Close Correlation Between Visceral Fat Accumulation and Uric Acid Metabolism in Healthy Men

S. Takahashi, T. Yamamoto, Z. Tsutsumi, Y. Moriwaki, J. Yamakita, and K. Higashino

We evaluated the effect of accumulation of intraabdominal visceral fat on the metabolism of uric acid in 50 healthy male subjects to elucidate any relationship between such obesity and hyperuricemia. The area of abdominal fat (visceral fat and subcutaneous fat) was measured at the level of the umbilicus by abdominal computed tomographic scanning. Serum and urinary concentrations of uric acid and creatinine were determined with an autoanalyzer. Uric acid clearance and the ratio of urinary uric acid to creatinine excreted in urine were calculated. Univariate and multivariate analyses were used to evaluate the relationship between uric acid metabolism and body fat. The size of the area of visceral fat was significantly correlated with the serum concentration of uric acid ($r = .37$, $P < .01$), uric acid clearance ($r = -.34$, $P < .05$), and the urinary uric acid to creatinine ratio ($r = .65$, $P < .0001$). The size of the area of subcutaneous fat was significantly correlated only with the urinary uric acid to creatinine ratio ($r = .38$, $P < .01$). Multivariate analyses, including body mass index (BMI), showed that the size of the visceral fat area was the strongest contributor to an elevated serum concentration of uric acid, a decrease in uric acid clearance, and an increase in the urinary uric acid to creatinine ratio. These results suggest that accumulation of visceral fat may have a greater adverse effect on the metabolism of uric acid than BMI or accumulation of subcutaneous fat. Clearly, patients with hyperuricemia should lose weight to reduce excessive visceral fat stores, to help avoid attacks of gout.

OBESE PEOPLE often have hyperuricemia, frequently leading to painful attacks of gout. It has been suggested that an elevation of the serum concentration of uric acid is closely associated with an increase in body fat mass, since the incidence of hyperuricemia is increased in accordance with the severity of obesity.[1] Obesity is categorized as involving visceral or subcutaneous fat.[2] The importance of visceral fat obesity as a syndrome that involves multiple risk factors for atherosclerotic diseases has been emphasized, since it frequently causes a derangement of the metabolism of glucose and lipid.[3] However, little is known about the relationship between visceral fat obesity and the metabolism of uric acid. We therefore investigated the relationship between accumulation of visceral fat and parameters for uric acid metabolism in 50 healthy male subjects.

SUBJECTS AND METHODS

Subjects

We evaluated 50 apparently healthy Japanese men (aged 29 to 78 years; mean, 46 ± 11), who provided informed consent before study participation. All had normal laboratory values, including serum aspartate aminotransferase, alanine aminotransferase, lactic dehydrogenase, and creatinine and fasting blood glucose. The study was performed in an outpatient department without any dietary restriction (daily purine intake, 150 to 250 mg), but alcohol consumption was prohibited during urine collection. None of the subjects had taken drugs that might affect uric acid metabolism.

Procedure

Blood was drawn after an overnight fast. Serum and urinary concentrations of uric acid were measured by the uricase method. Serum and urinary concentrations of creatinine were determined using a modified Jaffe reaction. Uric acid clearance was measured using blood and urine collected after an overnight fast. We calculated the urinary uric acid to creatinine ratio based on 24-hour urine data. Blood and plasma levels of glucose and immunoreactive insulin (IRI) were measured in a 75-g oral glucose tolerance test, and the area under the curve (ΣBS and ΣIRI) was calculated. The visceral fat area and subcutaneous fat area 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.[4]

Statistical Analyses

Values are expressed as the mean ± SD. Univariate correlation analyses were used to assess the association between body fatness (abdominal fat area and body mass index [BMI]) and serum uric acid level, uric acid clearance, and urinary uric acid to creatinine ratio. The association between these parameters of uric acid metabolism and the other measured variables was evaluated by multivariate regression analysis. A P value less than .05 was considered statistically significant.

