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PRELIMINARY REPORT

Relationships Between Apolipoprotein(a) Phenotype and Increase of Lipoprotein(a) by Troglitazone

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Troglitazone is a new oral hypoglycemic agent that reduces insulin resistance in non–insulin-dependent diabetes mellitus (NIDDM). However, this agent increases serum lipoprotein(a) [Lp(a)], which is known as an atherogenic lipoprotein. The relationships between the response of Lp(a) to troglitazone and the apolipoprotein(a) [apo(a)] phenotype were investigated in this study. Nineteen NIDDM patients were treated with troglitazone for 4 weeks. Lp(a) increased significantly from 20.1 ± 16.5 mg/dL to 44.1 ± 31.9 mg/dL ($P < .001$) in all study patients. Lp(a) increased from 25.7 ± 34.2 mg/dL to 50.1 ± 38.7 mg/dL ($P = .03$) in patients with smaller apo(a) phenotypes (S1S4 to S2S4). Lp(a) also increased from 17.5 ± 12.0 mg/dL to 41.3 ± 29.6 mg/dL ($P < .01$) in patients with larger apo(a) phenotypes (S3 to S4). Therefore, the increase of Lp(a) by troglitazone may be independent of the apo(a) phenotype.

TROGLITAZONE, an insulin action enhancer, has been reported to improve hyperglycemia, hyperinsulinemia, and hypertriglyceridemia in patients with non–insulin-dependent diabetes mellitus (NIDDM).[1,2] Recently, we demonstrated that troglitazone increased serum levels of lipoprotein(a) [Lp(a)], a coronary risk factor, in NIDDM patients.[3] Lp(a) contains apolipoprotein(a) [apo(a)]. The variation in the size of apo(a) is genetically determined, and apo(a) size is closely related to the plasma level of Lp(a).[4,5] Klausen et al[6] reported that the increase of Lp(a) by pravastatin is dependent on the apo(a) phenotype, and the increase of Lp(a) is greatest in patients with low–molecular weight apo(a) phenotypes.[6] We performed this study to investigate whether the increase of Lp(a) by troglitazone is related to the apo(a) phenotype.

SUBJECTS AND METHODS

Nineteen consecutive Japanese NIDDM patients (10 men and nine women aged 36 to 71 years) provided informed consent to participate in the study. The study protocol was approved by the ethics committee of Sasebo Chuou Hospital. Subjects had no disease of the heart, liver, or endocrine system or any severe diabetic complications. They were receiving either diet therapy alone (n = 15) or treatment with a sulfonylurea (SU) drug (n = 4). Of 15 patients treated with diet alone, 12 with fasting plasma glucose (FPG) less than 11.1 mmol/L were treated with troglitazone 400 mg daily. The remaining three patients with FPG higher than 11.1 mmol/L and four patients already treated with a SU drug were treated with a combined therapy of troglitazone and SU.

Clinical characteristics of the patients were as follows: age, 58.9 ± 10.8 years; duration of illness, 6.5 ± 5.2 years; body mass index, 25.5 ± 3.9 kg/m^2; and hemoglobin A_{1c}, 8.8 ± 1.5%. Before and after 4 weeks of treatment, FPG, fasting serum immunoreactive insulin (IRI), lipid, and Lp(a) levels were measured. The Lp(a) level was measured with a turbid immunoassay (Daiichi, Tokyo, Japan). Apo(a) phenotypes were determined by sodium dodecyl sulfate–polyacrylamide gel electrophoresis and immunoblotting with monoclonal apo(a) antibodies. Lp(a) isoforms were designated according to the terminology of Utermann et al.[4,5] F denotes a band with faster mobility than apo B-100, and S1, S2, S3, and S4 denote bands with progressively slower mobility than apo B-100.

Statistical analysis was performed with the Wilcoxon signed-rank test for paired data. Data are presented as the mean ± SD. Differences were considered statistically significant at a P level less than .05.

RESULTS AND DISCUSSION

After 4 weeks of treatment, FPG decreased from 8.9 ± 2.0 mmol/L to 6.3 ± 1.3 mmol/L ($P < .01$). Fasting IRI, a surrogate of insulin resistance,[7] also decreased from 83.8 ± 58.6 pmol/L to 48.4 ± 21.6 pmol/L ($P < .01$). Total, low-density lipoprotein, and high-density lipoprotein cholesterol did not change significantly. Triglycerides decreased significantly from 1.57 ±

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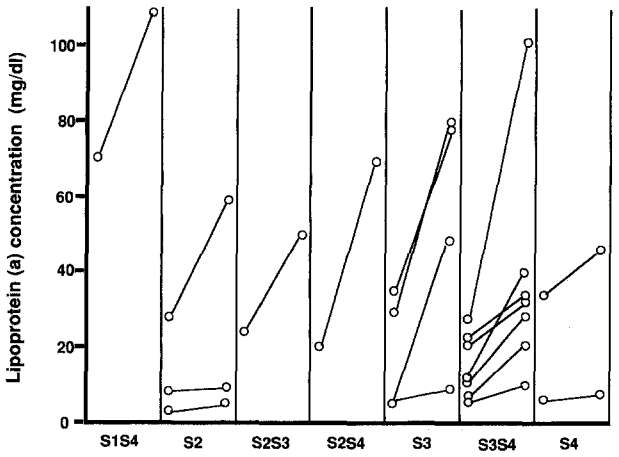

Fig 1. Changes in Lp(a) concentration by troglitazone treatment in patients grouped according to apo(a) phenotype.

