Nateglinide Reduces Carotid Intima-Media Thickening in Type 2 Diabetic Patients Under Good Glycemic Control

Tomoya Mita, Hirotaka Watada, Tomoo Shimizu, Yoshifumi Tamura, Fumihiko Sato, Takahiro Watanabe, Jong Bock Choi, Takahisa Hirose, Yasushi Tanaka, Ryuzo Kawamori

Objective—Postprandial hyperglycemia observed in type 2 diabetes mellitus is a risk factor for atherosclerosis. The aim of this study was to investigate the effect of strict glycemic control by nateglinide on common carotid far wall intima-media thickness in type 2 diabetic patients who were already under good glycemic control.

Methods and Results—We performed an open labeled randomized prospective trial on 78 drug-naïve type 2 diabetic patients whose HbA1c was less than 6.5%. Thirty-eight patients were randomly assigned to receive nateglinide (270 mg/dL) and 40 to control group (no treatment). After 12 months, a significant reduction in HbA1c was observed in the nateglinide group, whereas a significant increase of HbA1c was observed in the untreated group. The carotid intima-media thickness at the end of 1-year follow-up was significantly reduced in the nateglinide group compared with the untreated group (−0.017±0.054 mm/year versus 0.024±0.066 mm/year, P=0.0064). Whereas nateglinide treatment also reduced triglyceride, highly-sensitive C-reactive protein, and E-selectin, multiple regression analysis identified HbA1c as the only significant independent determinant of the change in carotid intima-media thickness.

Conclusion—In type 2 diabetic patients with good glycemic control, further strict glycemic control by nateglinide results in regression of carotid intima-media thickness. (Arterioscler Thromb Vasc Biol. 2007;27:000-000.)

Key Words: intima-media thickness ■ atherosclerosis ■ strict glycemic control ■ postprandial hyperglycemia ■ type 2 diabetes

Patients with type 2 diabetes mellitus are at high risk for developing cardiovascular diseases, which are also the most frequent cause of death in these patients. One of the main goals of diabetes management is to reduce the onset of cardiovascular diseases. However, there is no clear evidence that the risk of development of cardiovascular disease can be reduced by glycemic control in type 2 diabetes mellitus. The UK Prospective Diabetes Study (UKPDS), a large-scale prospective study of newly diagnosed type 2 diabetic patients, showed that every 1% decrease in HbA1c was associated with reduced incidences of myocardial infarction and stroke by 14% and 11%, respectively.1 However, the UKPDS failed to show significant reductions in the incidences of stroke and myocardial infarction in the intensive glycemic control group compared with the conventional glycemic control group over 15 years.2 In that study, the intensive control group only achieved HbA1c level 7.0%, thus a much stricter glycemic control may be required to prevent the onset of cardiovascular disease in diabetic patients. In addition, because recent epidemiological studies suggested that postprandial hyperglycemia is an independent risk factor for cardiovascular disease beyond and more powerful than fasting hyperglycemia; in glycemic control, much attention should be paid on the control of postprandial hyperglycemia.

The American Diabetes Association has proposed that the target HbA1c value in the management of type 2 diabetes should be less than 7.0%.4 In addition, according to Japan Diabetes Society, HbA1c value less than 6.5% is considered as a marker of good glycemic control.5 Recent data suggest that even in patients with HbA1c level less than 7.0%, the HbA1c level correlates negatively with the progression of atherosclerosis.6 Whereas our recent retrospective data demonstrated that further improvement of glycemic control in type 2 diabetes with HbA1c less than 6.5% may prevent the increase in intima-media thickness (IMT).7 there is no information on whether further reduction of HbA1c in type 2 diabetes with good glycemic control can prevent the progression of atherosclerosis.

