

# Improved Prandial Glucose Control With Lower Risk of Hypoglycemia With Nateglinide Than With Glibenclamide in Patients With Maturity-Onset Diabetes of the Young Type 3

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**OBJECTIVE** — To study the effect of the short-acting insulin secretagogue nateglinide in patients with maturity-onset diabetes of the young type 3 (MODY3), which is characterized by a defective insulin response to glucose and hypersensitivity to sulfonylureas.

**RESEARCH DESIGN AND METHODS** — We compared the acute effect of nateglinide, glibenclamide, and placebo on prandial plasma glucose and serum insulin, C-peptide, and glucagon excursions in 15 patients with MODY3. After an overnight fast, they received on three randomized occasions placebo, 1.25 mg glibenclamide, or 30 mg nateglinide before a standard 450-kcal test meal and light bicycle exercise for 30 min starting 140 min after the ingestion of the first test drug.

**RESULTS** — Insulin peaked earlier after nateglinide than after glibenclamide or placebo (median [interquartile range] time 70 [50] vs. 110 [20] vs. 110 [30] min,  $P = 0.0002$  and  $P = 0.0025$ , respectively). Consequently, compared with glibenclamide and placebo, the peak plasma glucose ( $P = 0.031$  and  $P < 0.0001$ ) and incremental glucose areas under curve during the first 140 min of the test ( $P = 0.041$  and  $P < 0.0001$ ) remained lower after nateglinide. The improved prandial glucose control with nateglinide was achieved with a lower peak insulin concentration than after glibenclamide (47.0 [26.0] vs. 80.4 [71.7] mU/l;  $P = 0.023$ ). Exercise did not induce hypoglycemia after nateglinide or placebo, but after glibenclamide six patients experienced symptomatic hypoglycemia and three had to interrupt the test.

**CONCLUSIONS** — A low dose of nateglinide prevents the acute postprandial rise in glucose more efficiently than glibenclamide and with less stimulation of peak insulin concentrations and less hypoglycemic symptoms.

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**M**aturity-onset diabetes of the young type 3 (MODY3) is a dominantly inherited form of diabetes caused by mutations in the hepatic nuclear factor 1 $\alpha$  gene (*HNF1 $\alpha$* ) (1). MODY3 is characterized by high penetrance, a low renal threshold for glucose, and defective insulin response to a glu-

cose stimulus combined with supranormal insulin sensitivity (1,2). The defect leads to a diminished insulin secretory response to glucose or arginine (3–5), and the fasting glucose concentration can remain normal for a long time despite postprandial hyperglycemia and elevated HbA<sub>1c</sub> (A1C) levels (6,7). Although insulin secretagogues such as sulfonylureas seem a logical treatment choice in MODY, patients with MODY3 often exhibit hypersensitivity to sulfonylureas compared with type 2 diabetic patients, and even low doses frequently result in hypoglycemia (8–11).

Nateglinide is a D-phenylalanine derivative, which, when taken 10 min before a meal, leads to a rapid and transient increase in insulin secretion, which returns to the premeal level within 2 h (12). In this study we compared the acute effect of a single dose of nateglinide, glibenclamide, and placebo on prandial glucose, insulin, C-peptide, and glucagon excursions in conjunction with a standard test meal and light exercise in patients with MODY3.

## RESEARCH DESIGN AND METHODS

This was a randomized, double-blind crossover study to compare the acute effect of nateglinide with that of glibenclamide or placebo on glucose and insulin concentrations during a test meal followed by light exercise in patients with MODY3. The diagnosis of MODY3 was based on a family history of autosomally dominantly inherited diabetes, mutation testing, and a 2-h plasma glucose measurement of at least 11 mmol/l during an oral glucose tolerance test. Fifteen patients (5 men and 10 women) with the Pro291fsInsC mutation in the *HNF1 $\alpha$*  gene were included. They had a median (interquartile range) age of 41.0 years (16.5), BMI 23.1 kg/m<sup>2</sup> (2.4), fasting plasma glucose (FPG) 7.9 mmol/l (3.9), and A1C 6.7% (2.3) (Table 1). Nine subjects were treated with oral hypogly-

