# β-Cell Response During a Meal Test

## A comparative study of incremental doses of repaglinide in type 2 diabetic patients

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**OBJECTIVE** — To assess the effects of incremental doses of repaglinide on postprandial insulin and glucose profiles after a standard 500-kcal test meal.

**RESEARCH DESIGN AND METHODS** — Sixteen diet-treated Caucasians with type 2 diabetes (mean $HbA_{1c}$ 8.4%) were enrolled in this randomized, open-label, crossover trial. Subjects received 0.5, 1, 2, and 4 mg repaglinide or placebo in a random fashion, followed by a standard 500-kcal test meal on 5 separate study days, 1 week apart.

**RESULTS** — The insulinogenic index (ΔI30/ΔG30) and insulin area under the curve (AUC) from 0 to 30 min ($AUC_{0-30}$) were higher with the 4-mg drug dose compared with the two lower doses and with 2 mg compared with 0.5 mg. On subgroup analysis, the incremental insulin responses were apparent only in the fasting plasma glucose (FPG) <9-mmol/l subgroup of subjects and not in the FPG >9-mmol/l subgroup. There was a significant dose-related increase in the late postprandial insulin secretion (insulin $AUC_{120-240}$), which resulted in hypoglycemia in four subjects. Proinsulin-to-insulin ratios at 30 and 60 min improved with increasing doses of repaglinide; higher drug doses (2 and 4 mg) were more effective than the 0.5- and 1-mg doses.

**CONCLUSIONS** — Significant dose-related increases in early insulin secretion were found only in less advanced diabetic subjects. In advanced diabetic patients, only the maximum dose (4 mg) was significant compared with placebo. Better proinsulin-to-insulin processing was noted with increasing drug doses.

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Characteristically, type 2 diabetic patients manifest abnormalities of insulin secretion in response to glucose or meal challenges. The insulin secretory defects are quantitative and qualitative and tend to develop early in the history of the disease (1).

The normal insulin response to an intravenous glucose bolus has a typical biphasic pattern when quantified using either a hyperglycemic clamp or an intravenous glucose tolerance test. A "first-phase" insulin secretory burst occurs within 3–5 min and is over by 10 min. This is followed by a sustained "second phase" of secretion that lasts several hours in parallel with the glycemic stimulus.

Following oral glucose administration, the two phases of secretion are less distinct, and a clear separation between them is virtually impossible. Several indexes of insulin secretion, derived from the insulin responses during the first 30 min of an oral glucose tolerance test or a standardized meal, correlate with the first phase of insulin secretion in response to intravenous glucose. The calculated secretion using these indexes has been called "early" insulin secretion to differentiate it from the true first phase of insulin secretion.

First-phase insulin has an important physiological role in the rapid switching of the metabolic processes between fasting and postprandial states, primarily inhibiting the endogenous hepatic glucose production (2). The absence of the first-phase insulin secretory burst in type 2 diabetes leads to unsuppressed postprandial glucose production by the liver, with subsequent worsening of postprandial glycemia (PPG) (3).

The therapeutic approach in type 2 diabetes has classically focused on fasting glucose. However, >40% of diabetic subjects with a fasting glucose <6.7 mmo/l and ~90% of those with $HbA_{1c}$ <7% have abnormal postprandial glucose excursions (4). Postmeal hyperglycemia has an estimated ~30% contribution to the overall $HbA_{1c}$ concentration, proportional with the amount of time the body spends in the postprandial state. Consistent with these observations, especially in the early diabetic stages, some patients are found to have an $HbA_{1c}$ >7% associated with "adequate" fasting glucose values (<7 mmol/l). Furthermore, therapies aimed at both fasting glucose and PPG may be more effective in lowering $HbA_{1c}$ (5).

Despite the PPG contribution to $HbA_{1c}$ and the growing body of evidence linking it to the genesis of cardiovascular disease, there is no consensus regarding routine glycemic monitoring and therapeutic targeting in the postprandial state. For example, the American Diabetes Association does not recommend routine monitoring of the PPG unless premeal glucose values are normal and $HbA_{1c}$ is >7% (6), while the American Association of Clinical Endocrinologists suggests rou-

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**Abbreviations:** AUC, area under the curve; FPG, fasting plasma glucose; PPG, postprandial glycemia.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

tine monitoring with a treatment target for PPG of <7.8 mmol/l (7,8).

