Modification of Postprandial Hyperglycemia With Insulin Lispro Improves Glucose Control in Patients With Type 2 Diabetes

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OBJECTIVE — Insulin lispro is a rapid-acting analog of human insulin that can be used to target the postprandial rise in plasma glucose. We designed an open-label randomized crossover study of type 2 diabetic patients with secondary failure of sulfonylurea therapy to determine whether improvement of postprandial hyperglycemia would affect total daily glucose control.

RESEARCH DESIGN AND METHODS — Twenty-five type 2 diabetic patients who were poorly controlled on a maximum dose of sulfonylureas were studied in a university hospital clinical research center. In one arm of the study, patients continued therapy with maximum-dose sulfonylureas. In the other arm, patients used a combination therapy with insulin lispro before meals and sulfonylureas. After 4 months, patients were crossed over to the opposite arm. Fasting plasma glucose (FPG) and 1- and 2-h postprandial glucose (after a standardized meal), HbA_{1c}, total, HDL, and LDL cholesterol, and triglyceride levels were measured at the end of each arm of the study.

RESULTS — Insulin lispro in combination with sulfonylurea therapy significantly reduced 2-h postprandial glucose concentrations, compared with sulfonylureas alone, from 18.6 to 14.2 mmol/l ($P < 0.0001$), and incremental postprandial glucose area from 617.8 to 472.9 mmol · min · l^{-1} ($P < 0.0007$). FPG levels were decreased from 10.9 to 8.5 mmol/l ($P < 0.0001$), and HbA_{1c} values were reduced from 9.0 to 7.1% ($P < 0.0001$). Total cholesterol was significantly decreased in the lispro arm from 5.44 to 5.10 mmol/l ($P < 0.02$). HDL cholesterol concentrations were increased in the lispro arm from 0.88 to 0.96 mmol/l ($P < 0.01$). The patients weighed significantly more after lispro therapy than after sulfonylureas alone, but the difference was small in absolute terms (sulfonylurea therapy alone, 90.6 kg; lispro therapy, 93.8 kg; $P < 0.0001$). Two episodes of hypoglycemia (glucose concentrations, <2.8 mmol/l) were reported by the patients while using lispro.

CONCLUSIONS — Previously, it has not been possible to address the effect of treatment of postprandial hyperglycemia specifically. We have now shown that the treatment of postprandial hyperglycemia with insulin lispro markedly improves overall glucose control and some lipid parameters in patients with type 2 diabetes.

Although type 2 diabetes is a disorder of insulin secretion and insulin action, most patients initially retain significant secretory reserves (1). Sulfonylureas, which stimulate insulin secretion and enhance insulin action, are often effective as an initial therapy when diet alone fails. Unfortunately, in a substantial number of patients, normoglycemia cannot be maintained with sulfonylureas or other oral agents alone (2). With chronic hyperglycemia, insulin deficiency progresses and exogenous insulin is required (2,3). When developing insulin therapeutic regimens, fasting and preprandial blood glucose levels are conventionally monitored. However, postprandial hyperglycemia may also contribute significantly to the development of cardiovascular complications (4,5). Until recently, insulin therapy that specifically targets postprandial hyperglycemia has not been available. With the development of the rapid-acting insulin lispro, postprandial glucose levels can be manipulated specifically.

Insulin lispro is an analog of human insulin. The amino acid sequence at B-28 and B-29 of human insulin is reversed in insulin lispro, resulting in lysine and proline at B-28 and B-29, respectively. Insulin lispro has a more rapid absorption and a shorter duration of action than regular insulin (6). This study explores the benefit of correcting postprandial hyperglycemia in a group of type 2 diabetic patients who had secondary failure of sulfonylurea therapy.

RESEARCH DESIGN AND METHODS

Participants

Twenty-five patients with type 2 diabetes who were poorly controlled on the maximum dose of various sulfonylureas were recruited from Duke University Medical Center clinics. Informed consent was obtained for participation in an open-label randomized crossover study of the effect of combination therapy with insulin lispro. Patient characteristics are shown in Table 1.

Protocol

Patients were enrolled in the study based solely on the following criteria: HbA_{1c} >8% or two fasting plasma glucose (FPG) measurements >9 mmol/l. Patients with significant renal, hepatic, or cardiovascular disease were excluded. To confirm the diagnosis of type 2 diabetes, C-peptide levels were measured in response to a mixed meal. With one exception (1.2 nmol/l), all patients selected had C-peptide levels >2 nmol/l. Patients were instructed by a dietitian in a weight-

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Abbreviations: FPG, fasting plasma glucose.

