an enzymatic method using an uricase-peroxidase system. Creatinine (Cr) in serum and urine was determined by the method of Jaffe.[10] Serum total cholesterol (T-Chol) and triglyceride (TG) levels were also determined by enzymatic methods. Serum high-density-lipoprotein cholesterol (HDL-C) level was determined by the heparin-calcium precipitation method. Fasting plasma glucose (FPG) level was measured by the glucose oxidase method and plasma immunoreactive insulin (IRI) level was determined by radioimmunoassay. Blood pressure was measured several times after a rest in the sitting position and the mean value was used. The blood sampling and 24-hour urine collection were performed for UA and Cr estimation for 3 consecutive

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Submitted July 15, 1997; accepted February 9, 1998.

Supported by a Grant No. 07671132 from the Ministry of Education, Science, Sports, and Culture of Japan, and by a grant from the Uehara Memorial Foundation, 1996.

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0026-0495/98/4708-0007$03.00/0

days during the first week after admission. The value was given as a mean of the data for 3 days, then UA clearance (Cua), creatinine clearance (Ccr), 24-hour urinary urate excretion (u-UA24h), and the ratio of Cua to Ccr (Cua/Ccr) were calculated as previously described.[5] Hyperuricemia was defined as a serum UA level ≥ 420 μmol/L; low urinary urate excretion was defined as a Cua/Ccr ratio of less than 4.0%; and overproduction of UA was defined as u-UA24h ≥ 3.6 mmol/d.

Body fat distribution was determined using a CT scan (General Electric CT/T scanner, Milwaukee, WI) according to our procedure, with patients in the supine position.[6,7] The intraabdominal visceral fat area (VFA, in square centimeters) and subcutaneous fat area (SFA, in square centimeters) were measured at the level of the umbilicus. The ratio of VFA to SFA (V/S ratio) was calculated and the subjects were divided into two groups according to the V/S ratio: subjects with a V/S ratio ≥ 0.4 were diagnosed as having VFO, and those with a V/S ratio less than 0.4 were diagnosed as having SFO.[7]

Statistical Analysis

Results are expressed as the mean ± SD. The significance of differences between mean values of various parameters for each group was determined by Student's *t* test (two-sided test) and ANOVA. The significance of differences in the frequency of individual types of hyperuricemia and the frequency of diabetic subjects were analyzed by χ^2 test. Linear regression analysis was used to investigate the relationship between the variables. A *P* value less than .05 was accepted as statistically significant.

RESULTS

Table 1 shows the clinical and metabolic characteristics of the obese male subjects. The mean age of the VFO group was higher than that of the control and SFO group. There was no significant difference between the VFO and SFO groups with respect to BMI. Serum T-Chol and TG levels were significantly higher in the VFO group than in the control or in the SFO group. There was no significant difference in serum HDL-C level among the three groups. Although the FPG level in the VFO group was significantly higher than in the control or the SFO group, there was no significant difference in the plasma IRI level among the three groups. Diastolic blood pressure (dBP) was significantly higher in the VFO group than in the control or SFO group. There was no significant difference in serum Cr level or Ccr among the three groups. Serum UA level was extremely high in both the SFO and VFO groups compared with that in the control group, although there was no significant difference in serum UA level between the SFO and VFO groups. The frequency of impaired glucose tolerance (IGT) in the obese groups was high compared with the control group, although there was no significant difference in the frequency of IGT subjects between the SFO and VFO groups.

Table 1. Clinical and Metabolic Characteristics of Obese Male Subjects

Characteristic	Controls	SFO	VFO
n	15	14	22
Age (yr)	44 ± 13	23 ± 8‡	47 ± 13‖
Body weight (kg)	57.3 ± 9.2	105.7 ± 15.1‡	91.3 ± 13.3‡
BMI	21 ± 1	35 ± 4‡	33 ± 4‡
Serum T-Chol (mmol/L)	4.24 ± 0.03	5.30 ± 1.21*	6.36 ± 1.58‡§
Serum TG (mmol/L)	1.23 ± 0.41	1.95 ± 1.12	3.76 ± 2.10‡‖
Serum HDL-C (mmol/L)	0.98 ± 0.36	1.13 ± 0.39	1.01 ± 0.28
FPG (mmol/L)	5.12 ± 0.58	5.05 ± 0.72	7.44 ± 2.78‡‖
Plasma IRI (pmol/L)	86 ± 40	102 ± 55	92 ± 50
sBP (mm Hg)	113 ± 12	133 ± 15*	139 ± 17‡
dBP (mm Hg)	68 ± 12	74 ± 8	86 ± 14*§
Serum Cr (μmol/L)	88.4 ± 8.8	88.4 ± 17.7	79.6 ± 26.5
Ccr (mL/s)	1.22 ± 0.35	1.59 ± 0.69	1.69 ± 0.68
Serum UA (μmol/L)	309 ± 48	492 ± 107‡	474 ± 90‡
Frequency of IGT subjects	0% (0/0)	71% (10/14)‡	77% (17/22)‡

