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POTENT INHIBITORY EFFECT OF TROGLITAZONE ON CAROTID ARTERIAL WALL THICKNESS IN TYPE 2 DIABETES

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ABSTRACT

There is increasing evidence that insulin resistance may be causally related to atherosclerosis. The measurement of common carotid arterial intimal and medial complex thickness (IMT) by B-mode ultrasound technique has been recognized as a powerful and non-invasive method to evaluate early atherosclerotic lesions. We investigated the effect of treatment with troglitazone, an insulin sensitizer, on IMT in a total of 135 Japanese subjects with type 2 diabetes. Troglitazone (400 mg daily) was administered for 6 months in 57 patients. Compared to control group (n=78), the group given troglitazone showed a significant decrease in IMT as early as 3 months after the administration (IMT change: -0.080[SE 0.016] mm *vs.* control 0.027[SE 0.007] mm, $P<0.001$). The decrease in IMT was also found after 6 months, although further decrease was not observed. Both HbA1c and postprandial serum triglycerides were decreased after troglitazone, but there was no statistically significant relation between a decrease in IMT and those in HbA1c or postprandial triglycerides. These findings indicate that troglitazone has a potent inhibitory effect on progression of early atherosclerotic lesions probably through the decreased insulin resistance in type 2 diabetes.

The measurement of common carotid arterial intimal and medial complex thickness (IMT) by B-mode ultrasound technique has been recognized as a powerful and non-invasive method to evaluate early atherosclerotic lesions (1, 2, 3). We have recently reported that both urinary C-peptide and insulin dosage show a significantly positive correlation with IMT in type 2 diabetes (4). We have also demonstrated that urinary C-peptide was positively related to plaque formation in type 2 diabetes (3). Furthermore, we have reported a case of pseudoacromegaly associated with hyperinsulinemia, which showed a marked increase in IMT (5). Folsom *et al* indicated that fasting insulin level was associated with IMT in nondiabetic subjects (6). These findings prompted us to postulate that both endogenous and exogenous insulin may be positively related to IMT (4). However, it remains to be elucidated whether this relationship between insulin and IMT may reflect the atherogenic action of insulin, as earlier proposed (7), or may be based on the association between insulin resistance and atherosclerosis, as recently stressed (8). It is expected that troglitazone, an insulin sensitizer (9), may have a beneficial effect on IMT through a decline in hyperinsulinemia associated with the decreased insulin resistance. Very recently we have reported, in a preliminary form, that troglitazone treatment for 3 months caused a significant decrease in IMT of type 2 diabetes (4). In the present study we have extended the study to investigate the effect of troglitazone on IMT in 135 subjects with type 2 diabetes for 6 months. We also examined the relationship between change of IMT and those of Hb1c, total cholesterol, HDL cholesterol, or postprandial triglyceride levels.

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SUBJECTS AND METHODS

Subjects & Measurements

A total of 135 Japanese subjects with type 2 diabetes (88 males and 47 females, age 61.8[SE 0.9] yrs) was included. All of them gave informed consent. The subjects were divided into two groups: troglitazone group and control. In troglitazone group (n=57), troglitazone (400 mg daily) was administered for 6 months. Before troglitazone treatment the patients had been treated with sulfonylureas (glibenclamide n=53 and gliclazide n=2), or diet alone (n=2). The control subjects were treated with sulfonylureas (glibenclamide n=53 and gliclazide n=18), or diet alone (n=7). Sulfonylureas in the same doses were continued in the both groups during the study.

IMT of common carotid artery was measured with ultrasound high-resolution B-mode ultrasonography (LOGIQ 500, GE Yokogawa Medical Systems Co, Tokyo, Japan) with an electrical linear transducer (midfrequnecy 7.5 MHz). IMT value was calculated as an average of the three determinations, as previously reported (2). Localized thickness more than 2.0 mm was excluded from the analysis as plaque (1, 2, 3). IMT measurement was performed before, 3 and 6 months after the administration of troglitazone.

Blood HbA1c, total cholesterol, or triglyceride levels were measured according to the standard procedures. Postprandial triglyceride levels were examined 2hrs after the conventional breakfast.

Statistical analysis

The difference of changes in IMT, HbA1c, total cholesterol, HDL choletserol, postprandial triglycerides in troglitazone and control groups were examined by Student's *t*-test and ANOVA. The relationship between a decrease in IMT and a change in HbA1c, total cholesterol, HDL choletsterol, and postprandial triglycerides were investigated with multiple regression analysis.

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RESULTS

There was no significant difference between the two groups in age, sex ratio, body mass index, blood glucose, HbA1c, total cholesterol, triglyceride or blood pressure.