Among the various hypoglycemic agents, there are only a few data on the efficacy of insulin secretagogues in preventing the progression of atherosclerosis.8 Nateglinide is a D-phenylalanine derivative and an insulinotropic agent with a rapid onset and short duration of action.9-11 It is used as a mealtime insulin secretagogue in the treatment of type 2 diabetes. By reducing the postprandial blood glucose peak, nateglinide lowers the 24-hour blood glucose profile and reduces the HbA1c level. Based on its mechanism of reducing blood glucose level, nateglinide therapy is associated with a

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low risk of hypoglycemia even in patients with good glycemic control.\(^{12}\)

In the present study, we elucidated the effect of strict glycemic control using nateglinide on the extent of common carotid far wall IMT in drug-naive type 2 diabetic patients who had already achieved HbA1c below 6.5%.

**Methods**

**Screening Study**

We screened type 2 diabetic patients who regularly attended Juntendo University Hospital, Junteikai hospital, and Chiba Tokushukai hospital, between January 2005 and August 2005. Among them, we selected those with the following criteria: (1) diagnosis of type 2 diabetes with > 1 year but < 10 years, (2) 40 to 75 years of age, (3) HbA1c of < 6.5%, (4) stable glycemic control with HbA1c variation of < 0.5% during the preceding 6 months, and (5) negative history of taking any antidiabetic agents. The diagnosis of type 2 diabetes was based on the current criteria set out by the World Health Organization. All patients were Japanese. The 105 diabetic patients enrolled in this study were compared with 36 nondiabetic age- and gender-matched healthy volunteers. The inclusion criteria for healthy volunteers were the absence of: (1) diabetes, (2) impaired glucose tolerance (IGT) assessed by an oral glucose tolerance test when their HbA1c was ≥ 5.4%, and (3) overt cardiovascular disease.

**Randomized Trial**

At the screening visit, patients with diabetic microangiopathy, severe renal or hepatic disease, overt cardiovascular disease, or malignancy were excluded. The remaining patients were asked to participate in this study. The hospital ethics committee approved the study protocol, and informed consent was obtained from each subject. Among the 105 drug naive type 2 diabetic patients, 78 patients were assigned to participate in an open labeled randomized trial. The patients were randomly divided into 2 groups matched for age, gender, and BMI after the screen through the use of a computer-generated random number sequence. Patients of the nateglinide group (n = 38) received nateglinide at a dose of 270 mg/d (90 mg TID) whereas the nontreated control group (n = 40) did not receive any antidiabetic agents during the study period. All the patients had been already educated about diet and exercise therapy according to treatment guide for diabetes 2007.\(^{4}\) The compliance of diet and exercise had been checked at regular visit. No restriction was imposed on patients taking other oral drugs such as blood pressure- and lipid-lowering drugs, and the dosage of the drugs was not changed during the study. None of the patients was being treated with antithrombotic agents (Figure 1).

**Assessment of IMT of the Common Carotid Artery**

Ultrasonography of the carotid arteries was performed using an echotomographic system (EUB-555; Hitachi Medico) with a linear transducer (midfrequency range of 7.5 to 10 MHz). Scanning of the extracranial carotid arteries in the neck was performed in 3 different longitudinal projections (anterior-oblique, lateral, and posterior-oblique) and in the transverse projection, as reported previously.\(^{13}\) This allowed the common carotid artery to be scanned bilaterally. All obtained images were photographed. The carotid IMT was defined as the distance between lumen/intima borderline and media/adventitia borderline on the far wall. In each longitudinal projection, the site of the greatest IMT thickness was detected by scanning along the vessel from the common carotid artery which defined the area from 10 mm to 20 mm below the flow divider. Three measurements of the IMT were made; 1 at the site of greatest thickness and 2 at other points (1 cm proximal and 1 cm distal to the site) on the anterior, lateral, and posterior projections of the far wall for each patient and always in plaque-free segments. These measurements were performed on both sides. The average value of 6 highest IMT measurements (3 from the left side and 3 from the right side) was used as the mean common carotid artery IMT for each patient. All scans were conducted by a single physician while all IMT measurements were performed by another physician, and both were blinded to the clinical information. We have previously demonstrated good intraday and interday reproducibility of our examination.\(^{1,14}\)

The annual change in IMT was calculated by using the following equation: annual change of IMT = (final IMT – initial IMT)/observation period and was used as a primary end point.

