Increased Visceral Fat Accumulation Further Aggravates the Risks of Insulin Resistance in Gout

Sumio Takahashi, Yuji Moriwaki, Zenta Tsutsumi, Jun-ichi Yamakita, Tetsuya Yamamoto, and Toshikazu Hada

We performed the present study to determine the degree of visceral fat accumulation and incidence of visceral fat obesity in 138 gout patients who were classified as overexcretion type (n = 53) and underexcretion type (n = 85) by their levels of uric acid clearance and urinary uric acid excretion. We also investigated the relationship between visceral fat accumulation and insulin resistance expressed by the homeostasis model assessment (HOMA) index. Visceral fat area (VFA)/surface body area (SBA) was significantly increased in patients with gout as compared with control subjects (79.7 ± 30.8 cm^2/m^2 *v* 65.1 ± 24.1 cm^2/m^2, *P* < .001). It was also shown that VFA/SBA in the gout overexcretion group was significantly increased as compared with the gout underexcretion group (88.3 ± 32.8 cm^2/m^2 *v* 74.3 ± 28.3 cm^2/m^2, *P* < .01). Although the incidence of visceral fat obesity (VFO) was not different between gout patients and control subjects, the incidence of VFO was significantly higher in the gout overexcretion type than the gout underexcretion type (19 of 53 *v* 11 of 85, *P* < .01). Further, there was a significant relationship between visceral fat area and HOMA index. Gout patients possess some factors that are included in the insulin resistance syndrome, irrespective of the presence of VFO, and the insulin resistance risk factors observed in gout become more prominent when it is complicated with VFO. Our results suggest that gout patients, especially the overexcretion type who have greater levels of visceral fat accumulation, may be more vulnerable to atherosclerotic diseases.

IT HAS BEEN suggested that serum uric acid concentration is closely associated with body fat mass, because the incidence of hyperuricemia increases in accordance with the severity of obesity.[1] Recently, obesity has been categorized as that which involves visceral and subcutaneous fat accumulation.[2] As a condition that involves multiple risk factors for atherosclerotic diseases, the importance of visceral fat obesity (VFO) has been emphasized, because it frequently causes a derangement of the metabolism of glucose and lipids.[3]

In a previous study, we found a close relationship between visceral fat accumulation and uric acid metabolism parameters in 50 healthy male subjects.[4] Moreover, it was recently shown that VFO is more closely associated with uric acid overproduction than subcutaneous fat obesity (SFO).[5] Therefore, in the present study, we investigated the degree of visceral fat accumulation and incidence of VFO in gout patients, who were classified as overexcretion or underexcretion type by their uric acid clearance and urinary uric acid excretion. Furthermore, we compared the factors involved in multiple risk factor clustering syndrome between gout patients and controls, with or without VFO.

SUBJECTS AND METHODS

Subjects

A total of 138 male patients who met the criteria for primary gout as outlined by the American Rheumatism Association (Table 1)[6] (age, 26 to 75 years; mean, 49.4 ± 12.0) and 66 apparently healthy male subjects (age, 26 to 78 years; mean, 47.7 ± 10.9) were included in this study. All were given detailed information regarding the study before informed consent was obtained from each. All of the subjects had normal laboratory values, except for their uric acid and lipid profiles. The study was performed on an outpatient basis without any dietary restriction (daily purine intake, 150 to 250 mg), except for total abstinence from alcoholic beverages during the urine collection portion. After specific informed consent was obtained, all medications for hyperuricemia or hyperlipoproteinemia were withheld from those in the patient group at least 1 month before the study. None of the control subjects were taking drugs that might have affected uric acid or lipid metabolism.

