Acute Effect of Nateglinide on Insulin Secretion After Meal Tolerance Test

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ABSTRACT

Background: Impaired postprandial early phase insulin secretion may cause postprandial hyperglycemia and hyperlipidemia. To determine the acute effect of nateglinide on postprandial hyperglycemia and early insulin secretion, changes in plasma glucose, insulin and lipid levels were measured during a meal tolerance test in type 2 diabetic patients.

Method: A meal was given to 17 type 2 diabetic patients (age 58.6±10.9 years, BMI 25.1±3.0, HbA1c 6.9±0.9%) with or without 90 mg nateglinide. Blood samples for measurement of blood glucose, insulin, triglyceride and nonesterified fatty acids (FFA) were collected before the meal and at 30-minute intervals for 180 minutes.

Results: After the meal without nateglinide, the plasma glucose level peaked at 60 minutes and remained high at 180 minutes compared to baseline. In the presence of nateglinide, however, the peak occurred at 30 minutes, and the plasma glucose value had returned to baseline at 180 minutes. The postprandial insulin level at 30 minutes was significantly higher after administration of nateglinide (51.2±35.0 vs 34.9±32.2 μU/ml, p<0.05), without any increase in total insulin secretion. The triglyceride level did not significantly increase after the meal. The FFA level significantly decreased after the meal, but there were no significant differences in the rate of decrease with or without nateglinide.

Conclusion: These results suggest that an increase in early insulin secretion induced by nateglinide improves postprandial hyperglycemia.

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KEYWORDS: nateglinide, meal tolerance test, postprandial hyperglycemia, insulin secretion
Postprandial hyperglycemia is associated with an increased risk of atherosclerotic diseases\(^1\)\(^3\), and postprandial glucose excursion poses an independent risk factor for cardiovascular diseases in individuals with impaired glucose tolerance (IGT) and type 2 diabetes\(^4\)\(^5\). The impaired kinetics of early phase insulin secretion contribute to postprandial hyperglycemia\(^6\). The conventional oral hypoglycemic agents (sulfonylureas) raise basal insulin secretion, which leads to a lower basal glucose level, but not to a lower postprandial glucose level\(^7\). Nateglinide is a new oral hypoglycemic agent with a phenylalanine-derivative that induces rapid, brief insulin secretion\(^8\). In animal studies Nateglinide has demonstrated to restore early insulin secretion\(^9\). There have been few studies to investigate whether nateglinide stimulates early insulin secretion or total insulin secretion in humans\(^9\)\(^10\). Furthermore, it is not known whether an improvement of postprandial hyperglycemia is due to enhancements of the early phase of insulin secretion or the total insulin secretion, or both.

To determine the acute effect of nateglinide, changes in postprandial glucose and serum insulin levels were measured during a meal tolerance test with or without nateglinide in type 2 diabetic patients.

**Subjects and Methods**

1. **Patients** (Table 1)

The subjects of this study were 17 type 2 diabetic patients treated by diet alone who had HbA\(_{1c}\) levels lower than 8%. None had a history of sulfonylurea agent use. They consisted of 11 men and 6 women, with the mean age of 58.6±10.9 years. Body mass index was 25.1±3.0, and the duration of diabetes was 5.9±6.3 years. Serum HbA\(_{1c}\) level was 6.9±0.9%, and insulin resistance index (HOMA-R), defined as fasting plasma glucose (mg/dl)×fasting insulin (\(\mu\) U/ml)/405, was 2.9±2.5. No patients had liver or renal dysfunction. All patients gave their written informed consent.

2. **Method**

The caloric value of the meal was 450 kcal, and it consisted of rice, salted salmon, miso soup, and vegetables (60% carbohydrate, 25% protein and 15% fat). The first meal tolerance test was performed after an overnight fast, and the meal was consumed within 15 minutes. Within 7 days a second meal tolerance test was performed after a single administration of 90 mg dose of nateglinide.