**Data Acquisition**

At screening visit, baseline laboratory data, blood pressure, body mass index (BMI), and IMT were determined for each subject. BMI was calculated as weight in kilograms divided by the square of height in meters. Blood samples were obtained between 8 and 10 AM after overnight fast for the measurement of blood glucose and lipids by standard laboratory techniques. Plasma insulin concentrations were determined by radioimmunoassay. Insulin resistance was determined by homeostasis model assessment of insulin resistance (HOMA-IR) calculated as the product of fasting plasma insulin (\(\mu\text{U/mL}\))×fasting plasma glucose (mmol/L)/22.5. Highly-sensitive C-reactive protein (hs-CRP), soluble intercellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1 (VCAM-1), and E-selectin were analyzed by a private laboratory (SRL Laboratory, Tokyo). Briefly, hs-CRP was measured by particle-enhanced immunonephelometry using a commercially available kit (Dade Behring Inc), and ICAM-1, VCAM-1, and E-selectin were measured by enzyme-linked immunosorbent assay (ELISA) using commercially available kits (R & D Systems). Blood pressure was measured twice with a mercury sphygmonanometer. Each patient was reviewed at least every 3 months, with their general health, compliance with medications, laboratory data, blood pressure, and diet and exercise status were checked at each visit. At approximately 1 year after enrollment, laboratory data, blood pressure, BMI, and IMT were again determined for each subject. The average laboratory values for the observation period were calculated from the data obtained at each visit. Hypertension was defined >140/90 mm Hg or taking an antihypertensive agents. Dyslipidemia was defined by fasting serum total cholesterol >5.7 mmol/L, triglyceride >1.7 mmol/L, HDL cholesterol <0.9 mmol/L, low-density lipoprotein cholesterol >3.5 mmol/L, and estimated glomerular filtration rate <60 mL/min/1.73 m².
Results

Table 1 summarizes the characteristics of the patients with type 2 diabetic and control subjects enrolled in this study. Because we enrolled only patients with good glycemic control, their mean HbA1c was 6.08%. For diabetic patients, the percentage of users of calcium channel blockers, angiotensin-converting enzyme inhibitors/angiotensin II type 1 receptor blockers, and statins were 11.4%, 12.4%, and 7.6%, respectively, while control subjects did not take any of these medications. With regard to metabolic parameters, fasting blood glucose, fasting plasma insulin, HOMA-IR, HbA1c, and triglyceride levels in the diabetics were significantly higher and HDL was significantly lower than the control subjects. With regard to markers of inflammation and endothelial injury, hs-CRP and E-selectin levels were significantly higher in the diabetics than healthy group.

The carotid IMT of diabetic patients was thicker than that of the control group. Univariate analysis including the combined data of patients and healthy subjects identified HbA1c (r = 0.292, P = 0.0004), ICAM-1 (r = 0.148, P = 0.003), and age (r = 0.282, P = 0.0007) as significantly associated with carotid IMT. A multivariate analysis including carotid IMT as the dependent variable and candidate risk factors (age, gender, BMI, smoking, blood pressure, glucose and lipid parameters, hs-CRP, ICAM-1 VCAM-1, and E-selectin) as independent variables, identified HbA1c as the only significant independent determinant of carotid IMT and explained 23% of the variability.

Among the 105 enrolled antidiabetic drug naïve type 2 diabetic patients, 78 were randomly divided into 2 groups matched for age, gender, and BMI (nontreated control group: n = 40, nateglinide group; n = 38). Of these, 70 patients (36 of the nontreated control group and 34 of the nateglinide group) completed the study (Figure 1).