Procedures

Blood was drawn after an overnight fast. Serum and urinary concentrations of uric acid and creatinine were measured by the uricase method and a modified Jaffe reaction, using an automated analyzer. Serum total cholesterol and triglyceride levels were measured by the enzymatic method. Fasting plasma glucose (FPG) was measured by the glucose oxidase method. Immunoreactive insulin (IRI) was measured by a solid phase radioimmunoassay using an insulin RIA bead kit (Dainabot, Tokyo, Japan). High-density lipoprotein (HDL)-cholesterol was measured by the heparin-calcium method. Uric acid clearance and/or fractional uric acid clearance were calculated based on the fasting blood samples and 24-hour urine data. Gout patients were further classified into 2 groups, overexcretion and underexcretion of uric acid. The uric acid overexcretion gout group was defined as those with excretion levels greater than 2.85 $mmol/m^2/d$, while the underexcretion group was defined as those with urinary uric acid excretion levels of less than 2.84 $mmol/m^2/d$ and uric acid clearance of less than 6 mL/min, according to the criteria of Yamamoto et al.[7] Visceral fat and subcutaneous fat areas in all subjects were measured at the level of the umbilicus by abdominal computed tomography (TCT 900S; Toshiba, Tokyo, Japan), according to the method of Tokunaga et al[8] and then corrected for surface body area (SBA). VFO was defined as a visceral fat area (VFA)/subcutaneous fat area (SFA) ratio ≥ 0.4 with a body mass index (BMI) of more than 26.4, and SFO as a VFA/SFA ratio less than 0.4 with a BMI of more than 26.4.[3] Information concerning the consumption of alcoholic beverages over the past month was gathered and used to represent the drinking habits of each individual using a questionnaire on frequency, quantity, and type, and then converted to daily alcohol consumption.[9] Information regarding dietary intake for a 3-day period in close temporal proximity to the intraab-

From the Third Department of Internal Medicine, Hyogo College of Medicine, Hyogo, Japan.

Submitted March 20, 2000; accepted October 16, 2000.

Address reprint requests to Yuji Moriwaki, MD, Third Department of Internal Medicine, Hyogo College of Medicine, Mukogawa-cho 1-1, Nishinomiya, Hyogo 663-8501, Japan.

0026-0495/01/5004-0005$35.00/0
doi:10.1053/meta.2001.21688

Table 1. Proposed Criteria for Acute Arthritis of Primary Gout

1. More than 1 attack of acute arthritis
2. Maximum inflammation developed within 1 day
3. Monoarthritis attack
4. Redness observed over joints
5. First metatarsophalangeal joint painful or swollen
6. Unilateral first metatarsophalangeal joint attack
7. Unilateral tarsal joint attack
8. Tophus (proven or suspected)
9. Hyperuricemia
10. Asymmetric swelling within a joint on x-ray
11. Subcortical cysts without erosions on x-ray
12. Monosodium urate monohydrate microcrystals in joint fluid during attack
13. Joint fluid culture negative for organisms during attack

NOTE. Data from Wallace et al.[6]

dominal fat area evaluation was also obtained by a questionnaire, and the average amount and ingredients were analyzed by a dietitian. The homeostasis model assessment (HOMA)[10] was used as an index of insulin resistance, and insulin resistance was defined as FPG (mmol/L) × IRI (μU/mL)/22.5.

Statistical Analysis

Data are expressed as the mean ± SD (SE). Bonferroni's inequality method was used to evaluate observed differences and a χ^2 test was used to assess frequency differences between the 2 groups. Pearson's regression model was used to analyze the relationship between 2 variables. A P value below .05 was considered to be statistically significant.

RESULTS

Clinical and Metabolic Profiles

Table 2 shows clinical and metabolic characteristics of the gout patients (n = 138) and control subjects (n = 66). Despite similar BMI results, serum concentrations of triglycerides were significantly higher in the gout patients than the control subjects, as has been reported previously.[11] This may have been due, in part, to the greater daily consumption of alcoholic beverages by the gout patients (gout *v* control, 30.7 ± 28.5 g/d *v* 22.3 ± 20.2 g/d, $P < .05$) (Table 3). Serum HDL-cholesterol was significantly lower in the gout patients than the control subjects (1.24 ± 0.30 mmol/L *v* 1.37 ± 0.29 mmol/L, $P < .005$), while serum total cholesterol was not different between the 2 groups. Further, the basal plasma concentration of IRI and the HOMA index were both significantly higher in the gout patients than the controls (8.1 ± 3.9 μU/mL *v* 6.9 ± 3.6 μU/mL, $P < .05$; 1.9 ± 1.0 *v* 1.6 ± 0.9, $P < .05$). These differences were also observed between gout overexcreters (n = 53) and gout underexcreters (n = 85) (IRI, 8.9 ± 4.2 μU/mL *v* 7.6 ± 3.6 μU/mL, $P < .01$; HOMA index, 2.1 ± 1.1 *v* 1.8 ± 0.9, $P < .005$). Moreover, BMI was significantly increased in gout overexcreters, as compared with underexcreters (25.6 ± 3.0 *v* 24.3 ± 2.5, $P < .001$).

