Therapy Focused on Lowering Postprandial Glucose, Not Fasting Glucose, May Be Superior for Lowering HbA1c

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OBJECTIVE — To compare the overall efficacy of combination therapies focused on fasting or postprandial blood glucose in patients with type 2 diabetes not adequately controlled with oral sulfonylurea agents alone.

RESEARCH DESIGN AND METHODS — A total of 135 patients were randomly assigned for 3 months to 1 of 3 combination regimens with glyburide (G) that addressed postprandial blood glucose with insulin lispro (L+G), premeal blood glucose with metformin (M+G), or fasting blood glucose (FBG) with bedtime NPH insulin (NPH+G).

RESULTS — At end point, HbA1c was significantly lower with all therapies (P = 0.001) and was significantly lower for L+G (7.68 ± 0.88%) compared with either NPH+G (8.51 ± 1.38%, P = 0.003) or M+G (8.31 ± 1.31%, P = 0.025). FBG at end point was significantly lower for NPH+G (8.49 ± 2.36 mmol/l) compared with either L+G (10.57 ± 1.97 mmol/l, P = 0.001) or M+G (9.69 ± 2.89 mmol/l, P = 0.029). The mean 2-h postprandial glucose after a test meal was significantly lower for L+G (10.87 ± 2.88 mmol/l) versus NPH+G (12.21 ± 3.12 mmol/l, P = 0.052) or versus M+G (12.72 ± 3.26 mmol/l, P = 0.009). The overall rate of hypoglycemia (episodes per 30 days) was low and not statistically significant between groups (P = 0.156).

CONCLUSIONS — Adding a second antihyperglycemic agent, regardless of its timing of action, lowers HbA1c and glucose values. However, when insulin lispro was used to focus on postprandial blood glucose, there was a greater impact on overall metabolic control. These data support the importance of lowering postprandial blood glucose to optimize overall glycemic control and thus improve long-term outcomes.

Diabetes Care 23:1236–1241, 2000
RESEARCH DESIGN AND METHODS

Study design

This randomized open-label 3-arm parallel group study, with type 2 diabetes, was conducted in the U.S. Secondary oral agent failure was defined as initial stabilization of blood glucose control for a minimum of 6 months followed by a lack of control using maximal doses of a sulfonylurea. Patients were instructed to monitor at least 2 times per day and to record those values. The goals of therapy for the entire study population met the guidelines established by the American Diabetes Association in their position statement on the standards of medical care for patients with diabetes, which were in effect at the time of the study (80–120 mg/dl preprandial glucose and 100–140 mg/dl bedtime glucose) (12). The investigators were instructed that if >20% of a patient's blood glucose monitoring values were >8.9 mmol/l (160 mg/dl) fasting or 10.0 mmol/l (180 mg/dl) pre-prandially, an appropriate adjustment in dosage should be made. For the NPH and insulin lispro groups, the suggested increase was 15–20% total insulin dose, and for the metformin group, the suggested increase was 500 mg (up to a maximum of 2,500 mg/day). The investigators made all increases in dosage based on all clinical information available, not just on blood glucose values. All investigators were instructed to provide for patient safety first when implementing these guidelines.

At randomization and 1- and 3-month visits, patients were given a Sustacal test meal. At 0, 60, and 120 min after the test meal, blood was drawn and shipped to a central laboratory, where blood glucose analyses were performed by the hexokinase enzymatic method using Boehringer Mannheim reagent, on Hitachi 747-200 chemistry analyzers. Additionally, patients used their home blood glucose monitors to collect 8-point blood glucose profiles 3 days and 1 day before the visits at randomization, 1 month, and 3 months. During those days, patients followed their usual diet, and home blood glucose measurements were obtained at 3:00 a.m., directly before and 2 h after the morning, noon, and evening meals; and at bedtime. A valid diabetes treatment satisfaction questionnaire (DTSQ) (13) with 6 treatment satisfaction questions was administered at baseline and final visits. The sum of the scores produced an overall measure of treatment satisfaction, with scores ranging from 0 (very dissatisfied) to 36 (very satisfied).

