# Therapy Focused on Lowering Postprandial Glucose, Not Fasting Glucose, May Be Superior for Lowering $HbA_{1c}$

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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, $HbA_{1c}$ 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 $HbA_{1c}$ 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.

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Response to diet and oral sulfonylurea agents in the treatment of type 2 diabetes is variable and often short-lived, with 5–10% of patients becoming nonresponsive each year (1). Multiple treatment options are available at the time of secondary sulfonylurea failure. Most commonly, the emphasis of these therapies is to focus on fasting and preprandial glucose values, and little attention is paid to postprandial glucose control (2,3).

The importance of postprandial glucose control is evident in the literature. Postprandial hyperglycemia has been associated with increased risk of microvascular (4–6) and macrovascular (7–10) complications. The risk of cardiovascular disease and all-cause mortality increases with increasing postprandial blood glucose values (7). The Honolulu Heart Study demonstrated an increased risk of fatal coronary heart disease events alone and in combination with nonfatal myocardial infarction that was independently related to increased postchallenge glucose levels (8). Furthermore, the Diabetes Intervention Study demonstrated that postprandial blood glucose was an independent risk factor for mortality in patients with newly diagnosed type 2 diabetes, but fasting blood glucose (FBG) was not (9). Therefore, intervention aimed at lowering the 2-h postprandial blood glucose may be important in reducing diabetic complications and mortality and may be an important focus for therapy.

The present study was designed to compare the efficacy and safety profile of 3 treatment strategies in patients with type 2 diabetes uncontrolled on sulfonylurea agents alone. These combination treatment regimens with glyburide (G) focused on either fasting glucose (bedtime NPH insulin plus glyburide [NPH+G]), postprandial blood glucose (preprandial insulin lispro plus glyburide [L+G]), or premeal glucose (metformin plus glyburide [M+G]) and allowed for the comparison of the impact of each on overall metabolic control.

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Abbreviations: ANOVA, analysis of variance; DCCT, Diabetes Control and Complications Trial; DTSQ, Diabetes Treatment Satisfaction Questionnaire; FBG, fasting blood glucose; L+G, preprandial insulin lispro plus glyburide; M+G, metformin plus glyburide; NPH+G, bedtime NPH insulin plus glyburide; UKPDS, U.K. Prospective Diabetes Study.

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

Table 1—*Patient baseline characteristics*

| | Total | L+G | M+G | NPH+G | *P* |
|---|---|---|---|---|---|
| *n* | 131 | 41 | 40 | 50 | |
| Sex | | | | | 0.607 |
| Men | 79 (60.3) | 27 (65.9) | 22 (55.0) | 30 (60.0) | |
| Women | 52 (39.7) | 14 (34.1) | 18 (45.0) | 20 (40.0) | |
| Mean age (years) | 56.8 | 55.9 | 58.1 | 56.6 | 0.599 |
| Race | | | | | 0.422 |
| Caucasian | 82 (62.6) | 29 (70.7) | 24 (60.0) | 29 (58.0) | |
| Non-Caucasian* | 49 (37.4) | 12 (29.3) | 16 (40.0) | 21 (42.0) | |
| Mean weight (kg) | 84.3 | 87.7 | 82.6 | 82.8 | 0.200 |
| Mean BMI (kg/m$^2$) | 28.4 | 29.2 | 28.2 | 27.9 | 0.235 |
| Mean duration of diabetes (years) | 7.7 | 7.1 | 8.9 | 7.3 | 0.403 |
| Mean FBG† (mmol/l) | 14.0 | 14.2 | 13.9 | 13.9 | 0.915 |
| Mean $HbA_{1c}$ (%) | 10.22 | 10.03 | 10.19 | 10.39 | 0.373 |

Data for sex and race are *n* (%). *Includes African-Americans, Hispanics, and other ethnicities; †determined from the baseline test meal.

## RESEARCH DESIGN AND METHODS

### Study design

This randomized open-label 3-arm parallel group study in patients with type 2 diabetes, as defined by the World Health Organization (11), and secondary oral agent failure was conducted at 22 centers 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. Uncontrolled diabetes was defined as an $HbA_{1c}$ value >8.5% with >20% of all recorded FBG values >8.9 mmol/l and/or premeal glucose values >10 mmol/l after maximal doses of a sulfonylurea during a 1-week period before the initial visit. The trial was conducted in accordance with the Declaration of Helsinki and guidelines for Good Clinical Practice. The protocol was approved by the ethical review board of each investigative site, and all patients gave written informed consent.

During a 2- to 4-week lead-in period, all patients received 10 mg glyburide by mouth twice daily. Patients were instructed to monitor their blood glucose a minimum of 2 times daily (before breakfast and before dinner).