VFA and SFA in Gout and Control Subjects

As shown in Fig 1, VFA/SBA was significantly higher in the gout patients than the control subjects (79.7 ± 30.8 cm^2/m^2 *v* 65.1 ± 24.1 cm^2/m^2, $P < .001$). In contrast, SFA/SBA in the gout patients did not differ from that in the control subjects (70.2 ± 25.3 cm^2/m^2 *v* 70.8 ± 29.3 cm^2/m^2, not significant [NS]). Furthermore, VFA/SBA in the overexcretion type gout patients was significantly increased when compared with the underexcretion type (88.3 ± 32.8 cm^2/m^2 *v* 74.3 ± 28.3 cm^2/m^2, $P < .01$). However, SFA/SBA in gout patients was not statistically different between the overexcretion and underexcretion types (72.8 ± 28.6 cm^2/m^2 *v* 68.7 ± 23.0 cm^2/m^2, NS).

Incidence of VFO in Gout and Control Subjects

The incidence of VFO was not different between the gout patients and control subjects (30 of 138 [21.7%] *v* 13 of 66 [19.7%], NS). However, it was significantly higher in the

Table 2. Clinical Data and Metabolic Profile of the Patients and Control Subjects

	Gout (138)			Control (66)	*P* Value	
	Total (138) 1	Overexcreter (53) 2	Underexcreter (85) 3	4	1 *v* 4	2 *v* 3
Age (yr)	49.4 ± 12.0	48.1 ± 11.4	50.1 ± 12.3	47.7 ± 10.9	NS	NS
BMI (kg/m^2)	24.8 ± 2.8	25.6 ± 3.0	24.3 ± 2.5	24.3 ± 2.6	NS	<.001
SBP (mm Hg)	134.9 ± 18.1	137.8 ± 15.9	133.1 ± 19.1	122.6 ± 15.8	<.001	NS
DBP (mm Hg)	80.6 ± 11.0	84.4 ± 10.7	80.8 ± 10.8	74.2 ± 9.1	<.001	NS
S-Ua (mmol/L)	0.51 ± 0.07	0.51 ± 0.05	0.51 ± 0.08	0.34 ± 0.06	<.001	NS
Cua (mL/min)	5.3 ± 1.8	6.5 ± 1.8	4.5 ± 1.2	8.3 ± 2.1	<.001	<.001
24-hr Uua (mmol/d)	4.30 ± 1.41	5.73 ± 0.82	3.41 ± 0.86	3.30 ± 0.97	<.001	<.001
T-chol (mmol/L)	5.64 ± 1.09	5.75 ± 1.20	5.57 ± 1.01	5.52 ± 0.85	NS	NS
TG (mmol/L)	2.09 ± 1.01	2.24 ± 0.94	2.00 ± 1.04	1.74 ± 0.93	<.05	NS
HDL-chol (mmol/L)	1.24 ± 0.30	1.26 ± 0.29	1.23 ± 0.31	1.37 ± 0.29	<.005	NS
FPG (mmol/L)	5.2 ± 0.5	5.3 ± 0.4	5.2 ± 0.5	5.1 ± 0.5	NS	NS
IRI (μU/mL)	8.1 ± 3.9	8.9 ± 4.2	7.6 ± 3.6	6.9 ± 3.6	<.05	<.01
HOMA index	1.9 ± 1.0	2.1 ± 1.1	1.8 ± 0.9	1.6 ± 0.9	<.05	<.005

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; S-Ua, serum uric acid; Cua, uric acid clearance; 24-hr Uua, 24-hour urinary uric acid excretion; T-chol, total cholesterol; TG, triglyceride; HDL-chol, high density lipoprotein cholesterol; FPG, fasting plasma glucose; IRI, immunoreactive insulin; HOMA index, homeostasis model assessment index; NS, not significant; 1, all gout patients; 2, gout overexcretion type; 3, gout underexcretion type; 4, control subjects.