Ideally, to be effective on the early postprandial insulin profile, a therapeutic agent has to exert its maximum effects within the first 1 h after a meal (9). Although pharmacological restoration of the normal biphasic secretory response of the β-cells is unlikely, an emulation of the biphasic pattern by boosting the early phase of secretion is possible. Short-acting insulin analogs are ideally suited for this purpose and have been shown to improve postprandial glucose tolerance (10). The inconvenience of multiple daily administrations, however, makes them unacceptable to a large segment of the early diabetic population. The rapidly absorbed D-phenylalanine analog nateglinide, as well as meglitinide derivatives (repaglinide, meglitinide, and metiglinide), reach maximum plasma concentration within 0.5–1 h and are thus able to stimulate the β-cells early postprandially (11). Several studies have shown that nateglinide (12) and repaglinide (13) stimulate early insulin secretion more effectively compared with the long-acting sulfonylureas glibenclamide and glimepiride, respectively. Among the sulfonylurea class members, the pharmacokinetic profile of a particular molecule is determinant for the effects on the early phase of insulin secretion. Thus, short-acting sulfonylurea agents such as glipizide can achieve β-cell stimulation in the early postprandial period, as shown recently by our group (14) and others (15).

This study was designed to look at the effects of various doses of repaglinide on the postprandial insulin and glucose profiles. As a surrogate approximation of first-phase insulin secretion, we used the early secretory responses (area under the curve [AUC] from 0 to 30 min [$AUC_{0-30}$]) after a standard meal challenge.

## RESEARCH DESIGN AND METHODS

— A total of 16 diet-treated Caucasians with type 2 diabetes were recruited into the study. Their ages varied between 40 and 70 years and all were being followed up regularly at the Diabetes Research Unit in Llandough Hospital, Cardiff. No patient was receiving hypoglycemic agents at the time of enrollment. Exclusion criteria included prior hypoglycemic medication, BMI >35 kg/m$^2$, positive islet cell and GAD antibodies, and uncontrolled dyslipidemia (fasting triglycerides >6.0 mmol/l, total cholesterol >6.5 mmol/l). Patients also were excluded if they had liver disease or persistent elevation of liver enzymes, renal disease, and active cardiovascular disease or uncontrolled hypertension (blood pressure >160/95 mmHg). Research participants gave written informed consent after thorough explanation and before initiation of research, in accordance with the Declaration of Helsinki. The study was approved by the local ethics committee.

The study used an open-label, crossover, placebo-controlled design. Participants were admitted in the morning of the tests in the Diabetes Research Unit. There were 5 study days, 1 week apart. The first day of tests followed within 7 days of the screening visit, and a follow-up visit was conducted within 7 days of the last study visit.

After a 10-h overnight fast, an intravenous cannula was inserted into a forearm vein and saline infusion was started. Each subject received placebo or 0.5, 1, 2, or 4 mg repaglinide in random fashion. Administration of the drug was followed 15 min later by a standard 500-kcal meal tolerance test (55% carbohydrate, 30% fat, and 15% protein), ingested over 10 min. Blood sampling for glucose, insulin, total and intact proinsulin, and C-peptide was performed at −30 and 0 min before the meal. Postmeal samples were collected every 30 min for a total of 4 h.

### Sample analysis

Blood samples were taken into fluoride oxalate for assay of plasma glucose (YSI2300; YSI, Aldershot, Hants, U.K.) and lithium heparin for assay of insulin, total and intact proinsulin, and C-peptide. Tubes were centrifuged and the plasma decanted and stored at −20°C before assay. Insulin was measured by a specific immunoassay (MLT Research, Cardiff, S. Glam, U.K.), and the cross-reactivity of proinsulin in the insulin assay was <2%. C-peptide was measured by immunoassay (Dako Diagnostics, Ely, Cambs, U.K.), which cross-reacted <2% with insulin and ~100% with proinsulin. Intact and total proinsulin were measured by immunoassay (MLT Research).