Blood samples for measurement of blood glucose, insulin (IRI), triglyceride (TG), and nonesterified free fatty acid (FFA) were collected before the meal and at 30-minute intervals for 180 minutes after a complete ingestion of the test meal. An efficacy analysis was performed to assess the effect of nateglinide on the total plasma glucose level (∑PG) during 180 minutes and the total insulin level during 180 minutes (∑IRI\(_{180}\)) and 30 minutes (∑IRI\(_{30}\)). Early phase insulin secretion was evaluated by calculating the insulinogenic index as the ratio of delta IRI to delta plasma glucose from baseline to 30 minutes after the meal. Then, the patients were divided into two groups according to their overall mean decrease in ∑PG after nateglinide administration (∆∑PG), which was 241.9 mg/dl; 8 patients who showed an improvement over the mean value of ∆∑PG were defined as the high-responder group, and 9 patients whose improvement was below the mean value of ∆∑PG were defined as the low-responder group.

IRI levels were measured by radioimmunoassay; plasma glucose, TG and FFA were measured by standard laboratory techniques.

The data are expressed as mean±SD and were analyzed by the paired t-test for comparisons between results of the meal tolerance tests, with or without nateglinide. The unpaired t-test was used for comparisons between the high-responder group and low-responder group. p values <0.05 were considered statistically significant.

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**Table 1** Clinical characteristics of the 17 patients with type 2 diabetes

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs.)</td>
<td>58.6±10.9</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>11/6</td>
</tr>
<tr>
<td>Duration of diabetes (yrs.)</td>
<td>5.9±6.3</td>
</tr>
<tr>
<td>Body mass index (kg/m(^2))</td>
<td>25.1±3.0</td>
</tr>
<tr>
<td>Diabetic retinopathy (+/−)</td>
<td>1/16</td>
</tr>
<tr>
<td>HbA(_{1c}) (%)</td>
<td>6.9±0.9</td>
</tr>
<tr>
<td>HOMA-R</td>
<td>2.9±2.5</td>
</tr>
<tr>
<td>Insulinogenic index</td>
<td>0.35±0.40</td>
</tr>
</tbody>
</table>

mean±SD
Results

1. Meal tolerance test (Fig. 1)

The plasma glucose level at baseline was $133.7 \pm 24.1$ mg/dl, and it significantly increased to a peak level of $222.8 \pm 43.4$ mg/dl at 60 minutes after the meal without nateglinide ($p < 0.001$). The plasma glucose level at 180 minutes was $166.8 \pm 61.1$ mg/dl; it was still significantly higher than baseline ($p < 0.001$). After the meal with nateglinide the baseline plasma glucose level ($129.6 \pm 27.7$ mg/dl) increased to a peak value of $184.9 \pm 40.6$ mg/dl at 30 minutes ($p < 0.001$), and returned to baseline at 180 minutes ($130.8 \pm 47.8$ mg/dl). The postprandial plasma glucose level with nateglinide was significantly lower ($p < 0.001$) than without nateglinide. The fasting IRI level without nateglinide was $8.7 \pm 6.5$ μU/ml and peaked at 90 minutes ($57.7 \pm 47.9$ μU/ml, $p < 0.001$). By contrast, the fasting IRI level ($7.8 \pm 3.9$ μU/ml) peaked at 60 minutes ($57.2 \pm 44.8$ μU/ml, $p < 0.001$) after nateglinide. The IRI level at 30 minutes was significantly higher with nateglinide than without nateglinide ($51.2 \pm 35.0$ vs $34.9 \pm 32.2$ μU/ml, $p < 0.05$). The baseline TG level was $131.0 \pm 84.8$ mg/dl and did not significantly change during the meal tolerance test without nateglinide. The TG level after nateglinide administration was $109.4 \pm 54.8$ mg/dl at baseline, $119.6 \pm 62.5$ mg/dl at 150 minutes and $124.3 \pm 66.5$ mg/dl at 180 minutes; the values at 150 minutes and 180 minutes were higher than baseline ($p < 0.05$). However, the increase in TG was modest. FFA levels during the meal tolerance tests with or without nateglinide were significantly lower compared to baseline ($p < 0.001$). However, there were no significant differences between FFA decreases with or without nateglinide.