Table 3. Comparison of Dietary Intake Between Gout and Control According to Uric Acid Excretion

	Gout (138)			Control (66)	*P* Value	
	Total (138) 1	Overexcreter (53) 2	Underexcreter (85) 3	4	1 *v* 4	2 *v* 3
Energy (cal)	2,154.2 ± 501.6	2,262.0 ± 686.1	2,080.3 ± 434.7	2,193.6 ± 501.6	NS	NS
Protein (g/d)	84.5 ± 23.4	91.8 ± 25.8	79.5 ± 20.2	85.6 ± 24.2	NS	<.01
Lipid (g/d)	59.8 ± 27.6	61.3 ± 31.9	58.8 ± 24.5	65.9 ± 25.4	NS	NS
Carbohydrate (g/d)	278.2 ± 79.1	290.7 ± 98.3	269.5 ± 62.1	274.1 ± 63.2	NS	NS
Purine (mg/d)	159.4 ± 63.6	187.0 ± 70.2	140.4 ± 51.0	165.9 ± 81.4	NS	<.001
Alcohol (g/d)	30.7 ± 28.5	30.8 ± 29.1	30.7 ± 28.2	22.3 ± 20.2	<.05	NS

Abbreviations are the same as in Table 2.

overexcretion type gout than in the underexcretion type (19 of 53 [35.8%] *v* 11 of 85 [12.9%], $P < .01$).

Relationship Between VFA and Insulin Resistance in Gout and Control Subjects

As shown in Fig 2, VFA/SBA was positively correlated with the HOMA index in gout patients ($r = .43$, $P < .0001$), as well as in all subjects ($r = .44$, $P < .0001$). In a similar manner, SFA/SBA was also correlated with the HOMA index (data not shown).

Comparison of Factors Included in Multiple Risk Factor Clustering Syndrome in Gout and Control Subjects With or Without VFO

Table 4 shows the differences between gout-VFO patients (n = 30) and gout-non-VFO patients (n = 108), with regard to the factors included in the multiple risk factor clustering syndrome. Serum triglyceride, FPG, and IRI, along with HOMA index, were significantly higher in gout-VFO patients than gout–non-VFO patients (2.59 ± 1.04 mmol/L *v* 1.95 ± 0.96 mmol/L, $P < .005$; 5.4 ± 0.5 mmol/L *v* 5.2 ± 0.5 mmol/L, $P < .05$; 10.9 ± 3.7 μU/mL *v* 7.3 ± 3.7 μU/mL, $P < .001$; 2.6 ± 0.9 *v* 1.7 ± 0.9, $P < .001$). However, blood pressure, HDL-cholesterol, and total cholesterol were not different between gout-VFO patients and gout–non-VFO patients. Further, there were no significant differences in blood pressure, serum lipids, FPG, IRI, or HOMA index between gout-VFO and control-VFO subjects (n = 13). Similarly, there were no significant differences in blood pressure, serum lipids, FPG, IRI, or HOMA index between overexcretion gout-VFO (n = 19) and underexcretion gout-VFO patients (n = 11) (data not shown). In contrast, significant differences were observed in blood pressure, serum triglyceride, HDL-cholesterol level, IRI, and