### Statistical analysis

Time-averaged mean insulin and glucose responses were computed as incremental AUCs (above baseline) using the trapezoidal rule, divided by the time interval (hours). Values at each individual time point were compared directly. Total glycemic exposure (glucose $AUC_{0-240}$) is also given with reference to zero (rather than the baseline) to account for the "negative" glycemia over the last 120 min.

The insulinogenic index (ΔI30/ΔG30) was calculated as an index of β-cell response as in the ADOPT (A Diabetes Outcome Progression Trial) study (16). Plasma proinsulin-to-insulin ratios were calculated by dividing the concentration of intact proinsulin (pmol/l) by insulin (mU/l) at 30, 60, and 90 min.

Paired Student's *t* test was used for normally distributed data. All direct comparisons were two tailed. Abnormally distributed variables were normalized by logarithmic transformation (results given as medians with min-max values). Data are presented as means ± SE unless otherwise specified.

Comparisons across different drug strengths were performed using ANOVA with dose as a within-subject factor. Post hoc comparisons were performed using the Bonferroni adjustment, with a significance level of <0.02% to account for multiple comparisons. All analyses were performed on SPSS v11.1 (SPSS, Chicago, IL).

## RESULTS

### Demographics

A total of 10 men and 6 women with a mean age of 57.7 ± 2.1 years were studied. They had a mean BMI of 29.3 ± 1.0 kg/m$^2$, a mean fasting plasma glucose (FPG) of 9.3 ± 0.5 mmol/l (range 6.5–14.2), and an $HbA_{1c}$ of 8.4 ± 0.4% (range 6.7–13.6).

### Insulin and C-peptide

Mean insulin profiles are given in Fig. 1. Within 30 min postmeal and thereafter, plasma insulin concentrations were significantly increased by all repaglinide dose levels compared with placebo. Maximum insulin concentration post repaglinide was reached at 94 ± 8.7 min ($t_{max}$), irrespective of the dose. Higher doses (2 and 4 mg) were more effective on the maximum insulin concentration than the 0.5-mg dose ($P < 0.001$, $P = 0.006$ for trend). The 4-mg repaglinide dose resulted in higher insulin levels at 30 (72.3 ± 10.6 mU/l) and 60 min (104.6 ± 12.3 mU/l) compared with the 0.5-mg