NOTE. Values are expressed as mean ± SD.
*$P < .05$, ‡$P < .001$, *v* control.
§$P < .05$, ‖$P < .001$, *v* SFO.

Figure 1 shows the comparison of the variables of UA metabolism in the subjects investigated. The u-UA24h was significantly higher in the VFO group than in the SFO group (3.75 ± 1.43 *v* 2.69 ± 1.12 mmol/d, respectively). There was no significant difference in the u-UA24h between the control and VFO groups, although the value of the VFO group tended to be higher than that in the control group (3.75 ± 1.43 *v* 3.16 ± 0.13 mmol/d, respectively). Cua and Cua/Ccr ratio in both the SFO and VFO groups were significantly lower than in the control group (Cua, 4.0 ± 1.9 and 5.6 ± 2.1 *v* 7.7 ± 1.8 mL/min; Cua/Ccr, 3.6% ± 1.7% and 5.9% ± 2.0% *v* 10.8% ± 2.2%, respectively). Cua and Cua/Ccr ratio were significantly lower in the SFO group than in the VFO group.

Table 2 shows the frequency of hyperuricemia and the type of hyperuricemia in these groups. The frequency of hyperuricemia in both the SFO and VFO groups was markedly high (71% and 73%, respectively), compared with 0% in the controls. The frequency of subjects with a low u-UA24h in the SFO group was markedly high (80%), while that in the VFO group was relatively low (31%). In contrast, the frequency of subjects with overproduction of UA in the SFO group was obviously low (0%), while that in the VFO group was relatively high (44%).

Table 3 gives the simple correlation coefficients between the various metabolic and anthropometric parameters in the obese subjects. Serum UA level was not correlated with BMI, VFA, SFA, or V/S ratio. Serum UA level was significantly correlated with serum TG level ($r = .39$, $P < .05$), but not with plasma IRI ($r = -.16$, not significant). The Cua/Ccr ratio was inversely correlated with SFA ($r = -.43$, $P < .05$) and positively correlated with V/S ratio ($r = .48$, $P < .05$). Cua was positively correlated with VFA ($r = 0.41$, $P < .05$). A positive correlation was observed between VFA and u-UA24h, but was not statistically significant ($r = .33$, $P = .07$).

DISCUSSION

Numerous epidemiological and clinical studies have shown that obesity is often accompanied by hyperuricemia.[11,12] In the current study, we confirmed a high frequency of hyperuricemia in obese subjects. However, the mechanism of elevation of serum UA level in obesity has not been fully elucidated. It is well known that serum UA level is determined by the balance between the rates of its production and urinary excretion. We previously reported that impairment of urinary urate excretion may be an important factor underlying hyperuricemia in massive obesity.[5] However, we did not assess the effect of body fat distribution on UA metabolism in that study.

Recent studies have shown that a clustering of multiple risk factors, including glucose intolerance, hyperlipidemia, and hypertension, is closely related to the occurrence of atherosclе-