After the lead-in period, patients meeting the criteria for secondary sulfonylurea failure were randomly assigned to 1 of 3 combination regimens for 3 months: L+G, M+G, or NPH+G. For all treatment regimens, glyburide was administered as 10 mg by mouth twice daily throughout the entire study. For randomized therapy, the initial recommended doses were 0.25 $U \cdot kg^{-1} \cdot day^{-1}$ insulin lispro administered subcutaneously in divided doses immediately before meals, 0.2 U/kg NPH insulin administered subcutaneously at bedtime, or 500 mg metformin by mouth twice daily. The protocol required that patients have weekly follow-up visits for 1 month after randomization. The patients were provided home blood glucose monitors and strips (Accuchek Advantage Meters and Advantage Test Strips; Roche Diagnostics, Indianapolis, IN) and were taught how to use them. The patients were asked 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 monitor values were >8.9 mmol/l (160 mg/dl) fasting or 10.0 mmol/l (180 mg/dl) preprandially, 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 validated 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).

$HbA_{1c}$ 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 $HbA_{1c}$ value. Safety variables included weight and hypoglycemic rate.

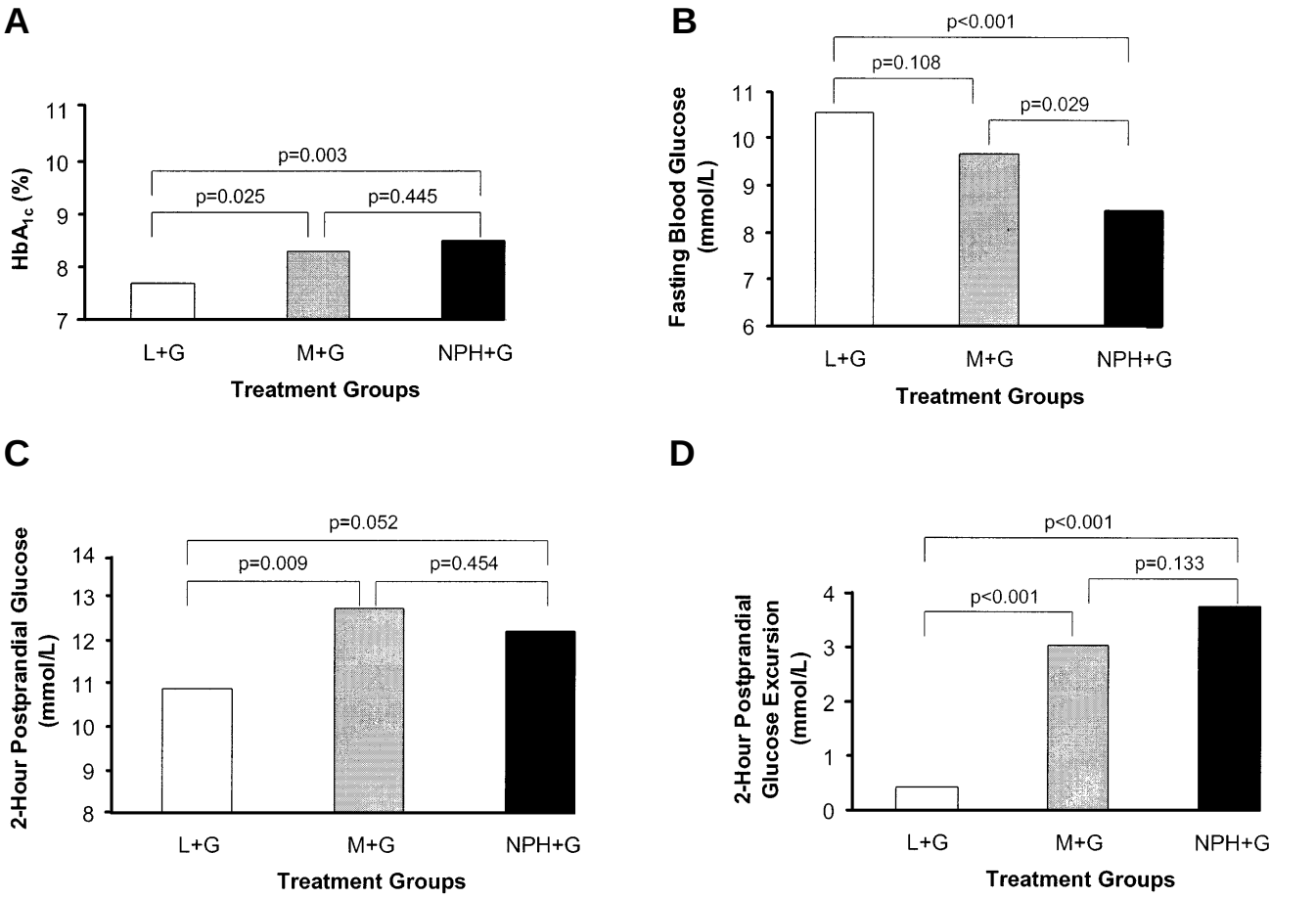


**Figure 1—**A: *The comparison of observed $HbA_{1c}$ at endpoint was statistically significantly lower for L+G versus M+G or NPH+G.* B: *The comparison of observed FBG at endpoint was statistically significantly lower for NPH+G versus M+G or L+G.* C: *The 2-h postprandial blood glucose after the test meal was significantly lower for L+G versus M+G or NPH+G.* D: *The 2-h postprandial glucose excursion after the test meal was significantly lower for L+G versus M+G or NPH+G.