Decreases in Serum Uric Acid By Amelioration of Insulin Resistance in Overweight Hypertensive Patients: Effect of a Low-Energy Diet and an Insulin-Sensitizing Agent

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Background: Hyperuricemia and hyperinsulinemia/insulin resistance are commonly seen in obese subjects and hypertensive patients. To clarify whether the insulin resistance plays a role in hyperuricemia, we investigated alterations in serum uric acid (UA) concentrations during treatment with a low-energy diet or an insulin-sensitizing agent in overweight hypertensive patients.

Methods: Twenty-eight overweight hypertensive patients (14 men and 14 women, mean age 61 ± 2 years) were assigned to a weight reduction program with a low-energy diet (3360 kJ/day for 3 weeks, n = 14) and to treatment with troglitazone (200 mg twice daily for 8 weeks, n = 14). Measurements of body weight, blood pressure (BP), serum UA, and a 75-g oral glucose tolerance test were performed at baseline and the end of the intervention periods.

Results: Body weight and BP decreased significantly in the diet group but not in the troglitazone group at the end of the intervention periods. Levels of blood glucose, plasma insulin, and homeostasis model assessment–insulin resistance index (HOMA-R) improved similarly in the two groups. Serum UA concentration decreased by treatment both in the diet (0.4 ± 0.2 mg/dL, P < .05) and troglitazone groups (1.0 ± 0.2 mg/dL, P < .001).

Conclusions: The amelioration of insulin resistance by either a low-energy diet or troglitazone decreased the serum UA level in overweight hypertensive patients. Insulin resistance or hyperinsulinemia, independent of body weight and BP, may play an important role in UA metabolism in multiple risk factor syndrome. Am J Hypertens 2002;15:697–701 © 2002 American Journal of Hypertension, Ltd.

Key Words: Obesity, hypertension, uric acid, troglitazone, insulin resistance.

Elevated serum uric acid (UA) is associated with a high incidence of cardiovascular events, and hyperuricemia is frequently observed in obese subjects and hypertensive patients. It has been shown that the prevalence of gout was threefold higher in hypertensive patients compared with normotensive subjects. The pathophysiologic mechanism of increased serum UA concentration in essential hypertension is suggested due to a disturbance in renal UA handling. The impaired renal UA excretion mainly contributes to hyperuricemia, although overproduction of UA is also involved in obese subjects.

Numerous epidemiologic and clinical studies have shown that obese subjects frequently have metabolic and circulatory disorders, such as impaired glucose intolerance, hyperlipidemia, hyperuricemia, and hypertension, which are linked to each other and called the multiple risk factor syndrome. It was suggested that insulin resistance was a major pathophysiologic factor in the multiple risk factor syndrome. The prevalence of insulin resistance is reported as 62.8% in subjects with hyperuricemia, and 95.2% in subjects combined with glucose intolerance, hyperlipidemia, hyperuricemia, and hypertension. It has been proposed that the attendant compensatory hyperinsulinemia caused by insulin resistance may contribute to the pathogenesis of hyperuricemia through its renal effect.

However, the association between serum UA concentration and insulin resistance is still not fully defined. Although it has been shown that weight reduction ameliorates hyperuricemia in obese subjects, there have been few studies examining the effect of improving insulin resistance without weight reduction on UA metabolism.
To date, the comparable effects of a weight reduction program and an insulin-sensitizing agent on serum UA have not been investigated. Troglitazone, a thiazolidinedione derivative, acts to augment insulin-mediated glucose uptake and to decrease plasma concentrations of glucose and insulin. In the present study, we investigated the serum UA concentration and insulin sensitivity before and after treatment with a low-energy diet or troglitazone in overweight hypertensive patients. The present study was completed before the withdrawal of troglitazone from the market, and the results of casual and ambulatory blood pressure (BP) were published previously.

