Nateglinide Improves Early Insulin Secretion and Controls Postprandial Glucose Excursions in a Prediabetic Population

OBJECTIVE — The purpose of this study was to evaluate the metabolic effectiveness, safety, and tolerability of nateglinide in subjects with impaired glucose tolerance (IGT) and to identify a dose appropriate for use in a diabetes prevention study.

RESEARCH DESIGN AND METHODS — This multicenter, double-blind, randomized, parallel-group, fixed-dose study of 8 weeks’ duration was performed in a total of 288 subjects with IGT using a 2:2:2:1 randomization. Subjects received nateglinide (30, 60, and 120 mg) or placebo before each main meal. Metabolic effectiveness was assessed during a standardized meal challenge performed before and after the 8-week treatment. All adverse events (AEs) were recorded, and confirmed hypoglycemia was defined as symptoms accompanied by a self-monitoring of blood glucose measurement ≤3.3 mmol/l (plasma glucose ≤3.7 mmol/l).

RESULTS — Nateglinide elicited a dose-related increase of insulin and a decrease of glucose during standardized meal challenges, with the predominant effect on early insulin release, leading to a substantial reduction in peak plasma glucose levels. Nateglinide was well tolerated, and symptoms of hypoglycemia were the only treatment-emergent AEs. Confirmed hypoglycemia occurred in 28 subjects receiving nateglinide (30 mg, 0 [0%]; 60 mg, 5 [6.6%]; 120 mg, 23 [26.7%]) and in 1 (2.3%) subject receiving placebo.

CONCLUSIONS — Nateglinide was safe and effective in reducing postprandial hyperglycemia in subjects with IGT. Preprandial doses of 30 or 60 mg nateglinide would be appropriate to use for longer-term studies to determine whether a rapid-onset, rapidly reversible, insulinotropic agent can delay or prevent the development of type 2 diabetes.

Diabetes Care 25:2141–2146, 2002

Several studies have shown that weight loss and exercise can delay or prevent progression from impaired glucose tolerance (IGT) to type 2 diabetes (1–3); however, such changes in lifestyle are notoriously difficult to maintain. Very recently, results from the Diabetes Prevention Program (4), the STOP-NIDDM Diabetes Trial (5), and the TRIPOD Study (6) have suggested that pharmacotherapy (with metformin, acarbose, and thiazolidinediones, respectively) is a valid approach to diabetes prevention in patients with IGT at high risk of developing diabetes, such as those with a family history of diabetes (5) or women with recent gestational diabetes (6). These data raise the question of whether another agent, acting by a different mechanism, may be equally or more effective in the prevention of type 2 diabetes.

The α-lipoylalanine derivative, nateglinide, is a new insulinotropic agent that specifically targets mealtime glucose excursions by restoring or replacing early prandial insulin release. Nateglinide, unlike most sulfonylureas (SUs), nateglinide is found to have a low risk of hypoglycemia in patients with diabetes (9,10) because its stimulation of insulin release is rapidly reversible and glucose dependent (11,12). Since nateglinide addresses the key factor that determines whether an individual with IGT progresses to overt diabetes (7), it may be a particularly attractive option for use in diabetes prevention.

However, an insulin secretion agent used in subjects with minimal fasting hyperglycemia must have an acceptably low hypoglycemic potential. Further, an agent used for an extended period of time must have an excellent overall safety and tolerability profile. Thus, before nateglinide could be used in a diabetes prevention study, it would be essential to demonstrate, in the target prediabetic population, that it has these properties. The purpose of the present study was to assess the safety, tolerability, and metabolic effectiveness of nateglinide in subjects with IGT and to identify an appropriate dose for use in long-term studies to assess its potential to delay or prevent the development of type 2 diabetes.
Nateglinide effects in IGT

RESEARCH DESIGN AND METHODS

Study protocol. This multicenter, double-blind, randomized, parallel-group fixed-dose study of 8 weeks’ duration was performed to define the maximum tolerated dose of nateglinide in a prediabetic population. The effects of nateglinide on prandial glucose and insulin, fructosamine, fasting plasma glucose (FPG), and HbA1c levels were also assessed. A total of 288 nondiabetic subjects (FPG <7.0 mmol/l) with IGT were randomized to receive 30 mg (n = 83), 60 mg (n = 76), or 120 mg (n = 86) nateglinide or placebo (n = 43) before (within 10 min of) each main meal using a 2:2:2:1 randomization. To determine the effects of nateglinide on prandial glucose and insulin levels, a standardized meal challenge was performed before the first dose (week 0) and after the final dose (week 8).