RESULTS

Demographic and Biochemical Findings

Table 1 shows clinical characteristics and laboratory data for the 50 subjects (BMI, 24.2 ± 2.5; range, 19.7 to 30.4). Although some subjects had an elevated serum uric acid level (>7.0 mg/dL), a decreased uric acid clearance (<6.0 mL/min), or an increased 24-hour urinary excretion of uric acid (>900 mg/d), the mean values for these parameters were all within the normal range. Mean values for other data were also within the normal range.

Univariate Analyses

Linear regression analysis was performed to investigate the relationships between the visceral fat area, subcutaneous fat area, and BMI and the serum uric acid level, uric acid clearance, and urinary uric acid to creatinine ratio. Figure 1 (upper panels) shows a significant correlation between serum uric acid level and visceral fat area ($r = .37$, $P < .01$), but no significant correlation between serum uric acid level and BMI or subcutaneous fat area. Figure 1 (center panels) also shows a significant inverse correlation between uric acid clearance and visceral fat

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

Submitted October 4, 1996; accepted March 7, 1997.

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

0026-0495/97/4610-0012$03.00/0

Table 1. Clinical Features and Laboratory Data of the Subjects (N = 50)

Parameter	Mean ± SD	Range	Normal Value
Age (yr)	46.3 ± 11.2	29-78	
BMI (kg/m²)	24.2 ± 2.5	19.7-30.4	18-26
Height (cm)	168.8 ± 5.7	157-182	
Body weight (kg)	69.1 ± 8.8	56-90	
VFA (cm²)	119.3 ± 39.9	40.4-205.4	
SFA (cm²)	118.3 ± 44.3	33.0-223.3	
S_{UA} (mg/dL)	5.4 ± 1.0	3.2-7.3	2.0-7.0
C_{UA} (mL/min)	8.5 ± 1.8	5.2-13.0	6.2-12.6
U_{UA} (mg/d)	755.6 ± 215.8	368-1,236	400-900
FBS (mg/dL)	91.1 ± 9.1	69-112	70-110
IRI (μU/mL)	7.2 ± 4.1	1.5-18.8	<17

Abbreviations: VFA, visceral fat area; SFA, subcutaneous fat area; S_{UA}, serum uric acid; C_{UA}, uric acid clearance; U_{UA}, 24-hour urinary excretion of uric acid; FBS, fasting blood sugar.

area ($r = -.34$, $P < .05$) and BMI ($r = -.31$, $P < .05$), but no correlation between uric acid clearance and subcutaneous fat area. Finally, Figure 1 (lower panels) shows a significant correlation between the urinary uric acid to creatinine ratio and the visceral fat area, as well as the subcutaneus fat area ($r = .65$, $P < .0001$ and $r = .38$, $P < .01$, respectively).

Multivariate Analysis

Since the visceral fat area, subcutaneous fat area, and BMI were all significantly correlated with the serum uric acid level, uric acid clearance, and urinary uric acid to creatinine ratio, we performed multivariate regression analysis to ascertain whether visceral fat area was independently correlated with these parameters of uric acid metabolism. Tables 2, 3, and 4 show that multivariate regression analysis demonstrated that visceral fat area was the only variable independently related to serum uric