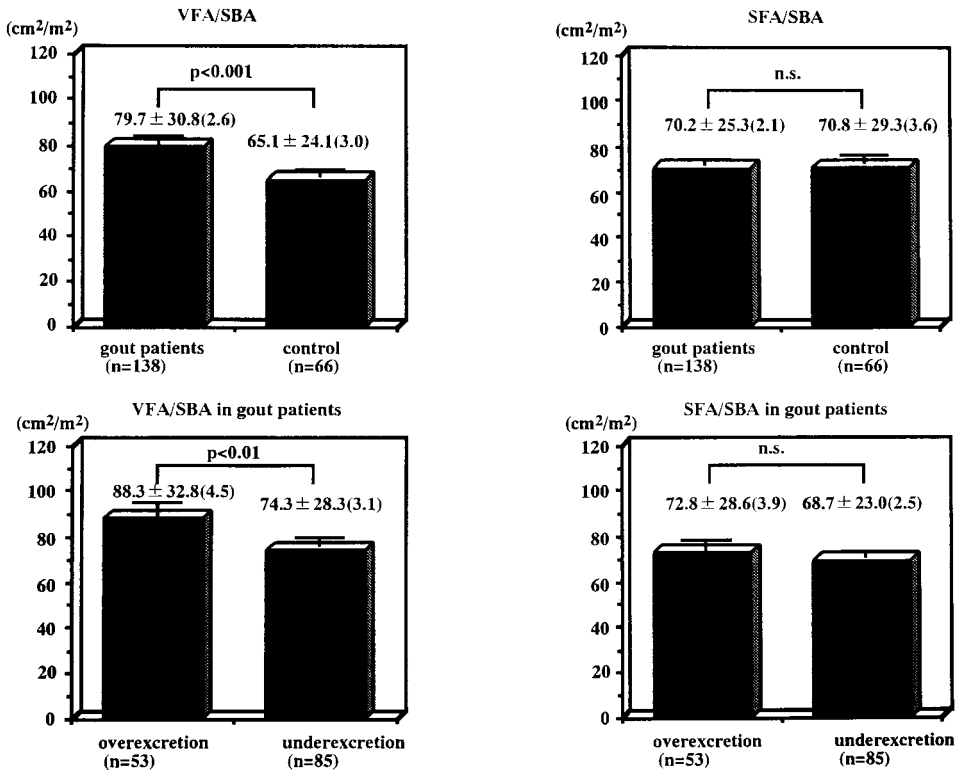

Fig 1. VFA and SFA in gout and control subjects. The area of visceral fat was significantly larger in the gout patients than control subjects and in the overexcretion type gout patients than in the underexcretion type. In contrast, SFA was not different between the 2 groups. Columns and bars indicate mean and SE.

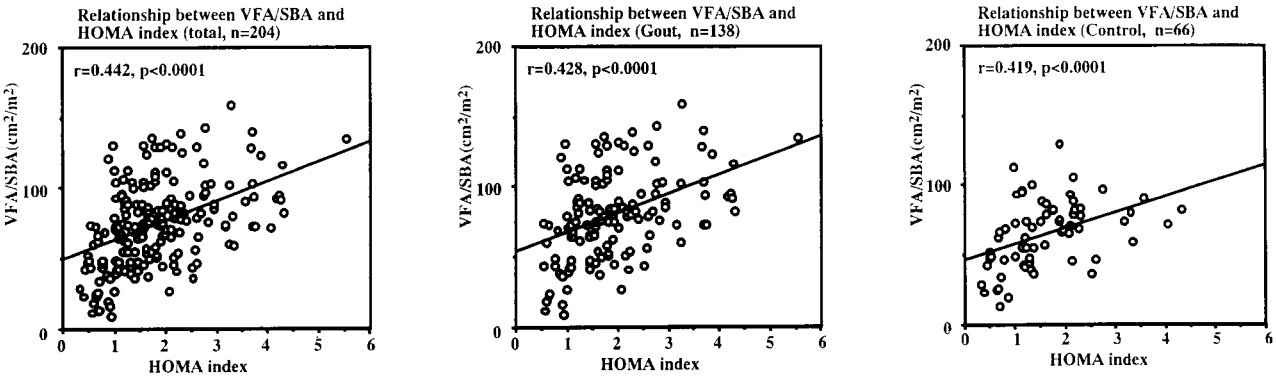

Fig 2. Relationships between VFA and insulin resistance in gout and control subjects. There were significant relationships between VFA and HOMA index in all subjects. Left, all subjects; middle, gout patients; right, control subjects.

HOMA index between gout–non-VFO patients and control–non-VFO subjects (n = 53) (Table 4).

Comparison of Dietary Intake Between Gout and Control Subjects According to VFO and Uric Acid Excretion

Dietary intake was investigated to clarify, if any, its association with over- or underexcretion of uric acid and VFO. Total calorie ingestion was not different between gout patients and control subjects or between gout overexcreters and gout underexcreters. However, protein and purine ingestion were significantly greater in gout overexcreters than gout underexcreters (Table 3). Total calorie ingestion was not different between gout-VFO patients and control-VFO subjects. Total purine intake was not different between gout-VFO and gout–non-VFO patients, or between control-VFO and control–non-VFO subjects (Table 5).