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**Abbreviations:** FPG, fasting plasma glucose; MODY3, maturity-onset diabetes of the young type 3.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—Clinical characteristics of the 15 patients with MODY3 participating in the study

Patient	Sex	Age (years)	FPG (mmol/l)*	A1C (%)	BMI (kg/m <sup>2</sup> )	Fat mass (%)	Systolic BP (mmHg)*	Diastolic BP (mmHg)*	Antihyperglycemic medication
1	F	23.9	4.3/4.0/4.3	5.4	25.0	34	130	81	None
2	F	44.9	7.0/8.4/7.4	6.6	22.4	32	109	70	None
3	F	30.8	10.8/—8.6/11.3	8.1	22.6	30	110	82	Meal-time regular insulin
4	M	34.2	7.0/6.2/6.8	6.4	21.9	17	115	77	Acarbose 25 mg twice a day
5	M	42.5	12.2/11.3/13.5	8.7	24.3	21	118	86	Glimepiride 2 mg once daily
6	F	50.6	11.3/10.3/—8.8	9.1	23.4	31	104	71	Glibenclamide 4 35 mg/day
7	F	41.1	5.3/6.4/6.1	6.7	28.2	36	121	81	None
8	F	62.6	5.2/4.4/4.8	6.5	24.7	34	144	83	Glimepiride 1 mg once daily†
9	M	32.9	7.5/7.3/8.5	7.8	22.3	15	136	78	None
10	M	46.5	7.9/7.8/8.1	7	23.9	22	166	106	None‡
11	M	66.1	16.2/15.5/14.2	9.9	23.4	23	165	88	Glibenclamide 35 mg/day
12	F	40.2	8.3/8.4/7.8	5.9	16.7	16	113	69	Acarbose 50 mg × 3
13	F	47.3	9.4/8.0/7.3	6.1	19.8	18	123	70	Acarbose 50 mg × 3
14	F	20.0	5.4/7.3/5.8	9	23.1	28	112	67	Glimepiride 1 mg once daily
15	F	28.0	5.0/6.5/7.6	6.7	21.2	25	125	70	None
Median (interquartile range)		41.0 (16.5)	7.9 (3.9)	6.7 (2.3)	23.1 (2.4)	25 (14)	121 (24)	78 (13)	

\*FPG is shown for each visit (ordered: nateglinide/glibenclamide/placebo, although the patients received the three drugs in random order). †Medication for coronary heart disease including β-blockers. ‡Antihypertensive medication. BP, blood pressure.

cemic agents, one with meal-time regular insulin (0–4 IU per meal), and five with diet only (Table 1). The patients were originally instructed to discontinue treatment with oral hypoglycemic agents 1 week before the study. However, two patients receiving glibenclamide (patients 6 and 11 in Table 1) developed hyperglycemic symptoms during the washout period, and were allowed to take short-acting repaglinide at meals except on the day before the tests. Similarly, those receiving acarbose or glimepiride discontinued treatment at least 2 days before the tests. The patients were instructed to avoid heavy exercise and consumption of

large quantities of carbohydrates during the day preceding the test but otherwise to eat normally.

The patients were randomly assigned to receive, after an overnight fast, on three occasions (at least 1 week apart), 1.25 mg glibenclamide or placebo 30 min before and 30 mg nateglinide or placebo 10 min before breakfast (Fig. 1). The 450-kcal breakfast consisted of 125 ml orange juice, three slices of mixed-rye bread (90 g) with cheese spread (30 g) and preserves (20 g), 200 ml of 1% low-lactose milk, and coffee or tea with non-nutritive sweetener, yielding 75 g carbohydrates. Starting 140 min after the ingestion of the

first test drug the subjects performed light bicycle exercise (Tunturi E310 ergometer with a Polar heart rate belt; Tunturi, Turku, Finland) at 50–60 rpm for 30 min with continuous heart rate monitoring. The target heart rate of 80–110 bpm was obtained by adjusting the resistance of cycling every 5 min. Blood samples were drawn for plasma glucose and serum insulin and C-peptide measurements –10 and 0 min before and +5, 10, 20, 30, 35, 40, 45, 50, 60, 70, 80, 90, 100, 110, 120, 140, 170, 200, 210, 240, and 260 min after the ingestion of the first test drug. Samples for plasma glucagon were taken at the same time points except at 5, 10,