The baseline characteristics investigated in this study were similar for both groups (Table 2). At the end of the follow-up period, we compared each end point value and the change from baseline in both groups (Tables 2 and 3). With regard to the changes between baseline and end point of each metabolic parameter, a significant decrease in HbA1c was observed in
Apart from HbA1c and triglyceride, no changes were noted in the study in the nateglinide group compared with baseline. Serum triglyceride level was significantly lower at the end of the follow-up period. The annual change in IMT was observed in the nateglinide group, whereas a significant increase in IMT was observed in the control group at the end of the follow-up period. The annual change in IMT was significantly different between the 2 groups (control group, 0.024±0.066 mm/year versus nateglinide group, −0.017±0.054 mm/year; P=0.0064). On the other hand, significant changes of vascular lumen diameter of the carotid artery from baseline to end point were not observed in both groups (data not shown). These data suggested that the carotid IMT changes reflected the atherosclerosis not just the changes in arterial diameter with diabetic treatment. In the next step, we performed a multivariate analysis to investigate the relationship between the annual change in carotid IMT as the dependent variable with changes in blood pressure, glucose and lipid parameters, hs-CRP, ICAM-1, and E-selectin as well as candidate risk factors such as age, gender, BMI, and smoking. Only HbA1c was identified as a significant independent determinant of changes in carotid IMT and explained 12.2% of the variability.

No symptomatic hypoglycemic events were recorded in the nateglinide group, whereas a significant increase in this parameter was observed in the control group. The change in HbA1c level between 2 groups was significantly different. In addition, HbA1c had been significantly decreased only in the nateglinide group since 6 months after the commencement of the treatment, whereas fasting glucose did not show significant changes in both groups during follow-up period (Figure 2). Serum triglyceride level was significantly lower at the end of the study in the nateglinide group compared with baseline. Apart from HbA1c and triglyceride, no changes were noted in the other metabolic parameters in the same group and between 2 groups. Significant decreases in hs-CRP and E-selectin levels were observed in the nateglinide group, and a significant increase in VCAM-1 was observed in the nontreated control group at the end of the follow-up period. The change in VCAM-1 between the 2 groups was significant.

With regard to carotid IMT, a modest decrease in IMT was observed in the nateglinide group, whereas a significant increase in IMT was observed in the control group at the end of the follow-up period. The annual change in IMT was significantly different between the 2 groups (control group, 0.024±0.066 mm/year versus nateglinide group, −0.017±0.054 mm/year; P=0.0064). On the other hand, significant changes of vascular lumen diameter of the carotid artery from baseline to end point were not observed in both groups (data not shown). These data suggested that the carotid IMT changes reflected the atherosclerosis not just the changes in arterial diameter with diabetic treatment. In the next step, we performed a multivariate analysis to investigate the relationship between the annual change in carotid IMT as the dependent variable with changes in blood pressure, glucose and lipid parameters, hs-CRP, ICAM-1, VCAM-1, and E-selectin as well as candidate risk factors such as age, gender, BMI, and smoking. Only HbA1c was identified as a significant independent determinant of changes in carotid IMT and explained 12.2% of the variability.

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pneumonia and cerebral infarction. For the nateglinide group, 2 were lost to follow-up, 1 withdrew because of mild liver dysfunction after nateglinide treatment, and 1 withdrew because of poor compliance.

Discussion

In this study, we demonstrated an increase in carotid IMT even in antidiabetic drug-naïve type 2 diabetic patients with good glycemic control, compared with age-matched control subjects. In contrast, treatment of such patients with nateglinide attenuated the progression of carotid IMT and decreased the levels of markers of inflammation and endothelial dysfunction. Significantly, a fall in HbA1c was noted in nateglinide-treated patients who showed reduction in IMT. Our results suggest that further decrease in HbA1c should be considered to prevent the progression of atherosclerosis in type 2 diabetes mellitus with good glycemic control.

We demonstrated previously carotid intima-media thickening of subjects with impaired glucose tolerance (IGT) or early-state type 2 diabetic under good glycemic control, compared with age- and gender-matched healthy population. A recent study also showed carotid intima-media thickening in newly diagnosed diabetic patients compared with healthy control subjects. In agreement with these studies, we demonstrated here a significant and advanced carotid intima-media thickening in well-controlled type 2 diabetic patients, compared with age- and gender-matched healthy population. In addition, the results of multiple regression analysis showed that carotid intima-media thickening was only significantly influenced by HbA1c. The relative contribution of postprandial glucose excursions to overall diurnal hyperglycemia is predominant in fairly controlled diabetics, whereas the contribution of fasting hyperglycemia increases gradually with worsening of diabetes. Thus, considering the study subjects, our results support the importance of postprandial hyperglycemia on the progression of atherosclerosis.