*

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 $HbA_{1c}$ 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 $HbA_{1c}$. At endpoint, the mean daily doses were 0.42 U · $kg^{-1}$ · $day^{-1}$ insulin lispro and 0.29 U · $kg^{-1}$ · $day^{-1}$ 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.

### $HbA_{1c}$

At baseline, $HbA_{1c}$ was not statistically significantly different among groups (Table 1). At endpoint, $HbA_{1c}$ was significantly lower when compared with baseline for each of the 3 therapy groups ($P < 0.001$ for each treatment). Mean changes in $HbA_{1c}$ 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 $HbA_{1c}$ value at end point 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. 1*A*). No significant difference was observed between M+G

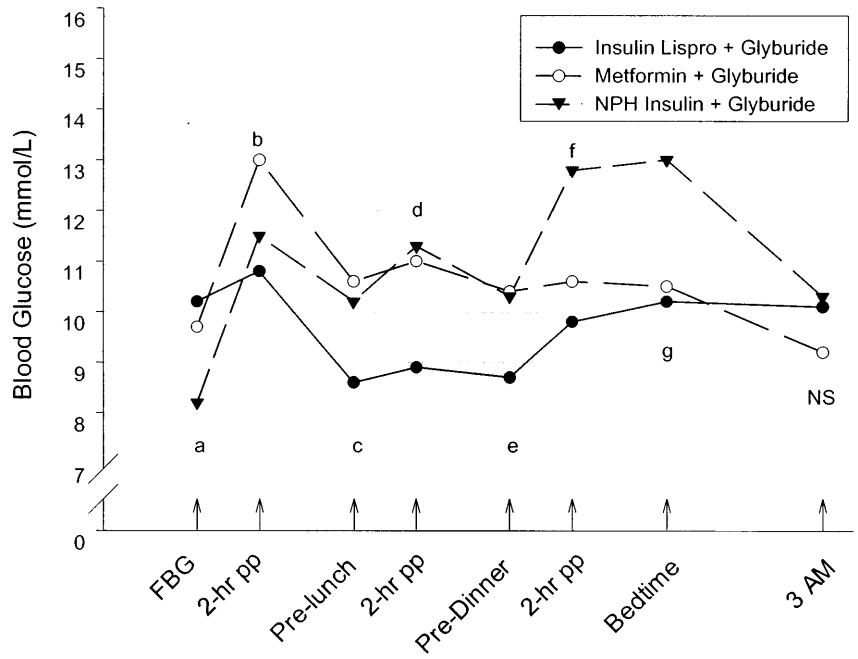


**Figure 2—** *An 8-point blood glucose profile as determined from home blood glucose monitoring. Curves represent endpoint mean blood glucose values for the 3 groups (the means of 8-point blood glucose profiles performed 3 days and 1 day before the final visit). 2-hr pp, 2-h postprandial;* a, *NPH+G vs. M+G (*P *= 0.015) or L+G (*P *= 0.001);* b, *L+G vs. M+G (*P *= 0.009);* c, *L+G vs. M+G (*P *= 0.006) or NPH+G (*P *= 0.030);* d, *L+G vs. M+G (*P *= 0.007) or NPH+G (*P *= 0.002);* e, *L+G vs. M+G (*P *= 0.033) or NPH+G (*P *= 0.039);* f, *L+G or M+G vs. NPH+G (*P *< 0.01 for both comparisons);* g, *L+G or M+G vs. NPH+G (*P *< 0.01 for both comparisons).*

and NPH+G. Of those patients for whom $HbA_{1c}$ was recorded, 66.7, 51.3, and 35.7% in the L+G, M+G, and NPH+G groups, respectively, attained an end point $HbA_{1c}$ of <8%, whereas 23.1, 7.7, and 9.5%, respectively, attained an end point $HbA_{1c}$ of <7%.