The study was carried out in 32 centers in six countries and enrolled male and female subjects with an FPG 7.0 mmol/l) with IGT were randomized to each meal using a 2:2:2:1 randomization. To determine the effects of nateglinide on prandial glucose and insulin levels, a standardized meal challenge was performed before the first dose (week 0) and after the final dose (week 8).

All subjects were provided with a home glucose monitoring device and were instructed to perform a fingertip glucose test for all episodes of suspected hypoglycemia. Confirmed hypoglycemia was defined as an event for which SMBG value was ≤3.3 mmol/l, corresponding to a plasma glucose ≤3.7 mmol/l.

Glucose was measured by an enzymatic method (Boehringer Mannheim, Mannheim, Germany) and fructosamine was measured by a spectrophotometric method (Roche Diagnostics, Basel, Switzerland) using a Cobas Bio analyzer (Roche). Blood levels of HbA1c were measured by high-performance liquid chromatography standardized to the Diamat ion-exchange method (upper limit of normal [ULN] = 6.0%). Insulin was measured by radioimmunoassay (Pharmacia, Uppsala, Sweden). All laboratory samples were analyzed at a central laboratory (CRL, Brussels, Belgium).

Data analysis. Baseline and demographic variables were compared among groups with an F test for numeric parameters and by a Mantel-Haenszel test for categorical variables. The primary safety evaluation was based on the incidence of confirmed hypoglycemia. Acceptable safety was defined prospectively as an incidence of severe (grade B—requiring assistance from an outside party) hypoglycemia <0.1% in the combined nateglinide groups and a discontinuation rate of <5% within a dose group. Binomial tests were performed on these two primary safety criteria. In post hoc analyses, the frequency of adverse events (AEs) was compared between groups by Fisher’s exact test (two-sided, not adjusted for multiplicity). Efficacy analyses were performed to assess the effects of nateglinide on prandial glucose and insulin (3-h area under the curves [AUCs] calculated by the trapezoidal method), FPG, HbA1c, and fructosamine. The change from baseline at week 8 was analyzed by ANCOVA with treatment and center as factors and baseline as covariate. Summary statistics of absolute values and changes from baseline by treatment group and time point were calculated for the intent-to-treat population. No formal hypothesis testing was performed. P values derived from the ANCOVA were explorative and were not adjusted for multiplicity.

RESULTS

Characteristics of the study population. Table 1 reports the baseline characteristics of the study population. There were no differences among treatment groups in demographics or in metabolic indexes (HbA1c, FPG, and fructosamine). Nearly all subjects were Caucasian, women outnumbered men by a ratio of 60:40, mean age was ~57 years (with ~25% of each treatment group >65 years), and the mean BMI in each group was 30 kg/m2. Reflecting the selection criteria, mean FPG ranged from 5.9 to 6.2 mmol/l in the four groups; HbA1c and fructosamine levels were near their respective ULNs.

Safety and tolerability. Nateglinide was very well tolerated. The overall incidence of AEs, other than symptoms of hypoglycemia, was low and similar among all treatment groups. No deaths occurred during the study, and the incidence of serious AEs (SAEs) was 1 (1.2%), 0, 1 (1.2%), and 2 (4.7%) in the nateglinide 30, 60, and 120 mg and placebo groups, respectively. Only one SAE was suspected to be related to study medication, but upon unblinding, this subject was found to be in the placebo group. Three (3.6%), two (2.6%), and none of the subjects in the 30, 60, and 120 mg nateglinide groups and one (2.3%) in the placebo-treated group, respectively, withdrew due to any AE other than hypoglycemia. The incidence of clinically notable laboratory parameters (hematology and biochemistry) was low in all subjects and none were dose-related.