Table 3. Changes From Baseline in the Nontreated Control and Nateglinide Group

<table>
<thead>
<tr>
<th></th>
<th>Nontreated Group (n=36)</th>
<th>Nateglinide Group (n=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index, kg/m²</td>
<td>−0.02±1.06</td>
<td>−0.05±0.61</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>0.9±9.7</td>
<td>1.1±11.8</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>−0.3±6.1</td>
<td>0.4±9.1</td>
</tr>
<tr>
<td>Immunoreactive insulin, µU/ml</td>
<td>0.05±2.64</td>
<td>−1.06±3.05</td>
</tr>
<tr>
<td>Fasting blood glucose, mmol/L</td>
<td>0.07±0.99</td>
<td>−0.27±1.07</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>0.05±0.94</td>
<td>−0.44±1.16</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>0.12±0.32</td>
<td>−0.17±0.27</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>0.06±0.66</td>
<td>−0.07±0.45</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>0.02±0.17</td>
<td>0.04±0.15</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>0.02±0.47</td>
<td>−0.03±0.36</td>
</tr>
<tr>
<td>Serum triglycerides, mmol/L</td>
<td>0.05±0.55</td>
<td>−0.13±0.35</td>
</tr>
<tr>
<td>(ln) hs-CRP, ln&lt;mg/L&gt;</td>
<td>−0.04±0.29</td>
<td>−0.159±0.27</td>
</tr>
<tr>
<td>ICAM-1, ng/ml</td>
<td>0.8±28.1</td>
<td>−7.3±38.4</td>
</tr>
<tr>
<td>VCAM-1, ng/ml</td>
<td>119.9±191.2</td>
<td>9.6±191.9</td>
</tr>
<tr>
<td>E-selectin, ng/ml</td>
<td>−3.8±10.9</td>
<td>−5.2±12.1</td>
</tr>
<tr>
<td>Intima-media thickness, mm</td>
<td>0.024±0.066</td>
<td>−0.017±0.054</td>
</tr>
</tbody>
</table>

Data are mean±SD. P values are for differences in changes of variables in each group, and determined by the unpaired t test or Mann-Whitney test (#). For abbreviations, see Tables 1 and 2.
In this study, we investigated the effect of further strict glycemic control on the progression of atherosclerosis in antidiabetic drug-naïve type 2 diabetic patients with good glycemic control. We used nateglinide, a rapid and short-acting insulin secretagogue, based on the conclusion that postprandial hyperglycemia is the main contribution to overall diurnal hyperglycemia in this study subjects. The results showed that the progression of carotid IMT could be attenuated by treatment with nateglinide. Furthermore, HbA1c was solely identified as a significant independent determinant of changes in carotid IMT in the nateglinide-treated patients. Thus, our data emphasize the importance of strict glycemic control, including postprandial state, in the prevention of progression of atherosclerosis in diabetic patients.

According to the previous data, other oral hypoglycemic agencies, α-glucosidase inhibitor20 and TZDs21,22 reduced carotid IMT. However, there are no clear data showing that sulfonylurea agents reduced IMT. In addition, comparing sulfonylurea agents, repaglinide and pioglitazone result in the significant reduction of IMT. These results suggest that the postprandial hyperglycemia which preferentially reduce postprandial hyperglycemia or insulin resistance may reduce IMT level.