**Methods**

**Patients**

Twenty-eight overweight Japanese patients with hypertension (14 men and 14 women, 37 to 80 years old) participated in this study. All patients were diagnosed as having essential hypertension, and none had overt diabetes mellitus or serious cardiovascular complications. Fifteen patients were not receiving treatment and the remaining 13 were being treated with one or two antihypertensive drugs. The antihypertensive treatment was continued without alteration throughout the study. All patients had a casual systolic BP of $\geq 140$ mm Hg, diastolic BP of $\geq 90$ mm Hg, or both, and a body mass index of $\geq 25.0$ kg/m$^2$ before they entered the study. Informed consent was obtained from all patients before their participation in the study.

**Procedure**

Fourteen patients (6 men and 8 women) were assigned to a weight reduction program with a low-energy diet and the remaining 14 patients (8 men and 6 women) were assigned to treatment with troglitazone. The assignment of these patients to groups was not randomized; however, patients in the two groups were matched for age and body mass index. Patients in the diet group were given a standard diet of 8400 kJ/day for 1 week (control period), followed by a low-energy diet of 3360 kJ/day for 3 weeks. Physical activity was kept constant, and dietary sodium intake was maintained at 120 mmol/day throughout the study procedure. Patients in the troglitazone group were treated with troglitazone (200 mg twice daily) for 8 weeks after a control period of 2 weeks. The duration of troglitazone treatment was determined to produce comparable improvement in insulin sensitivity in our preliminary study. Neither food intake nor physical activity was restricted in this group. Measurements of body weight, BP, serum UA, and a 75-g oral glucose tolerance test were carried out at the end of the control and intervention periods in both groups.

**Measurements**

Casual BP was measured twice with a standard mercury sphygmomanometer and a stethoscope. Blood glucose, and serum UA, were determined with an autoanalyzer (TBA-80M, Toshiba, Tokyo, Japan). Plasma insulin was measured by radioimmunoassay. Insulin resistance index was calculated from the following formula:

$$\text{HOMA-R} = \frac{\text{Fasting plasma insulin} (\mu U/L) \times \text{Fasting plasma glucose} (\text{mg/dL})}{22.5}$$

**Statistics**

Values are expressed as means $\pm$ SEM. Student $t$ test for paired and unpaired observations were used for comparison of two groups of data. $P < 0.05$ was considered statistically significant. Analyses were performed using Stat View software (Abacus Concepts Inc., Berkeley, CA).

**Results**

The baseline characteristics of the groups treated by diet and with troglitazone are shown in Table 1. There were no significant differences in serum UA, insulin resistance index (HOMA-R), or other laboratory parameters between the two groups at baseline. After 3 weeks of diet and troglitazone treatment, serum UA concentration and insulin sensitivity were decreased significantly in both groups. Troglitazone was found to be more effective than diet alone in reducing serum UA concentration and improving insulin sensitivity (Table 1).
significant differences between the two groups with respect to age, body weight, body mass index, casual BP, serum UA level, fasting blood glucose, plasma insulin, and HOMA-R. Average values for fasting and 120 min post-glucose insulin and HOMA-R in the study individuals were markedly higher than those in nonobese, nondiabetic and normotensive individuals studied in our institute (normal fasting insulin: average, 6.6 mU/L; range, 4.0 to 9.2 mU/L; average 120-min insulin: 38.4 mU/L; average HOMA-R, 1.53).

Table 1 also shows the effects of the low-energy diet and troglitazone treatment on body weight, BP, metabolic parameters, and insulin sensitivity. Body weight and BP significantly decreased in the diet group, but not in the troglitazone group. The levels of blood glucose, plasma insulin, and the HOMA-R decreased similarly in both groups. Serum UA concentrations also decreased significantly in both groups (Table 1, Fig. 1). The decrease in serum UA tended to be greater in the troglitazone group than in the diet group ($P = .07$).

![FIG. 1. Serum uric acid before (pre) and after (post) treatment with low-energy diet and troglitazone.](image)

**Discussion**

In the present study, the level of serum UA decreased significantly with either weight reduction or troglitazone in overweight hypertensive patients. These treatments similarly lowered plasma insulin and improved insulin sensitivity, although body weight and BP decreased with weight reduction but not with troglitazone. The present results strongly suggest that insulin resistance or hyperinsulinemia plays an important role in hyperuricemia in obesity-related hypertension.