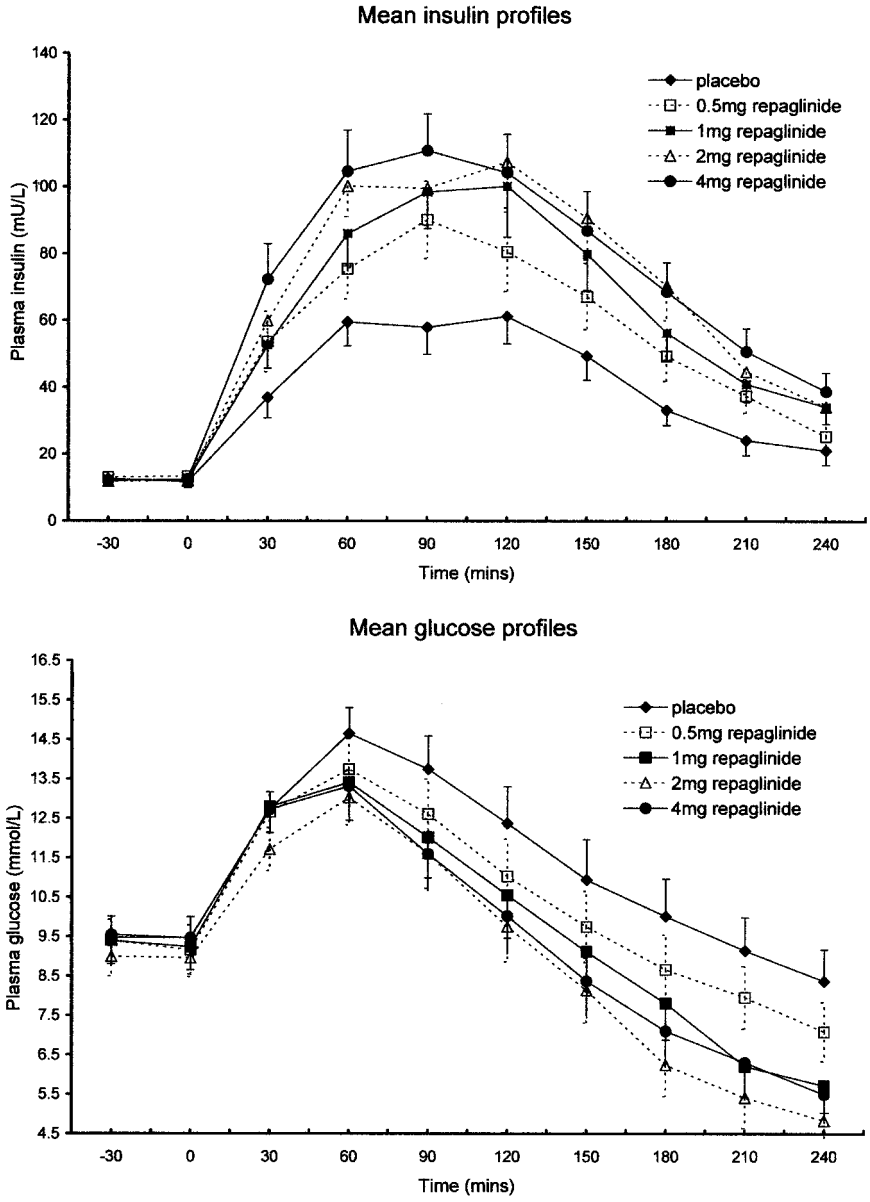



**Figure 1**—*Mean plasma insulin and glucose concentrations (±SE) after treatment with 0.5, 1, 2, or 4 mg repaglinide and placebo 15 min preprandial.*

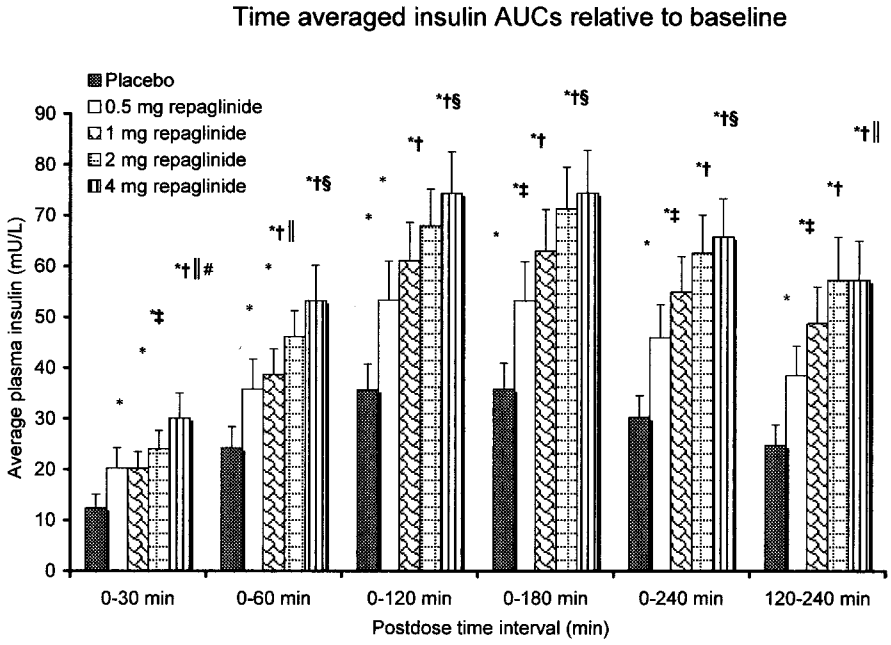
(53.6 ± 9.0 mU/l, $P = 0.001$ and 75.4 ± 8.9 mU/l, $P = 0.004$) and 1-mg (52.7 ± 7.0 mU/l, $P = 0.006$ and 85.9 ± 9.7 mU/l, NS) doses. The 2-mg dose level reached significance versus the 0.5-mg strength at 60 min ($P = 0.001$).