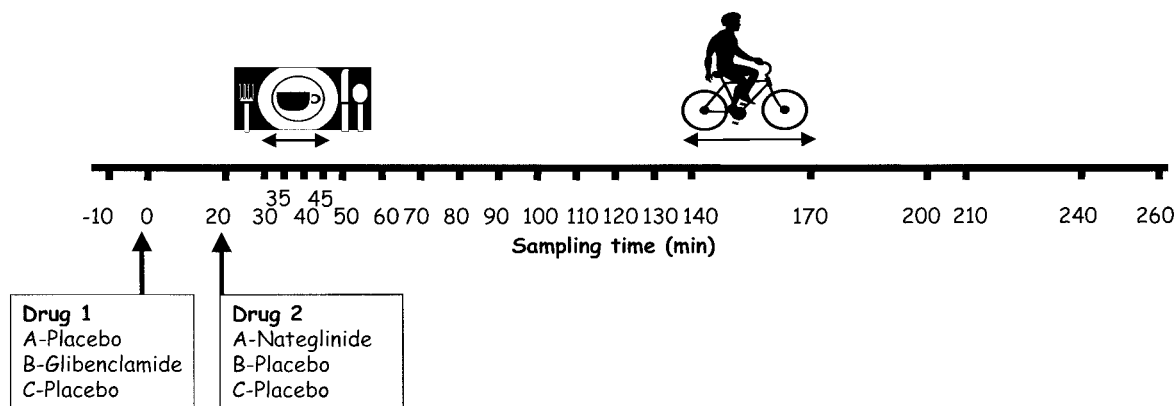


Figure 1—The study protocol. Each patient participated three times in double-blind random order and received placebo at time 0 min and 30 mg nateglinide at 20 min (A), 1.25 mg glibenclamide at 0 min and placebo at 20 min (B), or placebo at both 0 and 20 min (C). The subjects ingested a test meal between time 30 and 45 min and pedaled on an exercise bike between time 140 and 170 min. The timing of blood sampling is shown.

**Table 2—Comparison of glucose and insulin response to a test meal and nateglinide, glibenclamide, or placebo in the 15 patients with MODY3 patients**

	Nateglinide	P <sub>1</sub>	Glibenclamide	P <sub>2</sub>	Placebo	P <sub>3</sub>
Plasma glucose (mmol/l)						
Fasting	7.9 (5.6)	NS	7.8 (2.2)	NS	7.8 (2.7)	NS
Peak	9.8 (8.9)	0.031	11.5 (6.6)	0.031	12.7 (7.2)	<0.0001
140 min	9.1 (7.8)	0.029	7.1 (9.2)	0.0001	10.4 (9.9)	0.0038
170 min	7.3 (7.0)	0.004	6.3 (8.0)*	0.0005	8.3 (10.3)	0.0018
260 min	6.4 (4.9)	0.006	5.5 (3.9)†	0.0002	7.6 (7.8)	0.0124
Δ <sub>Peak</sub> ‡	3.3 (2.9)	0.031	4.5 (3.9)	NS	4.7 (3.5)	<0.0001
Δ <sub>140 min</sub> ‡	1.85 (2.85)	0.026	−0.3 (5.6)	0.0019	2.7 (4.7)	0.0008
AUC <sub>140 min</sub> §	101 (294)	0.041	186 (391)	0.027	250 (348)	<0.0001
Urine glucose (mmol/l)						
Fasting	0 (20.4)	NS	1.4 (37.1)	NS	(21.3)	NS
140 min	15.4 (59.8)	NS	42.7 (74.0)	NS	33.0 (97.0)	NS (0.06)
260 min	3.8 (52.8)	NS	10.4 (70.1)	NS	46.0 (67.9)	NS
Serum insulin (mU/l)						
Fasting	5.8 (4.3)	NS	5.2 (4.5)	NS	6.0 (5.4)	NS
Peak	47.0 (26.0)	0.023	80.4 (71.7)	0.0002	33.7 (24.9)	<0.001
AUC <sub>140 min</sub> §	2,912 (1,668)	0.024	3,253 (3,888)	0.0002	1,652 (2,150)	0.002
Hypoglycemia (n)	0/15	0.030	6/15	0.030	0/15	NS