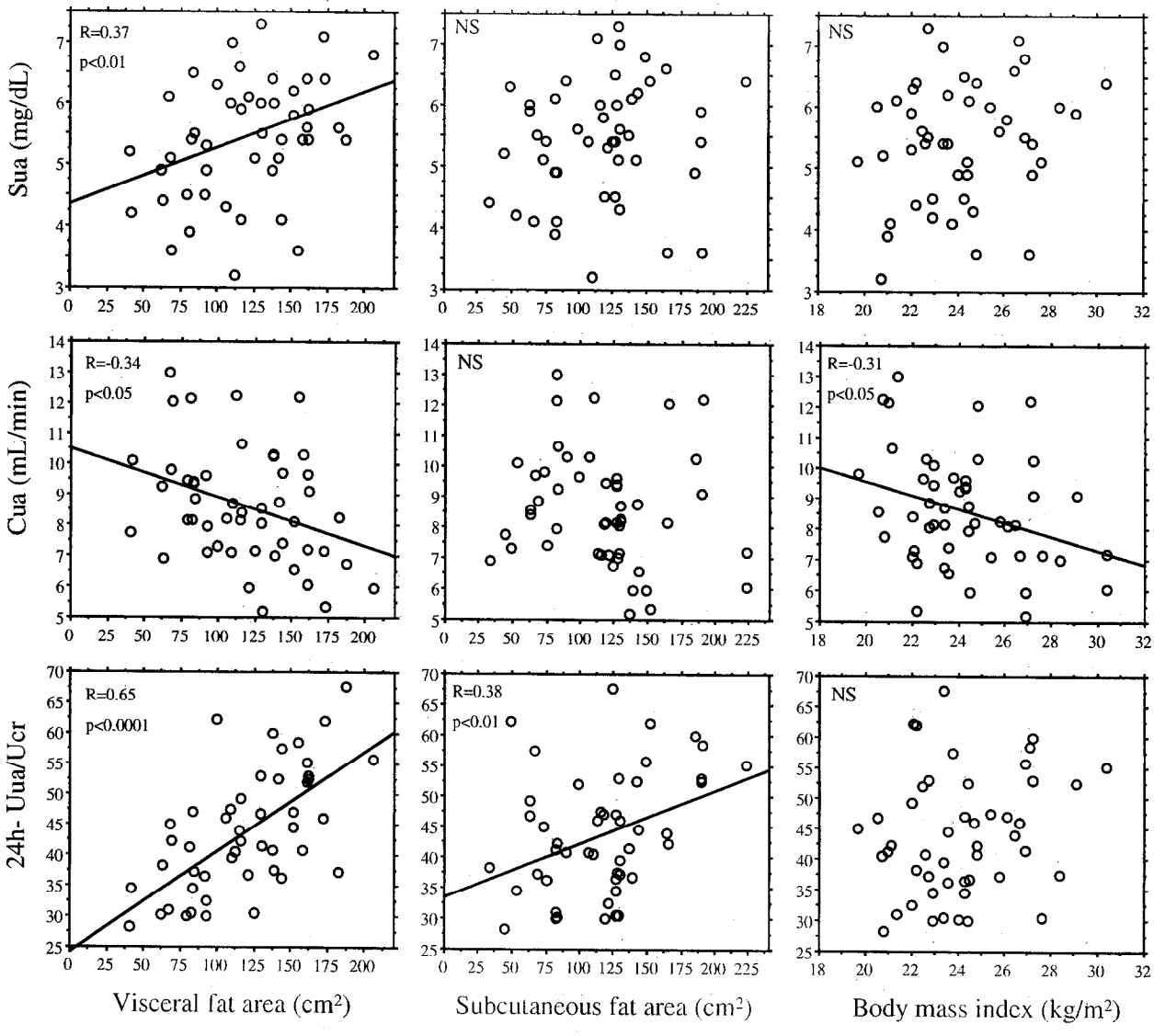

Fig 1. (Upper panels) Relationship between serum uric acid (Sua) concentration and abdominal fat area and BMI. A significant inverse correlation was observed only between Sua and visceral fat area. (Center panels) Relationship between uric acid clearance (Cua) and abdominal fat area and BMI. A significant inverse correlation was observed between Cua and visceral fat area and BMI, but not subcutaneous fat area. (Lower panels) Relationship between urinary uric acid to creatinine ratio (24 h Uua/Ucr) and abdominal fat area and BMI. A significant correlation existed between the 24-hour Uua/Ucr and both visceral and subcutaneous fat areas.