## 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. 1*B*). 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. 1*C*). 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. 1*D*).

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 $HbA_{1c}$ 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 end point $HbA_{1c}$.

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 significantly different among the 3 therapies. However, the morning FBG values were significantly lower for NPH+G, whereas the morning postprandial glucose and the pre-and postprandial glucose values at noon and dinnertime were statistically lower in the L+G group. Significant differences are noted in the figure. Both 2-h morning postprandial glucose values ($r = 0.327$, $P < 0.001$) and fasting glucose values ($r = 0.215$, $P = 0.019$), as determined by home blood glucose monitoring, correlated with end-point $HbA_{1c}$. Using partial correlation analysis and controlling for 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 end point $HbA_{1c}$.

## 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 compared, 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/m$^2$ for L+G, 0.4 ± 2.2 kg/m$^2$ for M+G, and 2.3 ± 2.4 kg/m$^2$ 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 $HbA_{1c}$.

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 $HbA_{1c}$, 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 the glycemic control for the entire day (2,3). FBG has been correlated with overall glucose control, as measured by $HbA_{1c}$ (26,27). However, treatment directed at control of postprandial blood glucose in gestational diabetes results in better control than treatment directed at preprandial glucose concentrations (4). Furthermore, a better correlation has been noted between $HbA_{1c}$ and mean postprandial glucose than between FBG and $HbA_{1c}$ (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 $HbA_{1c}$ 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 $HbA_{1c}$. 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 $HbA_{1c}$. 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 $HbA_{1c}$ 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 $HbA_{1c}$ 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 $HbA_{1c}$ 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 $HbA_{1c}$. 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 $HbA_{1c}$ (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 $HbA_{1c}$. Using partial correlation analysis and controlling for FBG, our study demonstrated a statistically significant linear relationship between end point $HbA_{1c}$ 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 $HbA_{1c}$.

The present study does have 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.

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References

1. Feinglos MN, Bethel MA: Oral agent therapy in the treatment of type 2 diabetes. *Diabetes Care* 22 (Suppl. 3):C61–C64, 1999
2. Holman RR, Turner RC: Optimizing blood glucose control in type 2 diabetes: an