Table 1—*Patient characteristics at recruitment*

n (M/F)	15/10
Age (years)	53.2 (37.0–69.0)
Duration of diabetes (years)	9.1 (2.0–26.0)
Weight (kg)	91.7 (65.5–143.2)
BMI (kg/m^2)	31.3 (23.3–44.4)
FPG (mmol/l)	14.4 (9.2–18.9)
HbA_{1c} (%)	9.7 (7.4–12.8)
C-peptide (nmol/l)	1.56 (0.40–3.24)
Total cholesterol (mmol/l)	4.98 (2.66–11.1)
HDL cholesterol (mmol/l)	0.76 (0.26–1.37)
LDL cholesterol (mmol/l)	2.81 (0.49–5.92)
Triglycerides (mmol/l)	3.33 (0.49–17.10)

Data are *n* or means (range).

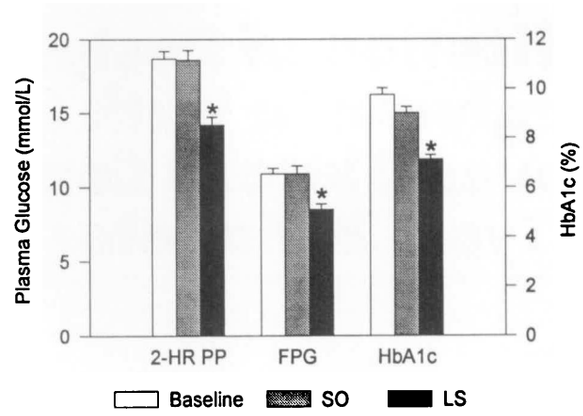

Figure 1—*Effect of the addition of preprandial lispro administration to sulfonylurea therapy on parameters of glucose control. Baseline, study initiation; LS, preprandial insulin lispro therapy; PP, postprandial; SO, sulfonylurea therapy alone.* *P < *0.0001.*

maintenance diabetic diet. The average diet consisted of 50% carbohydrate, 20% protein, and 30% fat. Patients were asked to eat three daily meals and a bedtime snack.

Four weeks later, patients were admitted to the Duke University Clinical Research Center, baseline studies were obtained, and patients were randomized to one of two treatment arms: continued therapy with the maximum dose of sulfonylureas for 4 months or combination therapy of insulin lispro and sulfonylureas for 4 months. After the initial treatment, patients were crossed over to the opposite arm. Insulin lispro was administered 5 min before each meal (nutrient content, >20% of daily caloric intake) at a dose individualized to patient needs. Initial doses were 0.08–0.15 U/kg (median final dose, 24 U/24 h; interquartile range, 19–37 U/24 h). Patients were contacted by telephone at least weekly to provide assistance with insulin adjustment according to accepted algorithms (7). Although 2-h postprandial values were periodically monitored, the adjustment was based on glucose values before meals and at bedtime. No intermediate or long-acting insulins were administered in this study.

Assays

At the beginning of the study and at the end of each 4-month treatment arm, the following laboratory values were obtained: FPG values obtained at 8:00 A.M., 5 min before the administration of a standard meal consisting of 469 calories (238 ml of Ensure Plus with 30 g of polycose powder); 1- and 2-h postprandial glucose levels (Kodak Ektachem 700XR Analyzer, Eastman Kodak, Rochester, NY); HbA_{1c} (normal range, 4.5–6.0%; IMx Boronate Affinity Method, Abbott Laboratories, Abbott Park, IL); fasting and 1-h poststimulated (Ensure Plus) C-peptide levels (radioimmunoassay, Serono, Allentown, PA); fasting and 1-h free insulin levels (radioimmunoassay, 1:1 mixture of specimen and PEG [INCSTAR, Stillwater, MN]); total cholesterol (Hitachi 911 Analyzer Enzymatic [cholesterol esterase] Method, Boehringer Mannheim, Indianapolis, IN); HDL cholesterol (Hitachi 911 Analyzer [as above], after pretreatment with dextran sulfate [50,000 molecular weight], Sigma, St. Louis, MO); LDL cholesterol (determined by calculation); and triglyceride levels (Hitachi 911 Analyzer Enzymatic [glycerol-blanked glycerol phosphate oxidase (GPO)] Method).