Because the purpose of this study was...
to determine the maximum tolerated dose and thus to define an appropriate dose for a long-term diabetes prevention study, particular attention was paid to hypoglycemia. There were no incidents of severe hypoglycemia (requiring assistance from an outside party) during this study. Given the sample size of 245 subjects in the combined nateglinide groups, the binomial CI for the true underlying incidence ranged from 0.0 to 1.2. A total of three subjects on nateglinide (1.2%) discontinued because of hypoglycemic symptoms (one on 60 mg and two on 120 mg). As reported in Table 2, the incidence of confirmed hypoglycemia in the nateglinide-treated groups was 0 in the 30 mg, 5 (6.6%) in the 60 mg, 23 (26.7%) in the 120 mg, and 1 (2.3%) in the placebo group. There was clear statistical evidence for a higher incidence in the 120-mg group, but other analyses should be interpreted with caution in view of the low number of events and sample size. All plasma glucose levels during any confirmed hypoglycemic episode in the 60-mg nateglinide group and in the group who took placebo were >3.1 mmol/l. In the 120-mg group, 11 subjects (12.8%) experienced hypoglycemia with a plasma glucose equivalent ≤3.1 mmol/l; however, the other 17 confirmed episodes had plasma glucose values >3.1 mmol/l. In all groups, a missed or delayed meal, strenuous exercise, or stress were the most frequently assigned precipitating factors, but no recognizable precipitating factor was identified by the subjects in most episodes observed with the 120-mg dose. Most hypoglycemic events occurred <4 h from the last meal and took <30 min to resolve following oral carbohydrate intake. All events occurred during the day, mainly during the afternoon, but many of the symptoms experienced by the subjects in the 120-mg group occurred during the morning.

**Effects on glucose regulation.** Figure 1 depicts the immunoreactive insulin (IRI) and glucose profiles during standardized breakfast challenges performed at weeks 0 and 8 of treatment with nateglinide (60 mg, before meals). This dose of nateglinide modestly and selectively increased the early insulin response to the meal and greatly reduced the prandial glucose excursion. A lower dose produced a smaller increment of insulin and decrement of glucose, and a higher dose produced a larger and more prolonged augmentation of meal-stimulated insulin release and a marginally greater reduction of postprandial glucose levels.

This is illustrated in Fig. 2, which shows the change from week 0 to week 8 in the 3-h prandial AUCs of insulin and glucose in the four treatment groups. The effects of nateglinide to increase insulin

---

**Table 1—Baseline demographic and background characteristics (randomized population)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Nateglinide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30 mg</td>
<td>60 mg</td>
</tr>
<tr>
<td>n</td>
<td>83</td>
<td>76</td>
</tr>
<tr>
<td>Male sex</td>
<td>34 (41.0)</td>
<td>32 (42.1)</td>
</tr>
<tr>
<td>Caucasian race</td>
<td>82 (98.8)</td>
<td>76 (100.0)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>56.4±11.0</td>
<td>57.6±10.9</td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>60 (72.3)</td>
<td>57 (75.0)</td>
</tr>
<tr>
<td>≥65 years</td>
<td>23 (27.7)</td>
<td>19 (25.0)</td>
</tr>
<tr>
<td>BMI (kg/m²)*</td>
<td>30.2±5.3</td>
<td>30.4±5.2</td>
</tr>
<tr>
<td>FPG (mmol/l)†</td>
<td>6.09±0.08</td>
<td>5.88±0.08</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.76±0.06</td>
<td>5.70±0.06</td>
</tr>
<tr>
<td>Fructosamine (µmol/l)</td>
<td>249±3</td>
<td>251±4</td>
</tr>
</tbody>
</table>

Data are n (%), *means ± SD, or †means ± SE. There were no statistically significant differences among groups in any baseline or demographic characteristic based on Cochran and Mantel-Haenszel tests or F tests.