HbA1c was determined at baseline, 1 month, and 3 months. Blood samples were collected and shipped to a central laboratory, where they were analyzed by the FDA-approved Bio-Rad-Diamat fully automated glycosylated hemoglobin analyzer system using ion-exchange high-performance liquid chromatography. This method has been certified by the National Glycohemoglobin Standardization Program. Hypoglycemic events were recorded in the patient diaries and collected at each visit. In this study, a hypoglycemic episode was defined as any time a patient had symptoms associated with hypoglycemia, or recorded a blood glucose level ≤3.9 mmol/l. Episodes for which a patient recorded hypoglycemic symptoms but did not measure a blood glucose value were included in the analysis.

Statistical analysis

Analyses were performed on end point values using the last observation carried forward for clinically evaluated patients. Four patients were not included in the analysis because protocol entry criteria not met (n = 1) and because of protocol violations (n = 3). The efficacy variables were fasting and 2-h postprandial glucose values and glucose excursions after the test meal, the 8-point home blood glucose profile, and the HbA1c value. Safety variables included weight and hypoglycemic rate.
Targeting postprandial glucose lowers HbA1c

The variables presented were summarized as the means ± SD. Treatment group differences in baseline characteristics were tested using analysis of variance (ANOVA) and \( \chi^2 \) tests. A 1-way ANOVA was used to analyze the continuous efficacy measures. Between-treatment comparisons were based on the protected least-significant difference. At endpoint, the FBG values and 2-h postprandial blood glucose values were analyzed using a partial correlation analysis to determine the importance of each factor in explaining HbA1c levels. A 2-sided nominal significance level of 0.05 was used for all tests and pairwise comparisons. Comparisons among all 3 pairs of treatment groups were of interest for all variables analyzed.

RESULTS — A total of 135 patients entered the study. Of the 135 randomized patients, 114 (84.4%) successfully completed this study. Six patients discontinued the study because of patient, physician, or sponsor decision, 6 were lost to follow-up, and 5 discontinued because of lack of efficacy perceived by the patient or physician. Four patients were not included in the analysis because protocol entry criteria were not met (n = 1) and because of protocol violations (n = 3). Of the 131 evaluated patients, 41 were randomized to L+G, 40 to M+G, and 50 to NPH+G. Of the 17 evaluated patients who discontinued the study, 12 were in the NPH+G group, 2 were in the L+G group, and 3 were in the M+G group. Patient baseline characteristics are presented in Table 1. At baseline, treatment groups did not differ significantly with respect to sex, age, race, weight, BMI, duration of diabetes, FBG, and HbA1c. At endpoint, the mean daily doses were 0.42 U \cdot kg\(^{-1}\) \cdot day\(^{-1}\) insulin lispro and 0.29 U \cdot kg\(^{-1}\) \cdot day\(^{-1}\) NPH insulin. Of evaluated patients randomized to the M+G group, 55% received the maximal dose of 2,500 mg/day metformin by the end of the 3-month study.

HbA1c

At baseline, HbA1c was not statistically significantly different among groups (Table 1). At endpoint, HbA1c was significantly lower when compared with baseline for each of the 3 therapy groups (\( P < 0.001 \) for each treatment). Mean changes in HbA1c were -2.4 ± 0.9% for L+G, -1.8 ± 1.4% for NPH+G, and -1.8 ± 1.3% for M+G (overall \( P = 0.096 \)). Additionally, the HbA1c value at endpoint was significantly lower for L+G (7.7 ± 0.9%) versus NPH+G (8.5 ± 1.4%, \( P = 0.003 \)) or versus M+G (8.3 ± 1.3%, \( P = 0.025 \) (Fig. 1A). No significant difference was observed between M+G and L+G.
HbA1c was recorded, 66.7, 51.3, and 86.4, respectively, attained an endpoint mean blood glucose value for the 3 groups (the means of 8-point blood glucose profiles performed 3 days and 1 day before the final visit). 2-hr pp, 2-h postprandial; 2-h postprandial blood glucose or FBG after the test meal, the postprandial glucose value (partial correlation r = 0.316, P < 0.001) but not the fasting glucose value (partial correlation r = 0.033, P = 0.718) was statistically significant in explaining endpoint HbA1c.