Peak and integrated insulin excursions were higher with all drug strengths compared with placebo. Peak insulin excursions were significant with 2 and 4 mg repaglinide compared with 0.5 mg ($P < 0.001$, $P = 0.006$ for trend). Integrated insulin excursions with 4 mg were higher than with 0.5 mg ($P = 0.004$, NS for trend). Mean integrated insulin changes relative to baseline presented as hourly averages for various time intervals are shown in Fig. 2.

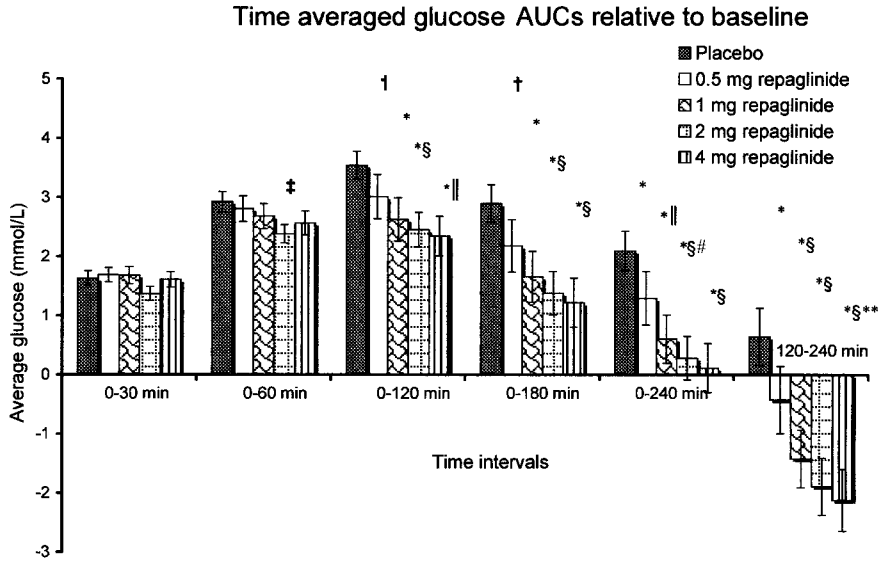
The early insulin secretion ($AUC_{0-30}$) increase over placebo was 1.61 ± 0.21-fold, 1.61 ± 0.17-fold, 2.05 ± 0.26-fold, and 2.62 ± 0.37-fold for 0.5, 1, 2, and 4 mg repaglinide, respectively. For pairwise comparisons, the 4-mg dose level reached significance vs. 0.5 mg ($P = 0.003$) and 1 mg ($P = 0.017$) and was nonsignificant versus 2 mg ($P = 0.047$). Subgroup analysis by FPG (<9 mmol/l, eight subjects and >9 mmol/l, eight subjects) found all significant differences in the first subgroup (FPG <9 mmol/l). In the second subgroup all interdose significance was lost and the three lowest strengths (0.5, 1, and 2 mg) were no different from placebo.

Toward the end of the meal test, the 4-mg dose level stimulated secretion >0.5 mg at 180 min (68.6 ± 8.8 vs. 49.2 ± 7.4 mU/l, $P = 0.008$), 210 min (50.7 ± 6.9 vs. 37.4 ± 5.1 mU/l, $P = 0.02$), and 240 min (38.7 ± 5.6 vs. 25.3 ± 3.7 mU/l, $P = 0.002$). The highest dose was also significant against 1 mg repaglinide at 180 min ($P = 0.02$), 210 min ($P = 0.013$), and 240 min ($P = 0.002$). The 2-mg dose level reached significance compared with the 0.5-mg strength at 180 min ($P = 0.01$) and 240 min ($P = 0.002$), while the 1 mg dose level was significant versus 0.5 mg at 240 min ($P = 0.002$).

Over the last 2 h of the test meal ($AUC_{120-240}$), the insulin increase over placebo was 1.67 ± 0.14-fold, 2.24 ± 0.23-fold, 2.40 ± 0.20-fold, and 2.41 ±




Difference against placebo: $P < 0.001$ (*). Difference against repaglinide 0.5 mg: $P < 0.001$ (†), $P < 0.03$ (‡). Difference against repaglinide 1 mg: $P < 0.005$ (§), $P < 0.02$ (‖). Difference against repaglinide 2 mg: $P < 0.05$(#.)