Analysis

Data from the two treatment conditions were compared using repeated-measures analysis of variance (PROC GLM, SAS for Windows, SAS Institute, Cary, NC), and statistical significance was set at $P < 0.05$. For glucose analysis, only laboratory values obtained during hospitalizations were used. The effects of treatment order were evaluated and found to be nonsignificant for all outcome variables. Thus, data from both treatment orders were combined for the comparisons of the sulfonylurea and lispro arms of the study. Given the crossover design, results are presented as the means for the two treatment conditions and the mean of the difference between treatments (± SE). Reported *P* values indicate the significance of the within-subject tests of the differences between treatment conditions.

RESULTS — Insulin lispro in combination with sulfonylureas significantly reduced 2-h postprandial glucose concentrations, compared with sulfonylureas alone (sulfonylurea therapy alone, 18.6 mmol/l; lispro therapy, 14.2 mmol/l). The mean of the difference between the two arms was 4.4 ± 0.4 mmol/l ($P < 0.0001$). The incremental postprandial glucose area, calculated from the 1- and 2-h postprandial glucose values, was 617.8 mmol · min · l^{-1} for the sulfonylurea arm and 472.9 mmol · min · l^{-1} for the lispro arm (mean of the difference, 144.8 ± 37.2 mmol · min · l^{-1}; $P < 0.0007$). FPG values also decreased significantly (sulfonylurea therapy alone, 10.9 mmol/l; lispro therapy, 8.5 mmol/l; mean of the difference, 2.4 ± 0.4 mmol/l; $P < 0.0001$), as was HbA_{1c} (sulfonylurea therapy alone, 9.0%; lispro therapy, 7.1%; mean of the difference, 1.9 ± 0.3%; $P < 0.0001$). These findings are summarized in Fig. 1. There was no effect of the order of presentation of the treatment arms. Only two episodes of significant symptomatic hypoglycemia (glucose concentrations, 2.1 and 2.2 mmol/l) were observed during the course of the study. Both episodes were corrected by the patients themselves with administration of oral carbohydrate. No other glucose values <2.8 mmol/l were reported by the patients.

Fasting and 1-h C-peptide levels were identical at the conclusion of both treatment arms (fasting C-peptide: sulfonylurea therapy alone, 0.93 nmol/l; lispro therapy, 0.86 nmol/l; and 1-h C-peptide: sulfonylurea therapy alone, 1.32 nmol/l; lispro therapy, 1.29 nmol/l). Fasting free insulin was unchanged by the addition of preprandial lispro insulin (sulfonylurea therapy alone, 110.4 pmol/l; lispro therapy, 105.0 pmol/l). One-hour postprandial insulin levels were significantly elevated in the

lispro arm, indicating rapid and significant absorption of insulin (sulfonylurea therapy alone, 196.8 pmol/l; lispro therapy, 499.2 pmol/l; mean of the difference, 302.4 ± 57.6 pmol/l; $P < 0.0001$). One-hour C-peptide and fasting free insulin concentrations were obtained in only 23 patients.

Weight was significantly increased in the lispro arm (sulfonylurea therapy alone, 90.6 kg; lispro therapy, 93.8 kg; mean of the difference, 3.2 ± 0.5 kg; $P < 0.0001$). Patients had a BMI of 30.9 kg/m^2 while on sulfonylurea therapy and a BMI of 32.0 kg/m^2 on lispro therapy (mean of the difference, 1.9 ± 0.2 kg/m^2; $P < 0.0001$). Total cholesterol was significantly decreased in the lispro arm (sulfonylurea therapy alone, 5.44 mmol/l; lispro therapy, 5.10 mmol/l; mean of the difference, 0.34 ± 0.14 mmol/l; $P < 0.02$). HDL cholesterol levels were increased due to study participation alone (Table 1), but were further increased in the lispro arm (sulfonylurea therapy alone, 0.88 mmol/l; lispro therapy, 0.96 mmol/l; mean of the difference, 0.07 ± 0.03 mmol/l; $P < 0.01$). LDL cholesterol levels, calculated only for patients whose triglyceride levels were <4.52 mmol/l in all conditions ($n = 21$), were not significantly changed (sulfonylurea therapy alone, 3.45 mmol/l; lispro therapy, 3.39 mmol/l). Triglyceride values were significantly decreased by insulin lispro (sulfonylurea therapy alone, 2.94 mmol/l; lispro therapy, 2.17 mmol/l; mean of the difference, 0.77 ± 0.28 mmol/l; $P < 0.01$).