DISCUSSION

The results of epidemiologic studies regarding whether uric acid is an independent risk factor for atherosclerotic diseases, including ischemic heart disease, are still controversial. Some investigators have suggested that increased uric acid is an independent risk factor for ischemic heart diseases,[12,13] while others have found that it is not.[14-17] Nevertheless, it is generally accepted that gout patients are frequently complicated with cardiovascular diseases.[18] The possibility of a direct association between hyperuricemia and atherosclerosis remains unclear, however, several studies have shown that dyslipidemia complications such as hypertriglyceridemia,[11] decreased HDL-cholesterol,[11] and increased Lp(a) concentrations,[19] which are known as risk factors for atherosclerotic diseases, are associated with gout. In addition, an increased level of von Willebrand factor in serum has been suggested,[20] while incidences of hypertension and impaired glucose tolerance are also high in gout. Thus, multiple risk factors for atherosclerotic diseases seem to be clustered in gout patients.

Recently, the concept of multiple risk factor clustering syndrome, which includes hypertension, hyperinsulinemia, hypertriglyceridemia, low HDL-cholesterol, and impaired glucose tolerance, also termed as metabolic syndrome X,[21] deadly quartet,[22] insulin resistance syndrome,[23] and VFO,[24] has been advocated. Moreover, Zimmet[25] suggested that hyperuricemia should be included in syndrome X, as syndrome X plus. Further, there have been reports showing a close relationship between uric acid and insulin resistance syndrome.[26-29] In our previous study, we also showed a close association between

Table 4. Comparison of Factors for Insulin Resistance Syndrome Between Gout and Control With or Without VFO

	Gout (138)		Control (66)		*P* Value		
	VFO (30) 1	non-VFO (108) 2	VFO (13) 3	non-VFO (53) 4	1 *v* 2	1 *v* 3	2 *v* 4
Age	45.3 ± 12.8	50.5 ± 11.5	46.0 ± 13.5	48.2 ± 10.3	<.05	NS	NS
BMI (kg/m²)	28.8 ± 2.2	23.7 ± 1.7	28.3 ± 2.2	23.4 ± 1.7	<.001	NS	NS
SBP (mm Hg)	135.9 ± 14.0	135.0 ± 19.1	132.0 ± 16.8	120.3 ± 14.9	NS	NS	<.001
DBP (mm Hg)	81.1 ± 7.5	80.4 ± 11.8	77.5 ± 11.4	73.9 ± 8.3	NS	NS	<.001
S-UA (mmol/L)	0.52 ± 0.07	0.51 ± 0.07	0.37 ± 0.04	0.33 ± 0.06	NS	<.001	<.001
T-chol (mmol/L)	5.88 ± 0.97	5.58 ± 1.11	5.85 ± 0.87	5.44 ± 0.83	NS	NS	NS
TG (mmol/L)	2.59 ± 1.04	1.95 ± 0.96	2.31 ± 1.04	1.60 ± 0.85	<.005	NS	<.05
HDL-chol (mmol/L)	1.16 ± 0.29	1.27 ± 0.30	1.27 ± 0.25	1.38 ± 0.36	NS	NS	<.01
FPG (mmol/L)	5.4 ± 0.5	5.2 ± 0.5	5.2 ± 0.4	5.1 ± 0.5	<.05	NS	NS
IRI (μU/mL)	10.9 ± 3.7	7.3 ± 3.7	10.9 ± 3.6	5.9 ± 2.8	<.001	NS	<.05
HOMA index	2.6 ± 0.9	1.7 ± 0.9	2.5 ± 0.9	1.4 ± 0.7	<.001	NS	<.05

Abbreviations: VFO, visceral fat obesity; 1, gout patients with VFO; 2, gout patients without VFO; 3, control subjects with VFO; 4, control subjects without VFO. Other abbreviations are the same as in Table 2.

Table 5. Comparison of Dietary Intake Between Gout and Control With or Without VFO

	Gout (138)		Control (66)		*P* Value			
	VFO (30) 1	non-VFO (108) 2	VFO (13) 3	non-VFO (53) 4	1 *v* 2	1 *v* 3	2 *v* 4	3 *v* 4
Energy (cal)	2,296.3 ± 463.8	2,117.9 ± 573.2	1,966.4 ± 409.3	2,242.0 ± 509.0	NS	NS	NS	NS
Protein (g/d)	88.9 ± 26.6	83.3 ± 22.5	77.2 ± 19.1	87.4 ± 24.9	NS	NS	NS	NS
Lipid (g/d)	62.3 ± 22.9	59.2 ± 28.8	52.1 ± 19.6	68.8 ± 25.6	NS	NS	NS	<.05
Carbohydrate (g/d)	289.8 ± 64.4	275.2 ± 82.5	252.4 ± 42.4	278.7 ± 66.2	NS	NS	NS	NS
Purine (mg/d)	162.6 ± 75.7	158.5 ± 60.5	140.6 ± 57.7	171.3 ± 85.0	NS	NS	NS	NS
Alcohol (g/d)	34.4 ± 41.8	29.7 ± 23.7	32.9 ± 26.0	19.7 ± 17.8	NS	NS	NS	<.05