Difference against placebo: $P < 0.001$ (*), $P < 0.01$ (†), $P = 0.03$ (‡). Difference against repaglinide 0.5 mg: $P < 0.003$ (§), $P < 0.02$ (‖). Difference against repaglinide 1 mg: $P < 0.005$ (#), $P < 0.05$ (**).

**Figure 2**—*Time-averaged incremental plasma insulin and glucose AUCs (±SE) after treatment with 0.5, 1, 2, and 4 mg repaglinide and placebo 15 min preprandial.*

0.18-fold for 0.5, 1, 2, and 4 mg repaglinide, respectively. The trend between drug doses was significant ($P < 0.000$).

Table 1 presents the intact proinsulin-to-insulin ratios and the insulinogenic indexes.

## Effects on glucose

Figure 1 depicts the mean glucose profiles post–meal challenge. Following drug administration, peak postprandial glucose was reached at 53 ± 5 min with all doses. Glucose excursions were 4.2 ± 0.3 and 4.1 ± 0.3 mmol/l with 2 and 4 mg, respectively, both of which were significant versus placebo (5.3 ± 0.3 mmol/l, $P < 0.004$). Integrated glucose excursion after placebo (3.2 ± 0.3 mmol/l) was lowered significantly by 1 mg (2.2 ± 0.3 mmol/l, $P = 0.02$), 2 mg (2.3 ± 0.3 mmol/l, $P = 0.01$), and 4 mg (2.3 ± 0.4 mmol/l, $P = 0.009$) repaglinide. Subgroup analysis found all significant differences in the subjects with FPG <9 mmol/l.

No significant lowering of the glucose $AUC_{0-30}$ and $AUC_{0-60}$ was found with any drug dose (Fig. 2). Mean glucose increase above baseline during the first 120 min postprandially ($AUC_{0-120}$) was 3.5 ± 0.2 mmol/l with placebo, and this

**Table 1—*Comparison of the ΔI30/ΔG30 and intact proinsulin-to-insulin ratios at 30, 60, and 90 min***

| | Placebo | Repaglinide dose | | | | ANOVA |
|---|---|---|---|---|---|---|
| | | 0.5 mg | 1 mg | 2 mg | 4 mg | |
| ΔI30/ΔG30 | 6.68 (0.79–17.13) | 9.26 (1.19–28.93)‡ | 10.64 (2.38–24.91)* | 14.54 (1.4–233.00)*‖ | 15.53 (4.07–75.36)*§¶ | 0.004 |
| Proinsulin-to-insulin ratio | | | | | | |
| 30 min | 0.50 (0.13–1.60) | 0.48 (0.15–1.29) | 0.43 (0.13–1.61)‡ | 0.33 (0.12–0.98)*§ | 0.38 (0.12–0.89)*§¶ | 0.001 |
| 60 min | 0.42 (0.20–2.33) | 0.46 (0.21–0.86) | 0.41 (0.18–1.22) | 0.34 (0.17–1.00)*§ | 0.36 (0.19–1.00)*§ | 0.003 |
| 90 min | 0.74 (0.23–1.77) | 0.58 (0.28–1.14) | 0.53 (0.24–1.24) | 0.55 (0.25–1.20)‡ | 0.54 (0.24–1.58)† | NS |

Data are median (range). ANOVA across different repaglinide doses. Significant difference against placebo: *$P < 0.001$, †$P < 0.009$, ‡$P < 0.02$. Significant difference against 0.5 mg repaglinide: §$P < 0.003$, ‖$P < 0.02$. Significant difference against 1 mg repaglinide: ¶$P < 0.004$.



was limited to 2.6 ± 0.4, 2.4 ± 0.3, and 2.3 ± 0.3 mmol/l by 1, 2, and 4 mg repaglinide, respectively. The two higher dose levels reached significance versus the 0.5-mg dose ($P = 0.49$ for the trend between doses). Total postprandial glycemic exposure ($AUC_{0–240}$ above zero) was reduced in a dose-dependent manner (up to the 2-mg dose level) versus placebo by 9 ± 2 (0.5 mg), 14 ± 2 (1 mg), 22 ± 2 (2 mg), and 18 ± 3% (4 mg) ($P < 0.000$ for trend).

