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Comparison of Bedtime Insulin Regimens in Patients with Type 2 Diabetes Mellitus

A Randomized, Controlled Trial

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Background: Compared with other insulin regimens, combination therapy with oral hypoglycemic agents and bedtime insulin produces similar improvement in glycemic control but induces less weight gain.

Objective: To determine whether bedtime insulin regimens differ with respect to their effects on weight gain in patients with type 2 diabetes.

Design: Randomized, controlled trial.

Setting: Four outpatient clinics at central hospitals.

Patients: 96 patients (mean age, 58 ± 1 years; mean body mass index, 29 ± 1 kg/m²) whose type 2 diabetes was poorly controlled with sulfonylurea therapy (mean glycosylated hemoglobin value, $9.9\% \pm 0.2\%$; mean fasting plasma glucose level, 11.9 ± 0.3 mmol/L [214 ± 5 mg/dL]).

Intervention: Random assignment to 1 year of treatment with bedtime intermediate-acting insulin plus glyburide (10.5 mg) and placebo, metformin (2 g) and placebo, glyburide and metformin, or a second injection of intermediate-acting insulin in the morning. Patients were taught to adjust the bedtime insulin dose on the basis of fasting glucose measurements.

Measurements: Body weight, biochemical and symptomatic hypoglycemia, and indices of glycemic control.

Results: At 1 year, body weight remained unchanged in patients receiving bedtime insulin plus metformin (mean change, 0.9 ± 1.2 kg; $P < 0.001$ compared with all other groups) but increased by 3.9 ± 0.7 kg, 3.6 ± 1.2 kg, and 4.6 ± 1.0 kg in patients receiving bedtime insulin plus glyburide, those receiving bedtime insulin plus both oral drugs, and those receiving bedtime and morning insulin, respectively. The greatest decrease in the glycosylated hemoglobin value was observed in the bedtime insulin and metformin group (from $9.7\% \pm 0.4\%$ to $7.2\% \pm 0.2\%$ [difference, -2.5 ± 0.4 percentage points] at 1 year; $P < 0.001$ compared with 0 months and $P < 0.05$ compared with other groups). This group also had significantly fewer symptomatic and biochemical cases of hypoglycemia ($P < 0.05$) than the other groups.

Conclusions: Combination therapy with bedtime insulin plus metformin prevents weight gain. This regimen also

seems superior to other bedtime insulin regimens with respect to improvement in glycemic control and frequency of hypoglycemia.

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In the United Kingdom Prospective Diabetes Study (UKPDS) 33, intensive blood glucose control with sulfonylureas or insulin in patients with newly diagnosed type 2 diabetes resulted in better glycemic control than conventional treatment (1). However, the group that received intensive treatment had more hypoglycemic episodes and gained more weight than the group that received conventional treatment (1). Overweight patients in a substudy of the same trial who received metformin gained less weight and had fewer hypoglycemic episodes than those treated with either insulin or sulfonylureas (2). Patients who received metformin also had a more favorable outcome with respect to the development of diabetes-related end points, all-cause mortality, and stroke (2). The UKPDS did not, however, address the usual clinical problem of how patients whose diabetes is poorly controlled with oral agents should be treated with insulin.

Previous controlled trials comparing various insulin regimens in patients whose type 2 diabetes is poorly controlled with oral agents are sparse and have included small numbers of patients; in addition, only a few have lasted 3 months or longer

See editorial comment on pp 440-441.

(3–8). In the largest of these studies, patients previously treated with sulfonylureas and metformin gained more weight when they received multiple insulin injections than when they received a combination of bedtime insulin, sulfonylurea, and metformin (6, 7). Whether the difference in weight gain was attributable to the number of insulin injections; serum insulin levels; or the use of sulfonylurea, metformin, or both remained unclear.

We compared four different bedtime insulin regimens to evaluate their effects on weight gain, frequency of hypoglycemic episodes, and glycemic control in patients with type 2 diabetes whose disease was inadequately controlled with sulfonylurea therapy alone. We randomly assigned 96 patients with type 2 diabetes to 1 year of treatment with bedtime insulin plus glyburide and placebo, metformin and placebo, glyburide and metformin, or a second injection of insulin.