Data are median (interquartile range). Each patient participated in the test three times receiving in double-blind random order: 1) placebo at time 0 min and 30 min nateglinide at 20 min, 2) 1.25 mg glibenclamide at 0 min and placebo at 20 min, or 3) placebo at both 0 and 20 min. The subjects ingested a test meal between 30 and 45 min. P<sub>1</sub>: nateglinide vs. glibenclamide visits; P<sub>2</sub>: glibenclamide vs. placebo visits; P<sub>3</sub>: nateglinide vs. placebo visits. \*n = 14 and †n = 12 due to hypoglycemia. ‡Difference between peak or 140 min glucose and fasting glucose. §AUC, incremental area under the curve during 0–140 min. ||Plasma glucose ≤3.5 mmol/l.

35, and 45 min. The patients emptied their bladder before the test and at 140 and at 260 min, and the urine glucose concentration was analyzed.

The test was interrupted, and glucose was administered orally if the plasma glucose decreased to <2.5 mmol/l or hypoglycemic symptoms occurred. Information about hypoglycemic symptoms was given at each visit together with glucose tablets to take home (Siripiri; Oriola, Espoo, Finland). The patients were instructed to avoid exercise during the rest of the day. Informed consent was obtained from all participants, and the study was approved by the Ethics Committee of the Helsinki University Central Hospital.

### Assays

The plasma and urine glucose concentrations were measured in duplicate on a glucose analyzer (Beckman Coulter, Fullerton, CA). A double-antibody enzyme-linked immunosorbent assay (Dako, Cambridgeshire, U.K.) was used to measure serum insulin concentrations with an interassay coefficient of variation (CV) of 8.9%. Serum C-peptide and plasma glucagon concentrations were measured using a radioimmunoassay (Linco Research, St. Charles, MO) with interassay CVs of 9.8 and 3.6%, respectively. The plasma glucagon assay had a cross-reactivity with enteric glucagon of 0.1%.

### Statistical methods

Statistical analyses were performed using the BMDP new system, version 1.12, for Windows (BMDP Statistical Software, Los Angeles, CA). Data are given as means ± SD or as median (interquartile range) unless indicated otherwise. Statistical significance of the difference between visits was tested by paired analysis and matched signed-rank test (continuous variables) or Fisher's exact test (frequencies). P < 0.05 was considered statistically significant.