**CONCLUSIONS** — The relentless decline in pancreatic insulin secretion is the result of gradual β-cell loss compounded by the "toxic" effects of hyperglycemia on the surviving islets (17). Consequently, the benefits of insulin secretagogue medication are expected to be maximal in the early stages of diabetes. With regard to $HbA_{1c}$, the diabetic population in our study had a relatively balanced distribution: five patients had $HbA_{1c}$ of 6.5–7.5% (early diabetes), eight patients $HbA_{1c}$ of 7.5–9%, and three patients $HbA_{1c}$ >9% (advanced diabetes).

Studies conducted in normoglycemic subjects have illustrated the importance of the first phase of insulin secretion to postprandial glucose homeostasis (18). This phase of secretion is virtually absent when FPG is >6.4 mmol/l (19). Therapeutic "mimicking" of the first phase in type 2 diabetes subjects, using intravenous insulin (20) or subcutaneous fast-acting insulin analogs (10), resulted in improved glucose tolerance. Furthermore, the higher the insulin surge, the better the subsequent glucose profile. An improved glucose profile might alleviate the "stress" imposed on the pancreas in the late postprandial phase, possibly delaying the β-cell decline.

We found significant dose-related increases in the insulin concentrations 30 and 60 min postprandially. The insulinogenic index also displayed a similar increase with higher drug doses, suggesting a dose-dependent improvement in β-cell function (Table 1). The insulinogenic index after an oral glucose tolerance test has been shown to be a good predictor of first-phase insulin secretion, correlating well with the hyperglycemic clamp data in nondiabetic control subjects (21). Similarly, after a mixed meal, 30-min incremental insulin response correlates with the acute insulin response (22). In our study, more insulin was secreted in the early phase ($AUC_{0–30}$) with the highest drug dose (4 mg) compared with the two lower doses and with 2 mg compared with 0.5 mg. However, these differential insulin responses to different drug strengths were only apparent in the FPG <9-mmol/l subgroup of subjects not in the FPG >9 mmol/l subgroup. Furthermore, the lack of significance against placebo with all but the 4-mg repaglinide dose in the latter group suggests that a single higher strength dose should probably be used in more advanced diabetic stages. Supporting these observations, the differences in the insulinogenic index were found exclusively in the FPG <9-mmol/l subgroup on separate analysis (data not shown).

The failing β-cell secretes an abnormally high amount of proinsulin relative to insulin, reflecting incomplete or defective proinsulin processing (1). This anomaly is apparent both in the basal state and poststimulation. The proinsulin–to–total immunoreactive insulin ratio was found to inversely correlate with the acute insulin response in diabetic subjects (23) and thus can be used as a marker for β-cell function. Pharmacological intervention with glibenclamide in type 2 diabetic subjects had no effect on the basal or arginine-stimulated proinsulin–to–total immunoreactive insulin ratio (24). In a different study, 6 months' treatment with glibenclamide was associated with higher basal proinsulin levels compared with metformin, despite similar glycemic control (25). In our study, we found an improvement in the proinsulin-to-insulin ratios 30 and 60 min postprandially with increasing doses of repaglinide; higher drug doses (2 and 4 mg) were more effective than the 0.5- and 1-mg strengths (Table 1). Lower proinsulin-to-insulin ratios suggest a better proinsulin-to-insulin processing with increasing doses of repaglinide. The significance of these findings following a meal challenge is unclear, and further confirmation is needed in longitudinal studies. To our knowledge, no previous studies on short-acting insulin secretagogues have reported on the effects of these drugs on the proinsulin-to-insulin ratios. Interestingly, the differences seen in the proinsulin-to-insulin ratios were similar in both patient subgroups (FPG <9 mmol/l and FPG >9 mmol/l).