Weight reduction and troglitazone may have different mechanisms to ameliorate insulin resistance. The adipocytes, especially in visceral fat, not only serve as the site of triglyceride storage but also secrete a number of biologically active substances such as free fatty acid, tumor necrosis factor-$\alpha$, leptin, and plasminogen activator inhibitor-1. It was suggested that free fatty acid decreases glucose usage in both skeletal muscle and peripheral tissue, and then induces insulin resistance. Tumor necrosis factor-$\alpha$ also leads to insulin resistance by restoring both protein levels and insulin-stimulated tyrosine phosphorylation of insulin receptor and insulin receptor substrate-1 on the serine residues. Therefore, the volume reduction of adipose tissue by low-energy diet therapy is suggested to lead to the amelioration of insulin resistance. Furthermore, the downregulation of insulin receptor would induce insulin resistance in obese subjects.

Taken together, the reason for amelioration of insulin resistance by weight reduction therapy might be due to improvements in insulin signal transduction and upregulation of insulin receptor in various tissues. In contrast, troglitazone ameliorates insulin resistance, by enhancing target tissue sensitivity to insulin owing to binding with a nuclear receptor, peroxisome proliferator-activated receptor-$\gamma$, which is particularly abundant in fat cells as its high-affinity ligand. Okuno et al recently reported in obese Zucker rats that troglitazone could increase the number of small adipocytes and loose large adipocytes by apoptosis in white adipose tissues without affecting the total mass of adipose tissue, presumably by way of through peroxisome proliferator-activated receptor-$\gamma$. These changes in fat tissue characteristics might induce improvement in insulin resistance.

In the present study, serum UA was significantly reduced by the improvement in insulin resistance induced by treatments with both low-energy diet and troglitazone. The effect of weight reduction in the serum UA level appeared to be consistent. Although there have been only a few
studies examining the effect of insulin-sensitizing agents on UA metabolism, Iwatani et al\(^9\) reported that troglitazone decreased the serum UA level in type 2 diabetic patients. However, Sironi et al\(^30\) observed no significant alterations in serum UA after troglitazone treatment in diabetic patients. The reason for the discrepancy is not clear, but is presumably due to differences in the dosage of troglitazone, because Sironi and colleagues used half the dose of troglitazone compared with the present study and the one by Iwatani and associates.

The mechanism of hyperuricemia in patients with obesity has not been fully elucidated. Serum UA level is determined from the balance between its production and urinary excretion. Several investigators have shown that the serum UA level is associated with insulin resistance.\(^7,11,31\) It is suggested that hyperuricemia in obese patients is mainly attributed to an impaired renal clearance of UA due to hyperinsulinemia related to insulin resistance.\(^6,7\) However, the pathogenesis of hyperuricemia in visceral fat obesity may be related to both low urinary UA excretion and overproduction of UA. Regarding the mechanism of overproduction of UA related to insulin resistance, Matsuura et al\(^7\) reported that fatty acid synthesis in the liver may be linked to de novo purine synthesis and accelerations in UA production. Troglitazone could also have some effects on UA production because Iwatani et al\(^9\) observed no changes in urinary excretion of UA or UA clearance, despite the reduction in serum UA in patients with type 2 diabetes after treatment with troglitazone. Therefore, the amelioration of insulin resistance by low-energy diet therapy or troglitazone might influence UA production.

In the present study, the reduction in serum UA tended to be greater in the troglitazone group than in the diet group. However, it remains unclear whether the mechanism of UA reduction by troglitazone is by way of peroxisome proliferator-activated receptor-\(\gamma\) and also either decreasing overproduction of UA or facilitating excretion of UA. Because multiple mechanisms may contribute to the pathogenetic roles of troglitazone, further studies are necessary to clarify the mechanism of UA metabolism induced by troglitazone.

In conclusion, the amelioration of hyperinsulinemia and insulin resistance by a low-energy diet or troglitazone decreased serum UA levels significantly in overweight hypertensive patients. The effect of the improvement of insulin resistance appears to be independent of changes in body weight or BP.

References