Methods

Design

The study protocol, which was investigator initiated, consisted of a 6-week run-in period and 12 months of insulin therapy. Patients were recruited from regional health centers to four trial centers by using the following inclusion criteria: age 40 to 70 years, body mass index less than 35 kg/m², fasting blood glucose level greater than 8 mmol/L [>144 mg/dL], duration of diabetes more than 3 years, previous oral therapy with either glipizide (>15 mg/d) or glyburide (>10 mg/d), and fasting serum C-peptide level more than 0.33 nmol/L (reference range, 0.33 to 0.69 nmol/L [>0.99 ng/mL; reference range, 1.0 to 2.0 ng/mL]). Exclusion criteria were congestive heart failure, myocardial infarction, or stroke in the past 6 months; epilepsy or other severe disease; liver disease, serum creatinine concentration greater than 120 μ mol/L [1.36 mg/dL], or macroalbuminuria; proliferative retinopathy or severe maculopathy; previous insulin therapy for more than 2 weeks; excessive alcohol consumption (>20 g/d); and night work. At each center, the patients gave written informed consent to participate in the study, which was approved by the respective ethical committees for human investigation.

Six Weeks before Study Entry

If they qualified for the study, patients visited the treatment center 6 weeks before the start of insulin therapy. The purpose of the run-in period was to ensure that the patients were able to accurately perform home glucose monitoring and that patients who still responded to conventional therapy would

not be unnecessarily treated with insulin. The patients were asked to measure their fasting blood glucose level daily and the diurnal blood glucose level weekly until the end of the first 3 months of insulin therapy and every other week thereafter. For the diurnal blood glucose level, measurements were taken before and 1.5 hours after breakfast, lunch and dinner; at 10 p.m.; and at 4 a.m. Patients were asked to record daily the occurrence of hypoglycemic symptoms. Fasting plasma glucose, glycosylated hemoglobin, serum C-peptide, creatinine, and liver enzyme levels were measured, and the urinary albumin excretion rate was determined from collection of overnight urine.

Three Weeks before Therapy

Patient skills in home glucose monitoring and results from laboratory tests were checked. If they were acceptable, patient data were sent to the coordinating center for randomization.

Randomization

Patients were randomly assigned to four groups (**Table**) in four centers (six patients per group within each center) by using minimization of differences (calculated for the variables listed below) between the treatment groups (9). The following variables (relative weight of each variable is given in parentheses) were considered: age (1 \times); sex (0.5 \times); body mass index (1.5 \times); duration of diabetes (0.5 \times); fasting glucose level (2 \times); fasting serum C-peptide level (1.0 \times); use of diuretics or β -blocking agents (0.25 \times), angiotensin-converting enzyme inhibitors (0.25 \times), or other drugs (0.25 \times); and family history of hypertension (0.25 \times).

All patients in each group injected intermediate-acting neutral human isophane insulin, 100 IU/mL (Orion, Espoo, Finland), at 9 p.m. Additional therapy consisted of glyburide (Euglucon, Orion), 10.5 mg, given as one 3.5-mg tablet before breakfast and two 3.5-mg tablets before dinner plus four tablets (two before breakfast and two before dinner) of metformin placebo; metformin (Metforem, Orion), 2 g, given as two 500-mg tablets before breakfast and two 500-mg tablets before dinner, and three tablets (one before breakfast and two before dinner) of glyburide placebo; metformin, 2 g, and glyburide, 10.5 mg, given as described above; or a second injection of neutral human isophane insulin before breakfast. Thus, the trial was only partially blinded. Insulin was injected subcutaneously in the abdomen.

Initiation of Insulin Therapy and Self-Adjustment of the Insulin Dose (0-Month Visit)

A similar educational program was used in all participating centers. Insulin therapy was started if