Blood glucose

Test meal challenge. FBG at the end point was significantly lower for NPH + G (8.5 ± 2.4 mmol/l) when compared with L + G (10.6 ± 2.0 mmol/l, P < 0.001) and M + G (9.7 ± 2.9 mmol/l, P = 0.029) (Fig. 1B). The 2-h postprandial glucose after the test meal was lower for L + G (10.9 ± 2.9 mmol/l) versus NPH + G (12.2 ± 3.1 mmol/l, P = 0.052) or versus M + G (12.7 ± 3.3 mmol/l, P = 0.009) (Fig. 1C). Likewise, the 2-h glucose excursion after the test meal was significantly lower for L + G (0.4 ± 2.4 mmol/l) versus NPH + G (3.8 ± 2.3 mmol/l) or versus M + G (3.0 ± 1.8 mmol/l) (P < 0.001 for both comparisons) (Fig. 1D).

At end point, both FBG (r = 0.260, P = 0.004) and 2-h postprandial blood glucose (r = 0.400, P < 0.001) after the test meal individually correlated with the HbA1c value. Using partial correlation analysis and controlling for either postprandial blood glucose or FBG after the test meal, the postprandial glucose value (partial correlation r = 0.316, P < 0.001) but not the fasting glucose value (partial correlation r = 0.033, P = 0.718) was statistically significant in explaining endpoint HbA1c.

Home blood glucose monitoring. The end point results of the 8-point blood glucose profiles determined from home blood glucose monitoring are shown in Fig. 2. The glucose levels at 3:00 A.M. were not statistically significant (P = 0.260), as determined by home blood glucose monitoring, controlling for either postprandial blood glucose or FBG, the 2-h postprandial glucose (partial correlation r = 0.276, P = 0.003) but not the FBG (partial correlation r = 0.068, P = 0.477) was statistically significant in explaining endpoint HbA1c.

Hypoglycemic episodes

At endpoint, the mean rates of hypoglycemic episodes per patient per 30 days were low in all groups: 0.6 ± 1.3 for NPH + G, 0.7 ± 1.5 for M + G, and 1.1 ± 1.4 for L + G. Treatment differences were not statistically significant (P = 0.156). When the timing of hypoglycemic episodes was considered, the largest number of episodes in the NPH + G group occurred between 6:00 A.M. and 11:59 A.M. (0.30 ± 0.887 episodes per patient per 30 days); in the L + G group, between 6:00 P.M. and 11:59 P.M. (0.46 ± 0.803 episodes per patient per 30 days); and in the M + G group, between 6:00 P.M. and 11:59 P.M. (0.25 ± 0.688 episodes per patient per 30 days).

Weight

All therapy groups experienced weight gain. Mean increases in weight were 3.4 ± 2.9 kg/m² for L + G, 0.4 ± 2.2 kg/m² for M + G, and 2.3 ± 2.4 kg/m² for NPH + G. Differences in the mean change from baseline were statistically significant for the comparisons of L + G or NPH + G versus M + G (P < 0.001) and were marginally significant for the comparison of L + G versus NPH + G (P = 0.051).

Treatment satisfaction

There were no statistically significant differences in the composite satisfaction scores at end point between the L + G, M + G, or NPH + G treatment groups, with patients being generally satisfied (30.45 ± 5.34 vs. 31.87 ± 5.45 vs. 31.25 ± 6.56, P = 0.562).

CONCLUSIONS — In this multicenter trial of patients with type 2 diabetes uncontrolled on oral sulfonylurea agents alone, we demonstrated that combination therapy focused on postprandial glucose is well-tolerated and has a greater impact on overall metabolic control compared with therapies that focused on fasting glucose control. The present study confirms previous reports that improved glycemic control can occur when a second antihyperglycemic agent is added, regardless of the regimen (14–19). The addition of a second antihyperglycemic agent, whether it primarily impacted on fasting, postprandial, or premeal glucose, resulted in lowered blood glucose and HbA1c.
The Kumamoto Study and the U.K. Prospective Diabetes Study (UKPDS) demonstrated that improved metabolic control in patients with type 2 diabetes, as assessed by lowering HbA1c, is associated with reduced risk for microvascular complications (20,21). Unfortunately, 75% of patients with type 2 diabetes on monotherapy with maximal doses of either sulfonylurea (22,23) or metformin (24) will fail to achieve the target glycemic goals (25) and will need to progress to combination therapy. Findings from our study indicate that, within 3 months, between one-third and two-thirds of patients can achieve these goals by the addition of a second antihyperglycemic agent.