Abbreviations are the same as in Tables 2 and 4.

visceral fat accumulation and uric acid metabolism in healthy subjects.[4] Thus, there seems to be a close relationship between hyperuricemia and multiple risk factor clustering syndrome, although to our knowledge, there have been no detailed studies investigating visceral fat accumulation and/or VFO in gout patients.

The present study showed that VFA was significantly increased in gout patients when compared with the control subjects, and also that VFA and VFO incidence was significantly more increased in overexcretion type gout patients than in the underexcretion type, which is compatible with the results found in obese patients by Matsuura et al.[5] However, we did not find that the incidence of VFO was different between gout patients and control subjects. The exact cause of the increased visceral fat accumulation observed in gout patients and the lack of significant difference in incidence of VFO between the gout and control groups cannot be explained solely by dietary intake and remains unclear, because dietary intake, except for alcohol consumption, was not different between the 2 groups (Tables 3 and 5). However, increased alcohol consumption may be related to these findings, because it is known to lead to fatty acid synthesis. Moreover, it may be difficult to explain the difference in the incidence of VFO between gout overexcreters and gout underexcreters by dietary information alone, as total calorie intake and alcohol consumption were not different between the 2 groups (Tables 3 and 5). Other complicating factors, such as physical activity, may be involved in the underlying mechanism(s) causing these differences.

As seen in Table 4, the present study also showed that blood pressure, serum triglyceride level, IRI, and factors of insulin resistance syndrome were significantly higher in the gout–non-VFO patients than the control–non-VFO subjects. Moreover, levels of triglyceride, FPG, and IRI, along with HOMA index in gout were significantly higher when complicated with VFO. These results suggest that gout patients have increased atherogenic disease risk factors, even without overt VFO, while VFO further aggravates the risks.

The present study also suggests a possible contribution of visceral fat accumulation/VFO to the high incidence of atherosclerotic diseases in gout. Moreover, the accumulation of visceral fat may have an adverse effect on the metabolism of uric acid, as shown in our previous study.[4] Therefore, gout patients with VFO are recommended to lose weight to reduce excessive visceral fat stores and break this viscious cycle. However, it remains uncertain whether overexcretion type gout patients, who have greater levels of visceral fat accumulation and a higher incidence of VFO than the underexcretion type, are more likely to be complicated with atherosclerotic diseases. A prospective study on the development of atherosclerotic diseases in gout patients, separately examining the 2 types, would be of great benefit.

The results of our study have led us to the following conclusions: (1) Visceral fat is more accumulated in gout, although the incidence of VFO was not different between gout patients and control subjects. (2) The incidence of VFO is significantly higher in gout overexcreters than in gout underexcreters, although the underlying mechanism remains unclear. (3) Gout patients possess some insulin resistance factors, irrespective of the presence of VFO, although the risk factors seen in gout become more apparent when complicated with VFO. (4) Visceral fat accumulation may be associated with factors for insulin resistance, however, the presence of gout has only a limited influence, as many risk factors associated with VFO were the same in gout patients and control subjects.

REFERENCES

1. Tokunaga K, Matsuzawa Y, Kotani K, et al: Ideal body weight estimated from the body mass index with the lowest morbidity. Int J Obes 15:1-5, 1991

2. Matsuzawa Y, Fujioka S, Tokunaga K: Classification of obesity with respect to morbidity. Proc Soc Exp Biol Med 20:197-201, 1992

3. Fujioka S, Matsuzawa Y, Tokunaga K, et al: Contribution of intra-abdominal fat accumulation to the impairment of glucose and lipid metabolism in human obesity. Metabolism 36:54-59, 1987

4. Takahashi S, Yamamoto T, Tsutsumi Z, et al: Close relationship between visceral fat accumulation and uric acid metabolism in healthy man. Metabolism 46:1162-1165, 1997