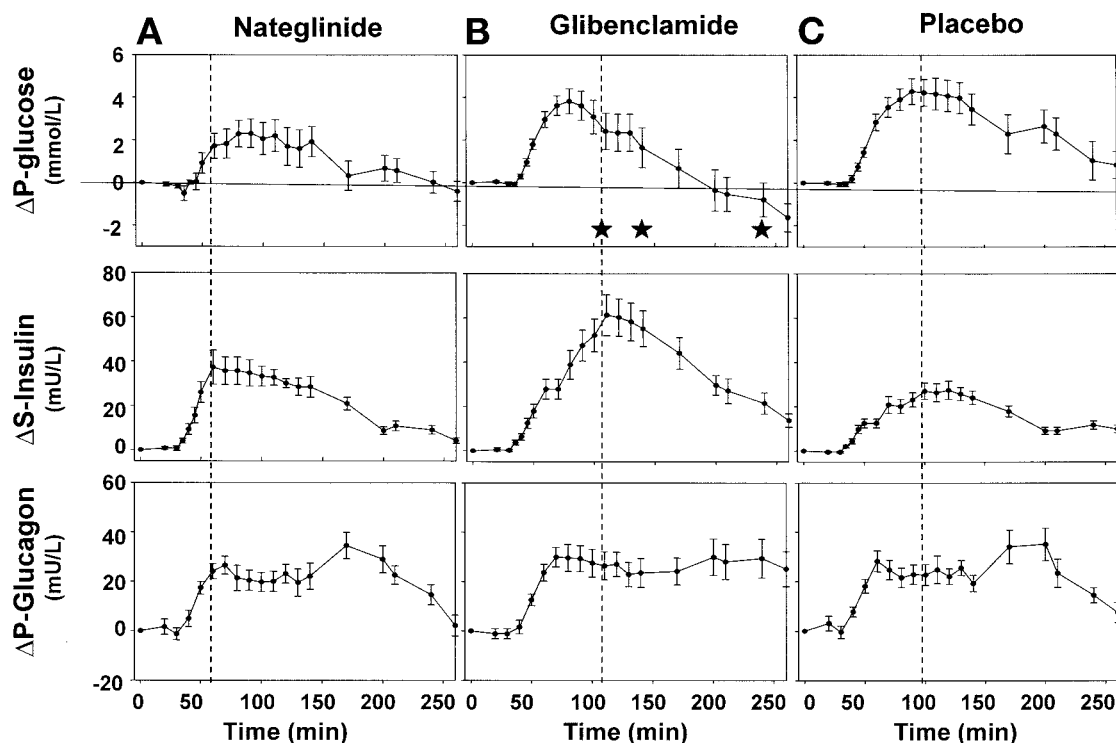
**RESULTS**— All 15 patients completed the three visits and roughly equal numbers received nateglinide, glibenclamide, or placebo during the first, second, and third visits (n = 6/5/4, 4/5/6, and 4/6/5, respectively).

### Glucose, insulin, and glucagon concentrations during the test meal

Serum insulin peaked significantly earlier in response to nateglinide compared with glibenclamide or placebo (median [interquartile range] time 70 [50] vs. 110 [20] vs. 110 [30] min; P = 0.0002 and P = 0.0025, respectively) (Table 2 and Fig. 2). Consequently, the peak plasma glucose (P = 0.031 and P < 0.0001), maximum increment in plasma glucose from fasting (P = 0.031 and P < 0.0001), and incremental glucose area under the curve dur-

ing the first 140 min of the test (P = 0.041 and P < 0.0001) remained significantly lower at the nateglinide visit compared with glibenclamide or placebo (Table 2). Compared with placebo, a significant effect of nateglinide on the prandial rise in glucose was seen already at 70 min (i.e., 50 min after taking the drug and 40 min after starting the meal), whereas the effect of glibenclamide was first seen after 100 min (Fig. 2). At 140 min when the exercise was started, there was no difference in plasma glucose between nateglinide and placebo (Fig. 2). The individual FPG concentrations fluctuated somewhat among the visits (Table 1), but this did not correlate with the maximum increment in plasma glucose at any of the visits (R<sup>2</sup> < 0.2). In keeping with the lower glucose concentrations, the prandial urine glucose concentration was lower after nateglinide than after glibenclamide or placebo, but the difference was not statistically significant (15.4 [59.8] vs. 42.7 [74.0] vs. 33.0 [97.0]; P = 0.345 and P = 0.059, respectively) (Table 2).

Of note, the improved prandial glucose control with nateglinide compared with glibenclamide was achieved with lower peak insulin concentration (median [interquartile range] 47.0 [26.0] vs. 80.4 [71.7] mU/l; P = 0.023) and incremental insulin area at 140 min (2,912 [1,668] vs. 3,253 [3,888] mU/l; P = 0.024) (Table