0.72 mmol/L to 1.19 ± 0.46 mmol/L ($P < .01$). These results agree with the previous report by Kumar et al.[1]

Lp(a) increased from 20.1 ± 16.5 mg/dL to 44.1 ± 31.9 mg/dL ($P < .01$) in all patients. Changes in the Lp(a) concentration in patients grouped according to apo(a) phenotype are illustrated in Fig 1. In contrast to the result obtained with pravastatin,[6] the increase of Lp(a) by troglitazone was apo(a) phenotype–independent. Lp(a) in patients with smaller apo(a) isoforms (S1S4 to S2S4) increased from 25.7 ± 24.2 mg/dL to 50.1 ± 38.7 mg/dL ($P = .03$). Lp(a) levels in patients with larger apo(a) isoforms (S3 to S4) also increased from 17.5 ± 12.0 mg/dL to 41.4 ± 29.6 mg/dL ($P < .01$). The low response in the increase of Lp(a) by troglitazone was observed in both smaller and larger apo(a) isoforms (S2, S3, S3S4, and S4). Thus, apo(a) polymorphism could not predict the increase of Lp(a) by troglitazone. Lp(a) concentrations greater than 25 mg/dL were associated with a twofold or threefold increase in the odds ratio for coronary heart disease.[8,9] Lp(a) levels during troglitazone treatment were higher than 25 mg/dL in all 10 patients with pretreatment Lp(a) levels over 20 mg/dL. The mean Lp(a) level in those patients increased significantly from 31.7 ± 14.9 mg/dL to 65.9 ± 26.6 mg/dL ($P < .01$) during troglitazone treatment. In contrast, Lp(a) levels during troglitazone were higher than 25 mg/dL in only three of nine patients with pretreatment Lp(a) levels less than 20 mg/dL. The mean Lp(a) level increased slightly but significantly from 7.2 ± 3.3 mg/dL to 19.9 ± 15.5 mg/dL ($P < .01$) during troglitazone treatment. Using the χ^2 test, a pretreatment Lp(a) level above 20 mg/dL predicted the significant increase in Lp(a) above 25 mg/dL during troglitazone treatment ($P < .01$).

Our study has some limitations. First, it is not known whether the increase of Lp(a) by troglitazone is related to atherogenesis in diabetic patients. Second, the association between Lp(a) above 25 mg/dL and coronary heart disease was reported mainly in caucasians. These associations are still unclear in the Japanese population. Third and most important, the number of patients in this study was too small to reach a conclusion. Thus, to confirm the hypothesis that the increase of Lp(a) by troglitazone is independent of apo(a) phenotype, further studies are needed in a larger number of patients.

REFERENCES

1. Kumar S, Boulton AJM, Beck-Nielsen H, et al: Troglitazone, an insulin action enhancer, improves metabolic control in NIDDM patients. Diabetologia 39:701-709, 1996

2. Petrie J, Small M, Connell J: "Glitazones," a prospect for non–insulin-dependent diabetes. Lancet 349:70-71, 1997

3. Matsumoto K, Miyake S, Yano M, et al: Increase of lipoprotein(a) with troglitazone. Lancet 350:1748-1749, 1997

4. Utermann G, Menzel HJ, Kraft HG, et al: Glycoprotein phenotypes. Inheritance and relation to Lp(a) lipoprotein concentration in plasma. J Clin Invest 80:458-465, 1987

5. Utermann G, Kraft HG, Menzel HJ, et al: Genetics of the quantitative Lp(a) trait. I. Relation of Lp(a) glycoprotein phenotypes to Lp(a) lipoprotein concentration in plasma. Hum Genet 78:41-46, 1988

6. Klausen C, Gerdes LU, Meinertz H, et al: Apolipoprotein(a) polymorphism predicts the increase of Lp(a) by pravastatin in patients with familial hypercholesterolemia treated with bile acid sequestration. Eur J Clin Invest 23:240-245, 1993

7. Godsland IF, Stevenson JC: Insulin resistance: Syndrome or tendency? Lancet 346:100-103, 1995

8. Schaeffer EJ, Fava SL, Jenner JL, et al: Lipoprotein(a) levels and risk of coronary heart disease in men. The Lipid Research Clinics Coronary Primary Prevention Trial. JAMA 271:999-1003, 1994

9. Chapman MJ, Huby T, Nigon F, et al: Lipoprotein(a): Implication in atherosclerosis. Atherosclerosis 110:S69-S75, 1994 (suppl)