Studies suggest that a near-normal FBG may determine glycemic control for the entire day (2,3). FBG has been correlated with overall glucose control, as measured by HbA1c (26,27). However, treatment directed at control of postprandial blood glucose ingestional diabetes results in better control than treatment directed at preprandial glucose concentrations (4). Furthermore, a better correlation has been noted between HbA1c and mean postprandial glucose than between FBG and HbA1c (28). Our finding of improved overall metabolic control with lower postprandial glucose, despite a higher FBG, adds further evidence to these latter reports.

Several possibilities may account for our patients having significantly lower HbA1c values despite having a higher fasting glucose values. First, the postprandial glucose value was lowest in the insulin lispro group and may fully explain the greater reduction in HbA1c. Second, the FBG at end point in the L+G group was lower than that at baseline, although the fasting glucose was higher in the L+G group than in the other 2 combination therapies. Third, insulin lispro therapy was also associated with preprandial glycemic improvement at noon and dinner. In tandem with the postprandial improvement, this led to a significant improvement in daylong glycemia, which may account for the overall reduction in HbA1c. Finally, the frequency of postprandial glucose intervention by insulin injection or the total insulin dose used may have been the determining factor in the greater reduction in HbA1c in the current study. A greater number of injections and a higher total insulin dose were used in the insulin lispro group compared with the NPH group or the metformin group (which received no insulin).

Previous reports would suggest that more frequent postprandial glucose interventions by insulin injection, and not an increase in the overall insulin dose, may be the important factor in overall glycemic control (14,20,29). Data from the Diabetes Control and Complications Trial (DCCT) and the Kumamoto studies indicate that the difference in the insulin dosage between the intensively and conventionally treated patient groups was <15% of the total daily dose (20,30), yet HbA1c was ~2% lower in the intensively treated group. In these 2 studies, the number of insulin injections in the intensively treated group (3–4 per day) was greater than that in the conventional therapy group (1–2 per day). In a study in which 3 premeal insulin lispro injections plus sulfonylurea was compared with 1 daily injection of NPH insulin plus sulfonylurea, the HbA1c was significantly lower in the 3-injection regimen, despite a similar insulin dose in both groups (14). These studies confirm the importance of lowering postprandial glucose by insulin replacement that more closely mimics the normal physiological insulin response. Moreover, they support the conclusion that the frequency of postprandial interventions, and not the total insulin dose, is most important for the improvement in metabolic outcomes.

In the present study, greater reduction in postprandial glucose was associated with a greater reduction in HbA1c. Both the DCCT and the Kumamoto Study reported that a reduction in the 2-h postprandial glucose or average daily blood glucose value, as well as FBG, can be concomitant with the improvement in HbA1c (20,29). Data from our 3 treatment groups also provided an index of the relative contribution of fasting glucose, postprandial glucose, or both pre- and postprandial glucose on overall control, as measured by HbA1c. Using partial correlation analysis and controlling for FBG, our study demonstrated a statistically significant linear relationship between end point HbA1c and postprandial blood glucose. This relationship was not demonstrated for FBG when controlling for postprandial blood glucose. This information, coupled with the observation that postprandial glucose values were consistently lower in the insulin lispro group, provides further support that postprandial glucose is an important determinant in overall glycemic control, as measured by HbA1c.

The present study has some limitations. Neither the patients nor the physicians were blinded to treatments. Some patients may prefer oral diabetes therapy to insulin injection. Using insulin instead of metformin resulted in a significant weight gain, which is an undesirable outcome of therapy for some patients. To evaluate the impact of some of these potential limitations, we used the DTSQ to assess satisfaction with therapy. Improvement in patient satisfaction scores was independent of randomized therapy, and may reflect patient well-being in the face of overall improvement in metabolic control (as was seen in all groups) regardless of the therapy given. This observation is in accord with the conclusions of the UKPDS, which found that the complications of diabetes and not the therapeutic intervention had more impact on quality of life and patient satisfaction (30).

In summary, in this study, we compare the tolerability and efficacy of 3 combination treatment strategies in patients with type 2 diabetes uncontrolled on oral sulfonylurea therapy. Antihyperglycemic therapy with insulin lispro, which focused on postprandial glucose control, had a greater impact on overall metabolic control compared with more traditional approaches of NPH insulin at bedtime or metformin and should be considered in this patient population. We conclude that postprandial glucose control is important in overall metabolic outcome and that treatment strategies for type 2 diabetes should also focus on this important metabolic parameter.

Acknowledgments — This material was presented in part at the American Diabetes Association 59th Scientific Sessions in San Diego, California, June 1999.


References
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