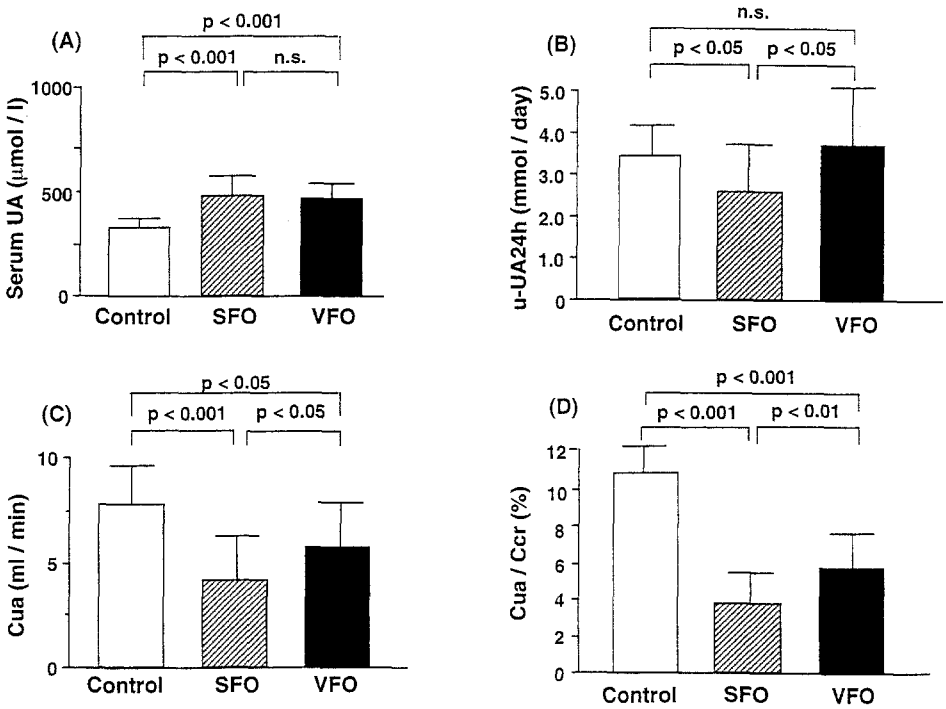

Fig 1. Comparison of UA metabolism between VFO and SFO. (A) Serum UA level, (B) u-UA24h, (C) Cua, and (D) ratio of Cua to CCr. Columns and bars represent means ± SD.

rotic diseases. One of the representative concepts is described by the term, "syndrome X," proposed by Reaven.[13] Furthermore, Zimmet also proposed the term, "syndrome X plus," as a more comprehensive concept, which included hyperuricemia as one of these components.[14] Several studies, including ours, have shown that intraabdominal visceral fat accumulation has an important pathogenic role in the clustering of multiple risk factors.[7,8,15-18] In the current study, we confirmed that VFO was more frequently associated with multiple risk factors in comparison with SFO. Although the serum UA level was equally high in both types of obesity, we found that the mechanism of hyperuricemia may differ between VFO and SFO dominance. The Cua/Ccr ratio in obese groups was lower than that in the control group, although the Cua/Ccr ratio was significantly higher in the VFO group than in the SFO group. Furthermore, urinary urate excretion in the VFO group was significantly higher compared with that in the SFO group. There was a significant negative correlation between SFA and Cua/Ccr ratio.

Table 2. Frequency and Type of Hyperuricemia in Male Obese Subjects

Variable	Obese Subjects		Control
	SFO	VFO	
Frequency of hyperuricemia	10/14 (71%)	16/22 (73%)	0/15 (0%)
Type of hyperuricemia			
Low urinary urate excretion	8/10 (80%)	5/16 (31%)†	0/15 (0%)
Overproduction of UA	0/10 (0%)	7/16 (44%)*	0/15 (0%)

NOTE. Hyperuricemia; serum UA level ≥420 μmol/L; low urinary urate excretion, Cua/Ccr ratio <4.0%; overproduction of UA, U-UA24h ≥4.8 mmol/d.

*$P < .05$, †$P < .01$, *v* SFO.

On the contrary, there was a significant positive correlation between the V/S ratio and the Cua/Ccr ratio, and urinary urate excretion tended to increase in proportion to the increase in VFA. These results suggest that subcutaneous fat accumulation might decrease urinary urate excretion, but that visceral fat accumulation may have little relationship with urinary urate excretion.

We considered that the pathogenesis of hyperuricemia in the VFO group might have been related to both low urinary urate excretion and overproduction of UA. As shown in Table 1 and Fig 1, serum UA levels of the SFO and VFO groups were significantly higher than that of the control group. Although there was no significant difference in serum UA level, Ccr, body weight, and BMI between the SFO and VFO groups, u-UA24h in the VFO group was significantly higher compared with the

Table 3. Simple Correlation Matrix (N = 36)

Variable	T-Chol	TG	FPG	Plasma IRI	Serum UA	u-UA24h	Cua/Ccr	Cua
BMI	−0.10	−0.04	−0.02	0.08	0.23	0.10	−0.38*	0.01
VFA	0.18	0.01	0.26	0.19	−0.12	0.33	−0.11	0.41*
SFA	−0.28	−0.36	−0.47†	0.11	0.05	−0.15	−0.43*	−0.14
V/S ratio	0.33	0.28	0.62‡	−0.12	−0.15	0.24	0.42*	0.29
T-Chol		0.73‡	−0.56†	−0.13	0.17	0.21	0.10	0.11
TG			0.60†	−0.26	0.39*	0.23	0.04	<0.01
FPG				−0.18	0.18	0.29	0.18	0.17
Plasma IRI					−0.16	0.02	0.04	0.17

*$P < .05$.
†$P < .01$.
‡$P < .001$.