$\Sigma$ PG after nateglinide administration was $1075.9 \pm 302.2$ mg/dl, significantly lower ($p < 0.001$) than without nateglinide ($1317.7 \pm 298.6$ mg/dl). Although the difference in $\Sigma$ IRI without or without nateglinide was not significant ($283.2 \pm 247.7$ μU/ml without nateglinide vs $288.4 \pm 202.1$ μU/ml with nateglinide), $\Sigma$ IRI was higher with nateglinide ($59.0 \pm 37.1$ μU/ml) than without nateglinide ($43.6 \pm 36.5$ μU/ml, $p < 0.05$).

2. Comparison of high-responder and low-responder groups

The mean $\Delta \Sigma$ PG value was $241.9$ mg/dl as a whole; $461.1 \pm 132.6$ mg/dl in the high-responder group, and $46.6 \pm 87.5$ mg/dl in the low-responder group. There were no significant differences in clinical background between the two groups (Table
Table 2 A comparison of high-responder and low-responder groups

<table>
<thead>
<tr>
<th></th>
<th>High-responder (N=8)</th>
<th>Low-responder (N=9)</th>
<th>p&lt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs.)</td>
<td>56.5±10.3</td>
<td>60.4±11.6</td>
<td>ns</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>6/3</td>
<td>6/3</td>
<td>ns</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.4±2.0</td>
<td>24.8±3.7</td>
<td>ns</td>
</tr>
<tr>
<td>Duration of diabetes</td>
<td>5.3±6.7</td>
<td>6.4±6.2</td>
<td>ns</td>
</tr>
<tr>
<td>HbA₁c (%)</td>
<td>7.2±1.0</td>
<td>6.5±0.7</td>
<td>ns</td>
</tr>
<tr>
<td>FPG (mg/dl)</td>
<td>136.8±25.5</td>
<td>131.0±23.9</td>
<td>ns</td>
</tr>
<tr>
<td>Fasting IRI (μ U/ml)</td>
<td>7.6±2.9</td>
<td>9.7±8.6</td>
<td>ns</td>
</tr>
<tr>
<td>HOMA-R</td>
<td>2.53±0.91</td>
<td>3.25±3.3</td>
<td>ns</td>
</tr>
</tbody>
</table>

FPG: fasting plasma glucose

Table 3 Changes in plasma glucose and IRI levels after meal due to the presence of nateglinide in high-responder and low-responder groups

<table>
<thead>
<tr>
<th></th>
<th>High-responder (N=8)</th>
<th>Low-responder (N=9)</th>
<th>p&lt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>without NG</td>
<td>with NG</td>
<td>without NG</td>
</tr>
<tr>
<td>Total plasma glucose</td>
<td>1429.1±309.7</td>
<td>949.1±224.1</td>
<td>1239.5±315.3</td>
</tr>
<tr>
<td>Total IRI (μ U/ml)</td>
<td>186.7±79.5</td>
<td>211.4±85.1</td>
<td>348.5±335.6</td>
</tr>
<tr>
<td>Total IRI during 30 minutes (μ U/ml)</td>
<td>32.6±14.0</td>
<td>53.4±24.4</td>
<td>52.9±50.5</td>
</tr>
<tr>
<td>Insulinogenic index</td>
<td>0.23±0.16</td>
<td>1.08±0.73</td>
<td>0.45±0.55</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01, ***p<0.001
NG: nateglinide

2. In the high-responder group Σ IRI₃₀ and the insulinogenic index significantly increased after nateglinide administration, but no significant changes were seen in the low-responder group (Table 3). In the high-responder group there was a positive correlation between the increase in delta IRI from baseline to 30 minutes before and after nateglinide administration and Σ PG (r=0.61, p<0.05) (Fig.2).