CONCLUSIONS — We have shown that premeal treatment with insulin lispro improved postprandial glucose, FPG, and HbA_{1c} levels in this group of type 2 diabetic patients, who had failed to achieve adequate glucose control with sulfonylurea agents. Currently used insulin regimens, including sulfonylurea plus bedtime insulin, intensified conventional therapy with mixed doses of insulin, and four-dose insulin regimens, have not proved effective in correcting postprandial hyperglycemia (8–11). Indeed, Cusi et al. (11) speculated that it may not be possible to normalize postprandial glucose excursions in type 2 diabetes. Taylor et al. (12) and Landstedt-Hallin et al. (13) addressed the usefulness of adding premeal regular insulin, compared with NPH insulin, to the regimen of patients with type 2 diabetes who were poorly controlled on sulfonylurea therapy alone. They showed that the primary difficulty in using premeal regular insulin is control of fasting blood glucose. In addition, Taylor et al. pointed out the increased frequency of hypoglycemia with premeal regular insulin, and Landstedt-Hallin et al. stressed the more pronounced weight gain. The profile of activity of insulin lispro allows postprandial hyperglycemia to be more specifically targeted, with less carryover of insulin activity than with regular insulin. It is noteworthy that we only had two reported episodes of hypoglycemia (glucose concentrations, <2.8 mmol/l), and patients were measuring and reporting home blood glucose readings to us throughout the study. Furthermore, although the patients did gain weight in the lispro arm, this was very modest in absolute terms, especially in view of the magnitude of the improvement in glucose control.

Although seldom addressed, postprandial hyperglycemia may be associated with a significantly increased risk of adverse cardiovascular events, even in the presence of normal FPG levels (4,5,14). In addition, adequate glucose control in type 2 diabetes may require large insulin doses, often resulting in substantially elevated levels of circulating insulin (15). Cusi et al. (11), using only bedtime NPH insulin, were able to decrease the postprandial glucose and lower HbA_{1c} significantly. However, the average insulin dose required in Cusi's study was 80 U/day. Endogenous hyperinsulinemia per se has been associated with an increased risk of atherosclerotic complications. While this association has not been demonstrated for exogenously administered insulin, the possibility of similar effects has been raised (16,17). Furthermore, weight gain, another cardiovascular risk, is a well-recognized consequence of insulin therapy (15,18). Thus, a treatment regimen that minimizes hyperinsulinemia is desirable.

Using insulin lispro, our patients achieved a 21% reduction in HbA_{1c} from 9.0 to 7.1% and a 22% reduction in FPG levels from 10.9 to 8.5 mmol/l (Fig. 1), while experiencing only a 3% change in weight. The physiological basis of improved FPG levels in our patients is unclear. Unchanged fasting plasma insulin levels demonstrate that the effect was not due to residual insulin lispro. Although stable C-peptide levels indicate that there was no substantial change in endogenous insulin secretory activity, a subtle improvement cannot be excluded. Our findings are consistent with a change in insulin sensitivity, but we did not measure any parameters of insulin action. Koivisto, in his review of insulin therapy in type 2 diabetes, highlights the increased insulin sensitivity that is reported in some studies after the initiation of insulin therapy (19). Further studies will be needed to explore the mechanism by which improvements in postprandial hyperglycemia produce such broad effects on glucose control. The only other agents currently capable of specifically targeting postprandial hyperglycemia are α-glucosidase inhibitors, such as acarbose and miglitol. Recent studies of these drugs have shown smaller effects on HbA_{1c} and particularly FPG levels than we have demonstrated, with no effect on cholesterol, implying that some of the changes in our study may be specific to insulin lispro therapy. (20–22).

The impact of treatment of postprandial hyperglycemia with insulin lispro on lipid parameters was modest but significant. Triglyceride values typically improve with any treatment used to lower glucose in patients with poorly controlled type 2 diabetes, and the decrease seen in our patients with the addition of insulin lispro is therefore not surprising. However, a number of studies have demonstrated that HDL and total cholesterol values do not necessarily improve with insulin treatment in patients with type 2 diabetes, especially those with failure of sulfonylurea therapy (23–25). Thus, it is worthy of attention that insulin lispro lowered total cholesterol and raised HDL cholesterol in this group of patients, improving the HDL/total cholesterol ratio, a good predictor of cardiovascular risk (11,26).

In conclusion, the treatment of postprandial hyperglycemia with insulin lispro improved overall glucose control and some lipid parameters in patients with type 2 diabetes who were poorly controlled with sulfonylureas. In this study, we were unable to assess the effect of insulin lispro alone in our patient population. Since these patients were failing with the maximum dose of sulfonylureas, insulin lispro alone may be sufficient therapy to duplicate the above results. Additional investigation is necessary to define the effect of preprandial insulin lispro, without basal insulin or other hypoglycemic agents, in patients with type 2 diabetes.

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