**Figure 2**—The y-axis shows the change in plasma glucose ( $\Delta P$ -glucose, upper panel), serum insulin ( $\Delta S$ -insulin, middle panel), and plasma glucagon ( $\Delta P$ -glucagon, lower panel) from fasting concentration. Each patient participated three times, receiving in double-blind random order: placebo at time 0 min and 30 mg nateglinide at 20 min (A), 1.25 mg glibenclamide at 0 min and placebo at 20 min (B), or placebo at both 0 and 20 min (C). The test included a meal (30 and 45 min) and light exercise (140–170 min). ★, three patients who interrupted the test during the glibenclamide visit due to symptomatic hypoglycemia; their results are included only until these time points. Data are means  $\pm$  SEM. The  $\Delta P$ -glucose concentrations differed significantly between A and C from 60 to 260 min ( $P < 0.00001$ – $0.020$ ), between A and B at 40–90 min ( $P = 0.008$ – $0.041$ ) and 140–260 min ( $P = 0.0007$ – $0.026$ ), and between B and C at 100–260 min ( $P = 0.0002$ – $0.047$ ). The  $\Delta S$ -insulin concentrations differed significantly between A and C from 40 to 100 min ( $P < 0.0001$ – $0.047$ ), between A and B at 50–260 min ( $P = 0.0001$ – $0.011$ ), and between B and C at 50–260 min ( $P < 0.00001$ – $0.015$ ).

2). Both nateglinide and glibenclamide increased the insulin concentrations significantly compared with placebo.

#### Glucagon response

There were no significant differences in the glucagon responses between the three protocols (Fig. 2). Of note, the glucagon concentration increased concomitantly with the glucose and insulin concentrations. No inhibition of glucagon secretion by increasing glucose concentrations nor stimulation of glucagon secretion by nateglinide and glibenclamide was seen.

#### Exercise and glycemia

At the placebo visit, the median [interquartile range] plasma glucose decreased (by 1.3 [1.7] mmol/l, i.e., from 10.5 [9.9] to 8.3 [10.3] mmol/l ( $P = 0.027$ ) during the 30-min exercise). The decrease in plasma glucose was of the same magnitude after nateglinide (1.0 [2.4] mmol/l). However, after taking glibenclamide, three patients had to interrupt the test due to hypoglycemia (vide infra). The plasma

glucose decrease in the remaining 12 subjects (1.8 [3.8] mmol/l) was not statistically different from that at the placebo and nateglinide visits.

**Hypoglycemia.** No hypoglycemia occurred during the nateglinide or placebo visits. Three patients (numbers 9, 8, and 7) interrupted the test during the glibenclamide visit because of hypoglycemia (plasma glucose 2.3, 2.5, and 3.5 mmol/l at 100, 140, and 247 min, respectively). The hypoglycemia was corrected with oral intake of 30–50 g glucose and a meal containing 50 g carbohydrates. In addition, three patients (numbers 1, 4, and 12) experienced mild hypoglycemia (plasma glucose 2.95, 3.15, and 3.2 mmol/l at 170, 130, and 260 min, respectively) and mild symptoms (visual disturbances, tremor, or ill comfort) but continued the test. For patient 12, the glibenclamide effect was long-lasting: she had to keep eating carbohydrates at home every hour for 12 h to keep her plasma glucose  $>4$  mmol/l.

**CONCLUSIONS**— The study was designed to acutely compare efficacy and safety of the short- and long-acting insulinotropic drugs nateglinide and glibenclamide in patients with MODY3, who are known to be sensitive to sulfonylureas (8–11) and insulin (2). The mechanism by which mutations in the *HNF1 $\alpha$*  gene cause unresponsiveness to glucose stimulus is unknown, but it seems to involve a defect in the early steps of glucose metabolism in pancreatic  $\beta$ -cells (13). Importantly, the use of either substrates that bypass the defect or drugs closing the ATP-sensitive  $K^+$  channel without metabolic stimulus corrects the insulin secretion defect (13,14). Thus, the insulin response to intravenous tolbutamide is similar in MODY3 patients and normoglycemic subjects but higher than the response in type 2 diabetic subjects (11,14). We chose a small dose of 30 mg nateglinide because 7–27% of subjects with IGT were reported to experience hypoglycemia with the regular doses (60–120 mg) of nateglinide (15). This was compared

with 1.25 mg glibenclamide, which is also lower than the 1.75–3.75 mg dose of the micronized drug commonly used in type 2 diabetes. As MODY3 patients frequently report hypoglycemia in conjunction with even mild exercise, we challenged them with light exercise after the meal to provoke hypoglycemia.