Discussion

In type 2 diabetic patients, postprandial hyperglycemia is an important risk factor for diabetic cardiovascular complications. In fact, acute elevations of plasma glucose concentrations trigger an array of tissue responses that may contribute to the development of vascular complications. Excessive postprandial hyperglycemia is one of the earliest manifestations of IGT and type 2 diabetes and is believed...
to often reflect impaired early insulin secretion\(^{(2)}\). In this study, the postprandial plasma glucose level peaked at 60 minutes without nateglinide and remained high at 180 minutes. These findings imply that once the plasma glucose level increases after a meal, it is difficult to suppress, even if insulin is secreted following the increase. With nateglinide, however, the plasma glucose level peaked at 30 minutes and had returned to baseline at 180 minutes following a selective increase in early insulin secretion without an increase in the total insulin secretion. However, previous studies show that nateglinide increased not only early phase insulin secretion, but the total amount of insulin\(^{(9,10)}\). The increase in the total secreted amount of insulin due to nateglinide in these studies might be a result of long-term administration of nateglinide. Our finding that early phase insulin secretion reduced postprandial glucose level without increase in total insulin secretion suggests that improvement in postprandial plasma glucose level depends more on early insulin secretion rather than on total insulin secretion, possibly because a rapid increase in portal insulin concentration suppresses hepatic glucose production, or because hepatic glucose uptake simultaneously significantly increases\(^{6)}\). As a result, glycemic response normalizes after the glucose load.

However, there are individual variations in the response to nateglinide\(^{(3)}\). The results of other analysis of high responders to nateglinide show that shorter diabetes duration, and maintenance of basic and early insulin secretion were important factors\(^{(3)}\). In this study, however, there were no significant differences in clinical background, insulin resistance, or basic insulin secretion between the high-responder group and low-responder group. In a rat pancreas study nateglinide increased insulin secretion in both the first and second phase\(^{6)}\). In the high-responder group in the present study there was a positive correlation between improved early insulin secretion in response to nateglinide and decreased plasma glucose levels after nateglinide administration. Therefore, maintenance of early insulin secretion is important factor in the efficacy of nateglinide. Early insulin secretion and the resultant suppression of hepatic glucose production and increasing hepatic glucose uptake are major determinants of postprandial glucose levels. Agents that selectively augment early insulin secretion, such as nateglinide may represent a particularly effective approach in reducing cardiovascular morbidity and mortality\(^{(4)}\).

Postprandial hyperlipidemia has also been associated with increased risk of atherosclerotic disease\(^{(15,16)}\). However, there was no significant increase in TG levels after the meal tolerance test in this study, suggesting that the amount of lipid in the meal was too low to evaluate changes in postprandial TG levels. Appropriate regulation of blood glucose and FFA levels after meals is critical, because elevation of either is correlated with the development of atherosclerosis\(^{(14,17,18)}\). Suppression of lipolysis in visceral fat has been indicated by early insulin secretion after meals as the mechanism by which FFA levels decrease after meals\(^{(4)}\). Some studies have found that nateglinide improves the decreased ratio in FFA levels after meals\(^{(4)}\), but no significant changes were observed in the present study. Augmented early phase insulin secretion improves not only postprandial hyperglycemia, but also suppressed endogenous lipolysis, resulting in suppression of FFA levels in type 2 diabetes.

In conclusion, the increase in early insulin secretion induced by nateglinide is a mechanism for controlling postprandial hyperglycemia, which may, in turn, prevent the development of diabetes-related atherosclerotic complications.

References

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(J): in Japanese
食事負荷試験におけるインスリン分泌に及ぼす
ナテグリニドの急性効果

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要約
目的：2型糖尿病患者におけるナテグリニド（NG）の食後の血糖値、インスリン（IRI）、脂質に及ぼす急性効果を食事負荷試験を行い検討した。

対象および方法：対象は17人の2型糖尿病患者で、90mgNG未投与と投与直後のそれぞれの条件下で食事負荷試験を行い、血糖値、IRI、中性脂肪、遊離脂肪酸を負荷前と負荷後は30分ごとに180分まで測定した。

結果：血糖値は、NG未投与では60分が頂値であったが、NG投与後は30分が頂値となり、その後速やかに低下した。負荷後30分のIRIはNG未投与34.9±32.2μU/mlより投与後は51.2±35.0μU/mlと有意に上昇（p<0.05）した。しかし、総IRI値はNG投与前後で有意差はなかった。一方、中性脂肪は食事負荷試験により有意な上昇を認めなかった。遊離脂肪酸は負荷後有意に低下したが、NG投与前後で有意差はみられなかった。

結論：NGは総インスリン分泌量の増加を伴わず、選択的に早期インスリン分泌のみを増加することにより食後高血糖を改善することが示唆された。