Table 2. Multiple Regression Analyses of the Association Between Serum Uric Acid and Various Factors

Variable	Partial Regression Coefficient	Standard Regression Coefficient	Partial F	P
Intercept	2.773			
BMI	0.078	0.084	0.866	.3572
VFA	0.009	0.004	5.107	.0288
SFA	−0.00003	0.005	0.005	.9412
ΣIRI	−0.002	0.004	0.305	.5837

Abbreviations: VFA, visceral fat area; SFA, subcutaneous fat area.

Table 4. Multiple Regression Analyses of the Association Between the Urinary Uric Acid to Creatinine Ratio and Various Factors

Variable	Partial Regression Coefficient	Standard Regression Coefficient	Partial F	P
Intercept	27.178			
BMI	0.227	0.063	0.089	.7664
VFA	0.112	0.482	10.271	.0025
SFA	0.026	0.123	0.379	.5412
ΣIRI	−0.071	−0.282	3.561	.0656

Abbreviations: VFA, visceral fat area; SFA, subcutaneous fat area.

acid level, uric acid clearance, and urinary uric acid to creatinine ratio when all other potential confounding variables were taken into account.

DISCUSSION

The multiple risk factor–clustering syndrome, which has also been designated syndrome X,[5] the deadly quartet, [6] and the visceral fat obesity syndrome,[7] has been emphasized as a cause of atherosclerotic disease. Patients with hyperuricemia or gout commonly exhibit elements of this syndrome.[8-11] Zimmet,[12] who added hyperuricemia to syndrome X, proposed the concept of syndrome X plus, and suggested a relationship between uric acid and the multiple risk factor–clustering syndrome. However, there are few studies on the relationship between the multiple risk factor–clustering syndrome and the metabolism of uric acid.[13,14] Our present investigation demonstrated a close relationship between accumulation of visceral fat and metabolism of uric acid. The effect of dietary intake of purine, protein, fat, and alcohol, as well as age, on the metabolism of uric acid is well known. For example, alcohol ingestion increases the level of serum uric acid by increasing purine degradation (increased 24-hour urinary excretion of uric acid),[15] whereas ingestion of protein increases uric acid clearance.[16] Thus, visceral fat accumulation may have only a supplemental effect on urinary excretion of uric acid and production of uric acid, with dietary factors directly mediating that link. Since the serum concentration of uric acid and uric acid clearance were determined after an overnight fast, a direct effect of dietary factors on uric acid may be excluded. The uric acid level in the 24-hour urine specimen may reflect the amount and/or kind of food ingested during that period.

In a previous study by Yamashita et al,[17] obese subjects demonstrated a high serum uric acid level as compared with controls. The fractional uric acid clearance (uric acid clearance to creatinine clearance ratio) was markedly reduced in these subjects. The investigators also demonstrated that fractional uric acid clearance was increased when body weight was reduced. A decrease in fractional uric acid clearance may play a role in increasing the serum uric acid level in obese subjects, although the cause of the decrease in fractional uric acid clearance has not been clarified. The present study showed that uric acid clearance was more closely related to the visceral fat area than were either the BMI or the subcutaneous fat area. This finding suggests that the relationship between uric acid clearance and obesity may reflect the relationship between uric acid clearance and visceral fat area, since visceral fat area was correlated with BMI (data not shown).

Table 3. Multiple Regression Analyses of the Association Between Uric Acid Clearance and Various Factors

Variable	Partial Regression Coefficient	Standard Regression Coefficient	Partial F	P
Intercept	16.054			
BMI	−0.294	−0.417	3.631	.0633
VFA	−0.015	−0.3261	4.258	.045
SFA	0.01	0.245	1.369	.2482
ΣIRI	0.002	0.039	0.056	.8139

Abbreviations: VFA, visceral fat area; SFA, subcutaneous fat area.