The two insulinotropic drugs compared in this study show different binding characteristics to the sulfonylurea receptor as well as timing of onset and length of action. The most commonly used sulfonylurea preparation in Finland, glibenclamide, binds to both the A and B sites of the sulfonylurea receptor, which produces a high-affinity block in the nanomolar range (16,17). In contrast, nateglinide is an amino acid derivative, which resembles the short-chain sulfonylurea tolbutamide in molecular modeling as well as in having reversible type A ligand binding to the sulfonylurea receptor in the micromolar range (16). Further, nateglinide as well as repaglinide can be distinguished from the sulfonylureas by their rapid elimination from the body and lack of apoptotic stimulus of the  $\beta$ -cells in vitro (17).

In the MODY3 patients, both nateglinide and glibenclamide significantly increased insulin secretion and decreased the glucose area under the curve compared with placebo. Similar to results in patients with IGT or mild type 2 diabetes (17,18), the peak insulin response occurred significantly earlier (at 70 min) after nateglinide than after glibenclamide (110 min) or placebo (110 min). As a result, nateglinide controlled the postprandial glucose excursion significantly better than glibenclamide, although the total amount of secreted insulin as estimated by the area under the curve was clearly lower, which is in concert with findings in patients with type 2 diabetes (19,20).

In addition to closing ATP-sensitive  $K^+$  channels, sulfonylureas and nateglinide have been shown to interact directly with the secretory machinery of  $\beta$ - and  $\alpha$ -cells, thereby stimulating  $Ca^{2+}$ -dependent exocytosis of insulin and glucagon, respectively (21,22). Against this, the lack of stimulation of glucagon secretion by nateglinide or glibenclamide was surprising. On the contrary, the glucagon secretion increased along with the glucose and insulin concentrations even during the placebo test meal. Whether hypoglycemia had an effect on glucagon secretion could not be analyzed, because blood sampling was interrupted when hypoglycemia occurred. However, in the patients

who continued the test despite mild hypoglycemia, no clear correlation between hypoglycemia and glucagon response could be seen (data not shown).

No hypoglycemic episodes occurred when subjects took nateglinide either after the test meal or during the light exercise, whereas 6 of the 15 patients experienced symptomatic hypoglycemia after the small dose of glibenclamide. In one patient, the tendency to hypoglycemia was prolonged for 12 h after the test. Thus, nateglinide or another short-acting insulinotropic agent seems to be a safe treatment alternative in MODY3. Despite treatment problems with the propensity for hypoglycemia after sulfonylureas, few randomized treatment trials have been conducted in patients with MODY3 (11). This may be due to the lack of a DNA-based diagnosis in the past. As inherent from the pathogenic defect in insulin secretion, metformin or thiazolidinediones would not be expected to be effective. In support of this hypothesis, metformin was less effective than the short-chain sulfonylurea gliclazide in reducing glycemia in a 6-week trial in 36 patients with MODY3 (11). These data clearly show that an insulin secretagogue is the drug of choice in MODY3.

For insulin-sensitive patients with a tendency for hypoglycemia, the theoretical drug of choice would be either an insulinotropic agent with rapid onset and short duration of action or a meal-time insulin analog, which has similar properties. In addition to nateglinide, repaglinide also fulfills these criteria. Although it has a slightly slower onset (time to 50% maximal inhibition 12 vs. 4 min) and more long-lasting effect (time to 50% relief of inhibition 175 vs. 35 min) than nateglinide (12), these differences might not have clinical significance. Acarbose, used by some of our patients, might also benefit patients with MODY3, as it prolongs the absorption of glucose, thus reducing the prandial excursions. However, its gastrointestinal side effects limit its use.

In summary, this acute study shows that a small dose of nateglinide prevents the rise in postprandial glucose excursions better than glibenclamide and with less stimulation of peak insulin concentrations and less hypoglycemic symptoms in patients with MODY3. With the increasing availability of a genetic diagnosis for MODY, randomized multicenter trials evaluating different treatment options in

this difficult-to-treat group should be planned.

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