approach based on fasting blood glucose measurements. *Diabetologia* 5:582–588, 1988
3. Trovati M, Burzacca S, Mularoni E, Massucco P, Cavalot F, Mattiello L, Anfossi G: A comparison of the predictive power for overall blood glucose control of a 'good' fasting level in type 2 diabetic patients on diet alone or with oral agents. *Diabetologia* 9:134–137, 1992
4. de Veciana M, Major CA, Morgan MA, Asrat T, Toohey JS, Lien JM, Evans AT: Postprandial versus preprandial blood glucose monitoring in women with gestational diabetes mellitus requiring insulin therapy. *N Engl J Med* 333:1237–1241, 1995
5. McCance DR, Hanson RL, Charles M, Jacobsson LT, Pettitt DJ, Bennett PH, Knowler WC: Comparison of tests for glycated haemoglobin and fasting and two hour plasma glucose concentrations in diagnostic methods for diabetes. *BMJ* 308: 1323–1328, 1994
6. Engelgau MM, Thompson TJ, Herman WH, Boyle JP, Aubert RE, Kenny SJ, Badran A, Sous ES, Ali MA: Comparison of fasting and 2-hour glucose and $HbA_{1c}$ levels for diagnosing diabetes: diagnostic criteria and performance revisited. *Diabetes Care* 20: 785–791, 1997
7. Lowe LP, Liu K, Greenland P, Metzger BE, Dyer AR, Stamler J: Diabetes, asymptomatic hyperglycemia, and 22-year mortality in black and white men: the Chicago Heart Association Detection Project in Industry Study. *Diabetes Care* 20:163–169, 1997
8. Donahue RP, Abbott RD, Reed DM, Yano K: Postchallenge glucose concentration and coronary heart disease in men of Japanese ancestry: Honolulu Heart Program. *Diabetes* 36:689–692, 1987
9. Hanefeld M, Fischer S, Julius U, Schulze J, Schwanebeck U, Schmechel H, Ziegelasch HJ, Lindner J: Risk factors for myocardial infarction and death in newly detected NIDDM: the Diabetes Intervention Study, 11-year follow-up. *Diabetologia* 39:1577–1583, 1996
10. Balkau B, Shipley M, Jarrett J, Pyörälä K, Pyörälä M, Forhan A, Eschwège E: High blood glucose concentration is a risk factor for mortality in middle-aged nondiabetic men: 20-year follow-up in the Whitehall Study, the Paris Prospective Study, and the Helsinki Policemen Study. *Diabetes Care* 21:360–367, 1998
11. Bennett PH: Classification and diagnosis of diabetes mellitus and impaired glucose tolerance. In *Textbook of Diabetes*. Vol 1. Pickup JC, Williams G, Eds. London, Blackwell Scientific Publications, 1991, p. 39
12. American Diabetes Association: Standards of medical care for patients with diabetes mellitus (Position Statement). *Diabetes Care* 20 (Suppl. 1):S5–S13, 1997
13. Bradley C: Diabetes treatment satisfaction questionnaire (DTSQ). In *Handbook of Psychology and Diabetes: A Guide to Psychological Measurement in Diabetes Research and Practice*. Bradley C, Ed. Lausanne, Switzerland, Harwood Academic Publishers, 1994, p. 115
14. Bastyr EJ, Johnson ME, Trautmann ME, Anderson JH, Vignati L, the IOCE Study Group: Insulin lispro in the treatment of patients with type 2 diabetes mellitus after oral agent failure. *Clin Ther* 21:1703–1714, 1999
15. Trischitta V, Italia S, Mazzarino S, Buscema M, Rabuazzo AM, Sangiorgio L, Squatrito S, Vigneri R: Comparison of combined therapies in treatment of secondary failure to glyburide. *Diabetes Care* 15:539–542, 1992
16. Klein W: Sulfonylurea-metformin-combination versus sulfonylurea-insulin-combination in secondary failures of sulfonylurea monotherapy: results of a prospective randomized study in 50 patients. *Diabetes Metab* 17:235–240, 1991
17. Calle-Pascual AL, Garcia-Honduvilla J, Martin-Alvarez PJ, Vara E, Calle JR, Munguira ME, Maranes JP: Comparison between acarbose, metformin, and insulin treatment in type 2 diabetic patients with secondary failure to sulfonylurea treatment. *Diabetes Metab* 21:256–260, 1995
18. Riddle MC, Hart JS, Bouma DJ, Phillipson BE, Youker G: Efficacy of bedtime NPH insulin with daytime sulfonylurea for subpopulation of type II diabetic subjects. *Diabetes Care* 21:623–629, 1989
19. Miller JL, Salman K, Shulman LH, Rose LI: Bedtime insulin added to daytime sulfonylureas improves glycemic control in uncontrolled type II diabetes. *Clin Pharmacol Ther* 53:380–384, 1993
20. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, Kojima Y, Furuyoshi N, Shichiri M: Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract* 28:103–117, 1995
21. U.K. Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998
22. Simonson DC, Kourides IA, Feinglos M, Shamoon H, Fischette CT: Efficacy, safety, and dose-response characteristics of glipizide gastrointestinal therapeutic system on glycemic control and insulin secretion in NIDDM: results of two multicenter randomized placebo-controlled clinical trials. *Diabetes Care* 20:597–606, 1997
23. Rosenstock J, Samols E, Muchmore DB, Schneider J: Glimepiride, a new once-daily sulfonylurea: a double-blind placebo-controlled study of NIDDM patients. *Diabetes Care* 19:1194–1199, 1996
24. DeFronzo RA, Goodman AM, the Multicenter Metformin Study Group: Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. *N Engl J Med* 333:541–549, 1995
25. American Diabetes Association: Standards of medical care for patients with diabetes mellitus (Position Statement). *Diabetes Care* 22 (Suppl. 1):S32–S41, 1999
26. Graf RJ, Halter JB, Porte D: Glycosylated hemoglobin in normal subjects and subjects with maturity-onset diabetes: evidence for a saturable system in man. *Diabetes* 27: 834–839, 1978
27. McCance DR, Ritchie CM, Kennedy L: Is $HbA_{1c}$ measurement superfluous in NIDDM? *Diabetes Care* 11:512–514, 1988
28. Jovanovic L: Rational for prevention and treatment of postprandial glucose-mediated toxicity. *Endocrinologist* 9:87–92, 1999
29. The Diabetes Control and Complications Trial Research Group: The relationship of glycemic exposure ($HbA_{1c}$) to the risk of development and progression of retinopathy in the Diabetes Control and Complications Trial. *Diabetes* 44:968–983, 1995
30. U.K. Prospective Diabetes Study (UKPDS) Group: Quality of life in type 2 diabetic patients is affected by complications but not by intensive policies to improve blood glucose or blood pressure control. *Diabetes Care* 22:1125–1136, 1999