---

**Table 2—Subjects with any AE or confirmed hypoglycemia (plasma glucose ≤3.7 mmol/l)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Nateglinide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30 mg</td>
<td>60 mg</td>
</tr>
<tr>
<td>n</td>
<td>83</td>
<td>76</td>
</tr>
<tr>
<td>Subjects with at least one AE</td>
<td>31 (37.3)</td>
<td>25 (32.9)</td>
</tr>
<tr>
<td>Signs or symptoms consistent with hypoglycemia††</td>
<td>10 (12.0)</td>
<td>10 (13.2)</td>
</tr>
<tr>
<td>Confirmed hypoglycemia</td>
<td>0</td>
<td>5 (6.6)§</td>
</tr>
<tr>
<td>Plasma glucose ≤3.1 mmol/l</td>
<td>0</td>
<td>1¶</td>
</tr>
<tr>
<td>Plasma glucose &gt;3.1, ≤3.7 mmol/l††</td>
<td>0</td>
<td>5 (6.6)**</td>
</tr>
</tbody>
</table>

P values are post hoc calculations based on Fisher’s exact test (two-sided, not adjusted for multiplicity). *P < 0.05 vs. placebo and 60 mg; †P < 0.005 vs. 30 mg, P < 0.05 vs. 60 mg; ‡P < 0.005 vs. 30 mg, P < 0.005 vs. 60 mg; §P < 0.05 vs. 30 mg; ¶P < 0.001 vs. placebo, 30 mg, and 60 mg; #P < 0.001 vs. 30 mg; **P < 0.005 vs. 30 mg, ††P < 0.05 vs. 60 mg, P < 0.01 vs. placebo, P < 0.001 vs. 30 mg; †‡whole-blood glucose <2.8, ≤3.3 mmol/l.
Nateglinide effects in IGT

![Figure 1](https://example.com/figure1.png)

**Figure 1**—Plasma insulin (IRI) and glucose during standardized breakfast challenges performed prior to the first dose at week 0 and after the final dose at week 8 with 60 mg nateglinide in 72 nondiabetic subjects with IGT. Mean ± SEM.

and to curb prandial glucose excursions were dose related, but only the highest dose (120 mg) significantly increased the total insulin exposure.

As would be predicted from the characteristics of the study population, the duration of study, and the mechanism of nateglinide action, this agent had no significant effect on FPG or on fasting insulin levels. The change from baseline HbA1c was not statistically significant except in the 120-mg group (Δ = −0.12 ± 0.04, P < 0.05). Nateglinide did, however, modestly but significantly decrease fructosamine levels (Δ = 30 mg, −8.3 ± 0.4; 60 mg −8.6 ± 2.1; and 120 mg, −8.1 ± 2.0 μmol/l; P < 0.05 vs. placebo), although the effect was not dose related.

**CONCLUSIONS** — The goal of this study was to assess the safety, tolerability, and metabolic effects of nateglinide in a prediabetic population and to thereby establish the feasibility of using nateglinide for a long-term study to determine whether an insulinotropic agent could delay or prevent the occurrence of type 2 diabetes, as has recently been established for concerted lifestyle modification and for metformin (4), acarbose (5), and thiglaze (6) monotherapy. It was found that nateglinide elicited a dose-dependent increase of early prandial insulin levels and reduction of prandial glucose excursions—both the amplitude of the basal to peak spikes (13) and the 3-h AUCs. This has been observed previously in patients with type 2 diabetes (9) and in healthy volunteers (11). Since the present study population represents a midpoint between the populations studied previously, this finding is not in itself unexpected. However, it does highlight the power of early insulin release. Thus, the lowest dose tested (30 mg) had no effect on overall insulin exposure, as assessed by the 3-h AUC, but produced more than half the maximal glucose-lowering effect. Thus, by restoring a physiologic insulin profile, nateglinide essentially normalized glucose tolerance—precisely what would be desired in an agent to be tested in a diabetes prevention study.

It would also be necessary to have an exceptionally “clean” safety and tolerability profile, since the agent would be taken for a prolonged period of time in subjects with minimal hyperglycemia. In the present study, as described previously (14), nateglinide was very well tolerated. The incidence of AEs other than hypoglycemia in nateglinide-treated subjects was indistinguishable from that in subjects who took a placebo. The non–hypoglycemia-related AEs that occurred more frequently in nateglinide than in the subjects who took a placebo were in no way dose related or suspected to be related to study medication.