In this study, we could not demonstrate the direct effects of postprandial glucose modulation on atherosclerosis because we did not measure postprandial glucose levels under free-living conditions. However, previous studies clearly demonstrated that nateglinide efficiently reduced postprandial hyperglycemia24,25 and postloaded hyperglycemia10,11 in the patients with IGT or diabetes with relatively good glycemic control. In addition, amelioration of postprandial glucose peaks by repaglinide was more effective on the reduction of carotid IMT than amelioration of hyperglycemia by glyburide even though the treatment of both drugs achieved similar level of HbA1c in type 2 diabetic patients. In this study, HbA1c was significantly decreased only in nateglinide group, whereas fasting glucose did not show significant changes in both groups (Figure 2). These results suggest that nateglinide reduces preferably postprandial hyperglycemia. Attenuating the progression of carotid IMT seems to be associated with the reduction of postprandial hyperglycemia.

Postprandial hyperglycemia results in acute endothelial dysfunction, as assessed by flow-mediated vasodilatation and endothelial markers, and also induces inflammation and overproduction of oxidative stress. Recent studies demonstrated that a single administration of rapidly-acting insulin secretagogues or short-acting insulin compounds decreased the postprandial generation of inflammation, oxidative stress, and endothelial dysfunction with a decrease in postprandial hyperglycemia in type 2 diabetic patients. In the present study, we confirmed that basal hs-CRP and E-selection in type 2 diabetes mellitus were higher than the control. In addition, we found that nateglinide treatment reduced hs-CRP and attenuated the increase in VCAM-1. Considering the harmful effect of acute postprandial hyperglycemia, repetitive episodes of postprandial hyperglycemia could result in irreversible injury of endothelial cells. By reducing postprandial hyperglycemia, nateglinide may reduce vascular inflammation and endothelial dysfunction and lessen carotid intima-media thickening.

On the other hand, we could not find the significant reduction of ICAM-1 and VCAM-1 by nateglinide treatment. We do not know the exact reason. ICAM-1 and VCAM-1 in this study population are not higher than control subjects (Table 1). This might be partly because some subjects are taking ARB/ACEs and statins which affect these markers. Thus, our results show that nateglinide does not have enough power to result in the further reduction of these markers within normal range.

Although we emphasized the effect of the reduction of postprandial hyperglycemia, we cannot rule out other effect of nateglinide on carotid IMT regression. Hyperinsulinemia may exert the athrogenic effects, however it is still unclear whether hyperinsulinemia could promote early-stage atherosclerosis. Previously we demonstrated that nateglinide reduces postprandial hyperglycemia with the augmentation of rapid intrinsic insulin secretion and the reduction of total insulin secretion in obese type 2 diabetics. Thus, the reduction of hyperinsulinemia may be another potential mechanism of preventing of atherosclerosis.

Our study has certain limitations. The number of study subjects was small, and the study was conducted by open label method. However, the study was randomized in design and the carotid IMT was measured under concealment of allocation. Thus, the above design should not weaken the significance of the results. In addition, because of the limited follow-up, we could not evaluate the clinical events. However, carotid IMT is an established surrogate marker of cardiovascular disease. The attenuation of progression of IMT by nateglinide may be a useful marker for a decrease in cardiovascular disease. Interestingly, 2 major studies are currently investigating the outcome of antidiabetic treatment on cardiovascular system. The first is the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) study designed to investigate the effect of nateglinide on the prevention of cardiovascular diseases in patients with impaired glucose tolerance. The second, the Japan-Diabetes Interventation Trial (J-DOIT3) study, has already commenced in Japan to evaluate the effect of aggressive intervention including the control of glucose and lipid metabolism and blood pressure on cardiovascular disease in type 2 diabetic patients. These studies may provide further insight into the role of nateglinide and strict glycemic control on the prevention of cardiovascular diseases.

In conclusion, we demonstrated in the present study a gradual worsening of the already thickened intima/media of the carotid arteries in antidiabetic drug-naïve Japanese type 2 diabetic patients who are otherwise under good glycemic control. However, further strict glycemic control including postprandial state with nateglinide attenuated the progression of IMT. Our results suggest that the target glycemic control necessary to suppress the progression of atherosclerosis in type 2 diabetic patients should be near the normal range.

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Disclosures

None.

References


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