5. Matsuura F, Yamashita S, Nakamura T, et al: 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. Metabolism 47:929-933, 1998

6. Wallace SL, Robinson H, Masi AT, et al: Preliminary criteria for the classification of the acute arthritis of primary gout. Arthritis Rheum 20:895-900, 1977

7. Yamamoto T, Moriwaki Y, Takahashi S, et al: Is the plasma uridine level a marker of the overproduction of uric acid? Metabolism 46:801-804, 1997

8. Tokunaga K, Matsuzawa Y, Ishikawa K, et al: A novel technique for the determination of body fat by computed tomography. Int J Obes 7:437-445, 1983

9. Thomson AD, Majumdar SK: The hazard to health from moder-

ate drinking, in Turner MR (ed): Nutrition and Health. A Perspective. Lancaster, UK, MTP, 1982, pp 87-107

10. Matthews DR, Hosker JP, Rudenski AS, et al: Homeostasis model assessment: Insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28: 412-419, 1985

11. Takahashi S, Yamamoto T, Moriwaki Y, et al: Impaired lipoprotein metabolism in patients with primary gout—influence of alcohol intake and body weight. Br J Rheumatol 33:731-734, 1994

12. Yano K, Reed DM, McGee DL: Ten-year incidence of coronary heart disease in the Honolulu Heart Program: Relationship to biologic and lifestyle characteristics. Am J Epidemiol 119:653-666, 1984

13. Liese AD, Hense H-W, Lowel H, et al: Association of serum uric acid with all-cause and cardiovascular disease mortality and incident myocardial infarction in the MONICA Ausburg cohort. Epidemiology 10:391-397, 1999

14. Brand FN, McGee DL, Kannel WB, et al: Hyperuricemia as a risk factor of coronary heart disease: The Framingham Study. Am J Epidemiol 121:11-18, 1985

15. Freedman DS, Williamson DF, Gunter EW, et al: Relation of serum uric acid to mortality and ischemic heart disease: The NHANES I Epidemiologic Follow-up Study. Am J Epidemiol 141:637-644, 1995

16. Wannamethee SG, Shaper AG, Whuncup PH: Serum urate and the risk of major coronary heart disease events. Heart 78:147-153, 1997

17. Culleton BF, Larson MG, Kannel WB, et al: Serum uric acid and risk for cardiovascular disease and death: The Framingham Heart Study. Ann Intern Med 131:7-13, 1999

18. Kelley WN, Schumacher HR Jr: Gout, in Kelley WN, Harris ED Jr, Sledge CB, et al (eds): Textbook of Rheumatology. Philadelphia, PA, Saunders, 1993, pp 1291-1336

19. Takahashi S, Yamamoto T, Moriwaki Y, et al: Increased concentrations of serum Lp(a) lipoprotein in patients with primary gout. Ann Rheum Dis 54:90-93, 1995

20. Tsutsumi Z, Yamamoto T, Takahashi S, et al: Atherogenic risk factors in patients with gout. Adv Exp Med Biol 431:69-72, 1998

21. Reaven GM: Role of insulin resistance in human disease. Diabetes 37:1595-1607, 1988

22. Kaplan NM: The deadly quartet. Arch Intern Med 149:1514-1520, 1989

23. DeFronzo RA, Ferrannini E: A hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care 14:173-194, 1991

24. Yamashita S, Nakamura T, Shimomura I, et al: Insulin resistance and body fat distribution. Diabetes Care 19:287-291, 1996

25. Zimmet PZ: Kelly West Lecture 1991. Challenges in diabetes epidemiology—From West to the rest. Diabetes Care 15:232-252, 1992

26. Modan M, Halkin H, Karasik A, et al: Elevated serum uric acid—A facet of hyperinsulinaemia. Diabetologia 30:713-718, 1987

27. Vuorinen-Markkola H, Yki-Jarvinen H: Hyperuricemia and insulin resistance. J Clin Endocrinol Metab 78:25-29, 1994

28. Quinones Galvan A, Natali A, Baldi S, et al: Effect of insulin on uric acid excretion in humans. Am J Physiol 268:EI-E5, 1995

29. Facchini F, Ida Chen Y-D, Hollenbeck CB, et al: Relationship between resistance to insulin-mediated glucose uptake, urinary uric acid clearance, and plasma uric acid concentration. JAMA 266:3008-3011, 1991