Standard sulfonylurea therapy can cause hypoglycemia as a major side effect (26). The frequency and severity of hypoglycemia is higher in the early diabetic stages (27) and with longer-acting agents (chlorpropamide and glibenclamide) compared with shorter-acting ones (gliclazide and glipizide). Repaglinide therapy is associated with less frequent hypoglycemic events compared with glibenclamide (28). However, despite its short plasma half-life, the drug has a prolonged residence time on the receptor site, resulting in continuing stimulation of the β-cells for several hours (29). Thus, an extension of the hypoglycemic actions beyond 2–3 h postdosing has been noted

with repaglinide (30). Our data support these observations; late insulin secretion (insulin $AUC_{120-240}$) displayed a gradual dose-related increase associated with a dose-related decrease in the late postprandial glucose (glucose $AUC_{120-240}$) ($P = 0.001$ for trend). Examination of the total postprandial glycemia (glucose $AUC_{0-240}$ above zero) revealed >50% extra lowering with each of the three higher doses compared with the lowest dose of repaglinide. The most significant contributions, however, were apparent over the last 2 h postmeal (glucose $AUC_{120-240}$). Related to these delayed postprandial actions, several subjects experienced symptomatic late hypoglycemia (glucose <3.5 mmol/l) with the 2-mg (three patients) and 4-mg (four patients, including three subjects mentioned earlier) dose. All hypoglycemic events with one exception were observed in the FPG <9-mmol/l subgroup.

Our observations are contradictory to those of Damsbo et al. (28), who reported no symptomatic hypoglycemic events in their repaglinide-treated group, even when omitting the lunch meal. By contrast, in healthy volunteers, Kalbag et al. (30) found prolonged hypoglycemic effects with repaglinide compared with nateglinide, which extended up to 8 h postprandially.

Our findings suggest that, at least at higher dose levels (2 and 4 mg), repaglinide tends to induce late postprandial hypoglycemia similar to the standard sulfonylurea class of drugs. Further support to our data are provided by longitudinal studies in which frequency of minor hypoglycemia with repaglinide treatment has been reported to vary between 15% (31) and 33% (32).

Early postprandial hyperglycemia is seen in the majority of diabetic subjects. As a result, there is an excess or "rebound" insulin secretion in the late postprandial period. In the early diabetic stages, the pancreas can sustain supranormal absolute levels of insulin production in response to hyperglycemia. By contrast, in advanced diabetic stages, β-cell mass loss eventually results in inappropriately low insulin secretion (33).

In our study, individuals with relatively preserved β-cell function (FPG <9 mmol/l) increased the insulin output both in the early and late postprandial periods with higher drug strengths. Thus, the potential benefits of higher early insulin secretion ($AUC_{0-30}$), insulinogenic index, and maximum insulin concentration in this subgroup must be balanced against the increased risk of late hyperinsulinemia and subsequent late hypoglycemia.

In addition to having an important contribution to hemoglobin glycosylation, postprandial glucose exposure has a role in the genesis of diabetes complications (34). It is still unclear, however, whether meal-related glucose excursions are more important than the overall postprandial glycemic exposure in this respect. Early insulin secretion burst has a significant impact on both, leading to more rapid postprandial normalization of hyperglycemia.

Despite the incremental actions on the insulin secretion, we found no significant effects on the early glycemic parameters even on subgroup analysis. This lack of hypoglycemic response could have several explanations. First, our study might not be sufficiently powered to allow the detection of minor differences in this population of unselected type 2 diabetic subjects with a wide range of insulin secretion and resistance. Second, the FPG level may account for up to 50% of the variability in the early postmeal hyperglycemia (glucose excursions, glucose $AUC_{0-30}$) even after baseline correction (35). Ideally, to minimize the influence of FPG, all study subjects should be admitted overnight and stabilized with glucose and insulin infusions before running the tests. Finally, intrasubject day-to-day variability in the rate of gastric emptying and the incretin effect could influence the absorption of the meal and subsequent early glucose rise even before sufficient time has elapsed for an effective inhibition of the hepatic glucose production.

In conclusion, we found significant interdose differences between the effects on the early insulin secretion and insulinogenic indexes in less advanced diabetic subjects. They were more prone to late hypoglycemia compared with advanced diabetic subjects who, by contrast, had a flat insulin secretory response limited to the highest drug dose. Dose-dependent improvements in the proinsulin-to-insulin processing were noted.

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