SFO group. It is possible that the production of UA might have been higher in the VFO group than the SFO group. Therefore, the hyperuricemia in the VFO group may also have some relationship with the overproduction of UA. The decreased Cua/Ccr ratio in the VFO group might have some relationship with subcutaneous fat accumulation and the increased u-UA24h in the VFO group might have been related to the overproduction of UA by visceral fat accumulation. Taken together, the hyperuricemia in the VFO and SFO groups might be mainly related to low urinary urate excretion caused by a decreased Cua/Ccr ratio. Furthermore, the hyperuricemia in the VFO group might also have some relationship with the overproduction of UA.

Several investigators have suggested that serum UA level may be related to insulin resistance.[19-22] In these reports, it was suggested that hyperinsulinemia due to insulin resistance may decrease urinary urate excretion parallel to a decrease in urinary sodium excretion in human subjects. However, in the present study, there was no significant correlation between plasma IRI level and serum UA level, u-UA24h, or Cua/Ccr ratio (Table 3). Numerous reports have suggested that hyperinsulinemia develops during the course of insulin resistance in obesity.[23-26] However, we have observed that there is a lack of expected hyperinsulinemia that would correspond to insulin resistance in a substantial proportion of obese Japanese subjects, probably due to their genetic susceptibility, which impairs the insulin-secreting ability as compared with other populations.[7] Accordingly, hyperuricemia may not be caused by the low urinary urate excretion associated with hyperinsulinemia, at least in Japanese obese subjects. However, the postprandial value of serum insulin or 24-hour urinary C-peptide excretion might have been significantly associated with serum UA level or urinary urate excretion. Further studies may be necessary to clarify this point, as well as elucidate the mechanism of the reduction of urinary urate excretion in proportion to the increase in subcutaneous fat tissue.

The mechanism by which overproduction of UA is associated with visceral fat accumulation has not been shown. Several studies, including ours, have indicated a relationship between serum UA and serum lipid metabolism in gout.[11,27-29] We previously reported a significant positive correlation between urinary urate excretion and serum TG level in gouty patients, regardless of the amount of alcohol intake.[27] In another report, we also showed that serum TG level was significantly increased in parallel to visceral fat accumulation in obesity.[7] The intra-abdominal visceral fat has been shown to have high activities in both lipogenesis and lipolysis. A high content of free fatty acids (FFA), a product of lipolysis, may flow into the liver directly through the portal vein in subjects with visceral fat accumulation.[30-32] It has also been demonstrated that excess FFAs may cause enhancement of TG synthesis in the liver, resulting in hypertriglyceridemia. In the current study, a significant positive correlation was observed between serum UA and TG levels, and the mean serum TG level in the VFO group was significantly higher than that in the SFO group, suggesting the overproduction of UA may be linked to increased TG synthesis in the liver induced by visceral fat accumulation.

The relationship between UA production and TG synthesis in the liver based on visceral fat accumulation has not been elucidated. UA is a purine base that may originate from increased turnover and degradation of various phosphate nucleosides, such as adenosine monophosphate, adenosine diphosphate, or adenosine triphosphate, or dinucleotides, such as NADP or NADPH.[33,34] It is likely that a common metabolic derangement may exist in purine and fatty acid synthesis in the liver. For example, NADPH produced in the hexose monophosphate cycle (pentose phosphate pathway), which provides pentose for de novo purine synthesis, is utilized for fatty acid synthesis, which leads to TG synthesis.[34,35] Several investigators have suggested that fatty acid synthesis in the liver may be linked to de novo purine synthesis and accelerate the production of UA. However, we predict that exogenous FFAs supplied through lipolysis of visceral fat tissue may become substrates for TG synthesis in the liver. Therefore, it is difficult to explain the relationship between overproduction of UA and TG synthesis in the VFO groups. Further studies are necessary to clarify this relationship.

In conclusion, we confirmed that there was a close relationship between subcutaneous fat accumulation and the impairment of urinary urate excretion. Furthermore, visceral fat accumulation was closely related to the increased production of UA, which may lead to hyperuricemia in obesity. Assessment of abdominal fat distribution is necessary when treating obese patients with hyperuricemia.

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