With regard to hypoglycemia, it is noteworthy that no severe hypoglycemia (requiring assistance from an outside party) occurred with any dose of nateglinide, likely due to its rapidly reversible (15) and glucose-dependent (12) insulinotropic action. No hypoglycemia occurred in any patient receiving the 30 mg dose of nateglinide, and all hypoglycemia that occurred in subjects given 60 mg was accompanied by a plasma glucose >3.1 mmol/l. In contrast, of the patients in the 120-mg group that did have confirmed hypoglycemia (26.7%), nearly half had one or more episodes during which plasma glucose levels fell below 3.1 mmol/l. In light of the increased incidence and severity of hypoglycemia in subjects receiving 120 mg nateglinide, and given the minimal additional metabolic benefit it provides, this highest dose does not appear to be a good option in subjects with IGT.

The 120 mg dose of nateglinide is used safely and effectively in the vast majority of patients with type 2 diabetes treated with nateglinide, and it was recently reported that in a 24-week study in patients with only moderately elevated FPG (≤7.8 mmol/l), 120 mg nateglinide preprandially normalized HbA1c levels (≤0.0%) in 40% of subjects, with an acceptable incidence of hypoglycemia (5.3%, plasma glucose ≤3.3 mmol/l) (16). However, it is not surprising that a lower dose would be appropriate in non-diabetic subjects with IGT. From the present findings, it appears that either 30
vascular complications were not convincingly established the benefit of tight glycemic control to reduce microvascular complications (13,17,21,22). Indeed, it has been suggested that postprandial hyperglycemia, which selectively augments early insulin release, may be a particularly effective approach to reducing cardiovascular morbidity and mortality.

Accordingly, a diabetes prevention study using nateglinide, which was shown here to substantially reduce postprandial glycemia, or glucose spikes rather than total glycemic exposure, may play a key role in the cardiovascular morbidity and mortality associated with IGT (17,18).

Increased mortality associated with IGT (17,18). Indeed, it has been suggested that postprandial hyperglycemia, or glucose spikes rather than total glycemic exposure, may play a key role in the cardiovascular morbidity and mortality associated with IGT (13,17,21,22). Indeed, it has been reported that postprandial hyperglycemia, but not impaired fasting glucose, is a risk factor for cardiovascular disease (23). Since early insulin release and the resultant suppression of hepatic glucose production is a major determinant of postprandial glucose levels (8), an agent such as nateglinide, which selectively augments early insulin release, may be a particularly effective approach to reducing cardiovascular morbidity and mortality.

or 60 mg would be acceptable for a long-term study to determine whether this rapid-onset/short-duration insulinotropic agent can delay or prevent manifest diabetes in a prediabetic population and reduce the increased mortality and morbidity associated with IGT (17,18).

Although the Diabetes Control and Complications Trial (DCCT) in patients with type 1 diabetes and the U.K. Prospective Diabetes Study (UKPDS) in patients with type 2 diabetes have convincingly established the benefits of tight glycemic control to reduce microvascular complications (19,20), macrovascular complications were not significantly reduced by insulin or oral secretagogues. Many correlative studies have suggested that postprandial hyperglycemia, or glucose spikes rather than total glycemic exposure, may play a key role in the cardiovascular morbidity and mortality associated with IGT and diabetes (13,17,21,22). Indeed, it has been reported that postprandial hyperglycemia, but not impaired fasting glucose, is a risk factor for cardiovascular disease (23). Since early insulin release and the resultant suppression of hepatic glucose production is a major determinant of postprandial glucose levels (8), an agent such as nateglinide, which selectively augments early insulin release, may be a particularly effective approach to reducing cardiovascular morbidity and mortality.

In summary, augmenting early insulin secretion is a remarkably effective mechanism to control postprandial hyperglycemia. Low-dose nateglinide could be used to determine the potential of this mechanism to prevent or slow the progression of type 2 diabetes and may well become a therapeutic option for prediabetic subjects with only moderately disturbed glucose homeostasis.

References


Nateglinide effects in IGT


12. Temelkova-Kurtschiev TS, Koehler C, Hanefeld M: Postchallenge plasma glucose and glycemic spikes are more strongly associated with atherosclerosis than fasting glucose or HbA1c level. *Diabetes Care* 23:1830–1834, 2000


23. The NAVIGATOR Trial Steering Committee: Nateglinide and valsartan in impaired glucose tolerance outcomes research: rationale and design of the NAVIGATOR trial (Abstract). *Diabetes* 51:1116, 2002