Considering the relationship between an accumulation of visceral fat and a decrease in uric acid clearance, it does not seem probable that decreased uric acid clearance causes accumulation of visceral fat. However, it is possible that the hyperinsulinemia caused by visceral fat accumulation may be responsible. An association between hyperinsulinemia and/or insulin resistance and hyperuricemia has been suggested.[10,18,19] Insulin acts on the renal tubules to increase the reabsorption of sodium and uric acid, thereby decreasing uric acid clearance.[20,21] However, in the present study, ΣIRI was not correlated with uric acid clearance (Table 3). Some other factor related to visceral fat accumulation may therefore contribute to the decrease in uric acid clearance. The relationship between the urinary uric acid to creatinine ratio and visceral fat is likely to be complex, and eludes a simple explanation. There may be a link between the production of uric acid and an excess of free fatty acid derived from visceral fat in the liver, which accelerates the production of very–low-density lipoprotein, a major constituent of triglyceride. The accumulation of visceral fat may therefore cause hypertriglyceridemia, as well as an increase in hepatic production of uric acid. This hypothesis appears to be supported by a previous study that found a significant association between serum triglyceride level and urinary excretion of uric acid.[22] Since obesity is usually the result of too much food and not enough exercise, excessive intake of purines may also influence the urinary uric acid to creatinine ratio. In any case, the accumulation of visceral fat suggests an increase in the urinary uric acid to creatinine ratio.

In conclusion, we have demonstrated that accumulation of visceral fat was positively related to the serum uric acid level and urinary uric acid to creatinine ratio and inversely related to uric acid clearance. This suggests a close relationship between uric acid metabolism and accumulation of visceral fat. Thus, hyperuricemic patients who gain weight and exhibit an increase in visceral fat may develop a worsening of the hyperuricemia and painful attacks of gout. To reduce the serum level of uric acid, it is therefore important to evaluate the extent of, and to reduce the accumulation of, visceral fat.

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. 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

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

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

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

8. 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

9. Wyngaarden JB, Kelley WN: Gout, in Stanbury JB, Wyngaarden JB, Fredrickson DS, et al (eds): The Metabolic Basis of Inherited Disease (ed 5). New York, NY, McGraw-Hill, 1983, p 1043

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

11. Denis G, Launay MP: Carbohydrate intolerance in gout. Metabolism 18:770-775, 1969

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

13. Cigolini M, Targher G, Tonoli M, et al: Hyperuricaemia: Relationship to body fat distribution and other components of the insulin resistance syndrome in 38-year-old healthy men and women. Int J Obes 19:92-96, 1995

14. Gillum RF: The association of the ratio of waist to hip girth with blood pressure, serum cholesterol and serum uric acid in children and youths aged 6-17 years. J Chronic Dis 40:413-420, 1987

15. Faller J, Fox IH: Ethanol-induced hyperuricemia. Evidence for increased urate production by activation of adenine nucleotide turnover. N Engl J Med 307:1598-1602, 1982

16. Matzkies F, Berg G, Madl H: The uricosuric action of protein in man. Adv Exp Med Biol 122A:227-231, 1980

17. Yamashita S, Matsuzawa Y, Tokunaga K, et al: Studies on the impaired metabolism of uric acid in obese subjects: Marked reduction of renal urate excretion and its improvement by a low-calorie diet. Int J Obes 10:255-264, 1986

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

19. Quinones Galvan A, Natali A, Baldi S, et al: Effect of insulin on uric acid excretion in humans. Am J Physiol 268:E1-E5, 1995

20. Holmes EW, Kelley WN, Wyngaarden JB: The kidney and uric acid excretion in man. Kidney Int 2:115-118, 1972

21. 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

22. Matsubara K, Matsuzawa Y, Jiao S, et al: Relationship between hypertriglyceridemia and uric acid production in primary gout. Metabolism 38:698-701, 1989