The troglitazone group showed a significant decrease in IMT after 3 months compared to the control group (IMT change: -0.080 [SE 0.016] mm *vs.* control 0.027[SE 0.007] mm, $P<0.001$). The significant decrease in IMT was also observed after 6 months, although further decrease was not found compared to that after 3 months (IMT change: -0.080[SE 0.015] mm *vs.* control 0.030[SE 0.004] mm, $P<0.001$) as shown in Fig 1). In troglitazone group, both HbA1c and postprandial triglyceride levels were significantly decreased (HbA1c change: -0.449[SE 0.134] % *vs.* control -0.121[SE 0.107] %, $P<0.05$; postprandial triglyceride change:-37.2[SE 7.7] ng/ml *vs.* control 10.8[SE 8.6] ng/ml, $P<0.0001$), whereas there was no significant change in total cholesterol, HDL cholesterol, or blood pressure. Multiple regression analysis indicated that there was no statistically significant relation between a decrease in IMT and those in HbA1c or postprandial serum triglycerides.

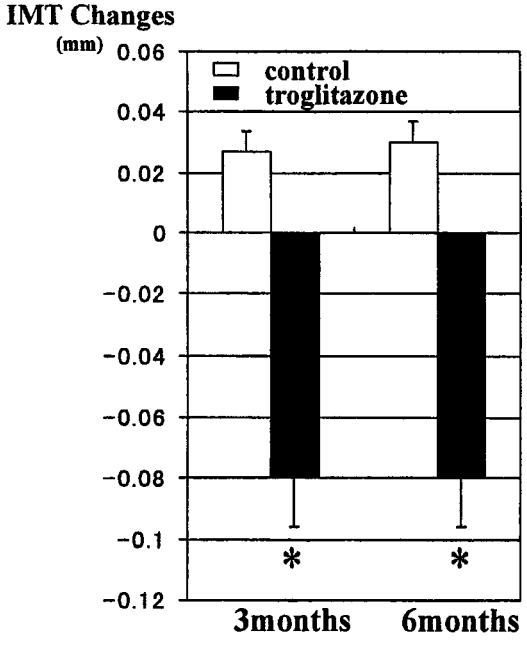

Fig 1 Effect of troglitazone (400 mg/day, 6 months) on IMT in subjects with type 2 diabetes. Mean[SE] changes of IMT (3 and 6 months) are shown. *$P<0.001$ *vs.* control.

DISCUSSION

Although it has been reported that troglitazone markedly inhibits vascular smooth muscle cell growth and intimal hyperplasia in the rat (10), there has been no report about the effect of troglitazone on atherosclerosis in humans, until we have recently reported its inhibitory effect on IMT in a preliminary form (4). The present study confirmed a potent inhibitory effect of troglitazone on IMT in type 2 diabetes. The decrease in IMT reached statistical significance as early as 3 months after the administration of troglitazone. The decrease in IMT was also observed after 6 months, indicating that the inhibitory effect of troglitazone on IMT was not transient, although further decrease was not found. The magnitude of this decrease in IMT after troglitazone (-0.080 mm/3 months) was more profound than those reported with pravastain, a 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor [0.010 mm/yr *vs.* control 0.029 mm/yr) (11) or -0.0043 mm/yr *vs.* control 0.009 mm/yr (12)].

Troglitazone has been reported to have other effects than improving glycemic control, such as lowering blood pressure (13), or decreasing fasting triglycerides (9, 14). In the present study both HbA1c and postprandial triglyceride levels were decreased after troglitazone, although there was no relation between a decrease in IMT and a change in HbA1c or postprandial triglycerides. Postprandial triglyceride level has been indicated to be associated with atherosclerosis (15). It is likely that the effect of troglitazone on IMT is related to a decline in hyperinsulinemia associated with the decreased insulin resistance and that a lack of association between IMT and HbA1c in a multivariate analysis may be explained by the small sample size.

Taken together, it is plausible that the relationship between insulin and IMT, which we and other investigators have reported (3, 4, 6), does not reflect the atherogenic action of insulin (7), and that it is based on the association between insulin resistance and atherosclerosis (8). Furthermore, troglitazone is considered to prevent atherosclerotic progression through the decreased insulin resistance. This explanation is consistent with two recent reports using intravenous glucose test, which have suggested that IMT is negatively related to insulin sensitivity in either nondiabetic or diabetic subjects (16, 17). It is also compatible with the notion that insulin resistance is the underlying defect of atherosclerosis in type 2 diabetes (7). Furthermore, our result may alleviate the concern that insulin treatment in type 2 diabetes could increase the risk of atherosclerosis (18). However, the present study does not contradict a recently proposed hypothesis that insulin has both atherogenic and antiatherogenic actions, the latter of which is selectively inhibited in type 2 diabetes (19): it is possible that troglitazone may suppress solely antiatherogenic action of insulin. However, it cannot be excluded that an antioxidant activity of troglitazone (20) may be involved in its antiatherogenic action.

In summary, the present study suggests a potent inhibitory action of troglitazone on progression of early

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atherosclerotic lesions in type 2 diabetes, although its exact mechanism remains to be elucidated. The prospective trial may be justified to investigate whether troglitazone prevents coronary restenosis after angioplasty in type 2 diabetes, although its possible hepatotoxicity should be taken into consideration.

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