Table. Baseline Clinical and Biochemical Characteristics*

Characteristic	Bedtime Insulin Plus Glyburide Group (n = 22)	Bedtime Insulin Plus Metformin Group (n = 19)	Bedtime Insulin Plus Glyburide and Metformin Group (n = 23)	Bedtime and Morning Insulin Group (n = 24)
Age, y	61 ± 2	57 ± 2	55 ± 2	58 ± 2
Men, %	59	58	61	67
Body mass index, kg/m ²	29.7 ± 1.0	28.9 ± 1.1	29.5 ± 0.9	28.5 ± 1.1
Waist-to-hip ratio	0.93 ± 0.02	0.93 ± 0.02	0.95 ± 0.02	0.94 ± 0.02
Glycosylated hemoglobin value, %†	9.8 ± 0.3	9.8 ± 0.4	9.9 ± 0.3	10.1 ± 0.4
Fasting blood glucose level, mmol/L‡	11.7 ± 0.5	12.3 ± 0.5	11.5 ± 0.6	12.1 ± 0.5
Fasting serum C-peptide level, nmol/L§	1.1 ± 0.1	1.1 ± 0.2	1.0 ± 0.1	1.1 ± 0.1
Antihypertensive drugs, %				
Thiazides or β-blockers	8	7	3	7
Angiotensin-converting enzyme inhibitors	9	10	9	7
Other drugs, %	50	42	40	42
Serum triglyceride level, mmol/L	2.7 ± 0.5	2.4 ± 0.4	2.3 ± 0.2	2.6 ± 0.5
Serum high-density lipoprotein cholesterol level, mmol/L	1.1 ± 0.1	1.2 ± 0.1	1.1 ± 0.1	1.2 ± 0.1
Serum total cholesterol level, mmol/L	5.7 ± 0.2	5.9 ± 0.3	5.8 ± 0.2	5.8 ± 0.3
Mean arterial blood pressure, mm Hg	106 ± 2	105 ± 2	108 ± 2	103 ± 3
Median urinary albumin excretion rate (25th, 75th percentiles), μg/min	26 (8, 37)	10 (9, 22)	10 (8, 31)	11 (7, 31)

* Unless otherwise specified, data are expressed as the mean ± SE. All data except lipid measurements were obtained 6 weeks before the start of therapy; lipid data were obtained at the 0-month visit.

† Reference range, 4.0% to 6.0%.

‡ To convert to mg/dL, divide by 0.05551.

§ Reference range, 0.33 to 0.67 nmol/L (1.0 to 2.0 ng/mL). To convert to ng/mL, divide by 0.333.

|| To convert to mg/dL, divide by 0.00259.

the fasting glucose level still exceeded 8 mmol/L (144 mg/dL). The initial bedtime insulin dosage (measured in IU/d) was equal to the fasting blood glucose level (measured in mmol/L). Patients were given written instructions for self-adjustment of the insulin dose: increase the dose by 4 IU/d if the fasting glucose level exceeds 8 mmol/L on three consecutive measurements and by 2 IU/d if the fasting glucose level exceeds 6 mmol/L (108 mg/dL) on three measurements. The goal was to decrease the fasting glucose level to less than 6 mmol/L, which was predicted to decrease the hemoglobin A_{1c} value to less than 7.5% (6). Doses of oral agents remained the same. Before the start of insulin therapy, levels of glycosylated hemoglobin, fasting serum free insulin, C-peptide, triglycerides, cholesterol, and high-density lipoprotein cholesterol; waist-to-hip ratio (10); and blood pressure were measured. The patients were not instructed to change their diet (except for treatment of hypoglycemia) or exercise habits because of insulin therapy.

Follow-up Visits

Follow-up visits took place at 3 and 6 weeks and every 3 months for 1 year. At these visits, body weight, blood pressure, insulin dose, and side effects were recorded and fasting blood glucose was measured. Glycosylated hemoglobin was measured every 3 months. Measurements of serum C-peptide and lipids and waist-to-hip ratio were repeated at 12 months. Compliance, monitored through pill counting, was more than 95% for patients who completed the study.

Analytical Methods

Home blood glucose monitoring was performed by using the Hypocount Home Blood Glucose Monitor (Oriola, Espoo, Finland). Levels of serum free insulin (11), glycosylated hemoglobin (7), serum C-peptide (7), high-density lipoprotein cholesterol (12), total cholesterol, and triglycerides (7) were measured as previously described. Liver enzyme, serum creatinine, and blood glucose levels were measured by using standard techniques at each local treatment center.

Statistical Analysis

Comparison of normally distributed variables between the groups (in patients who completed the trial) during the 12-month treatment period was performed by using analysis of variance for repeated measures. If analysis of variance for repeated measures had significant results, post hoc pairwise comparisons between the four groups were performed by using a Bonferroni correction. For comparison of means when the variance was not normally distributed (symptomatic hypoglycemic episodes), the Kruskal-Wallis test was used. The GraphPad Prism program (GraphPad Software, San Diego, California) was used to fit data relating indices of glycemia to frequency of biochemical hypoglycemia by searching for the best fit among linear and various nonlinear regression models. Goodness of fit was evaluated by the runs test and the *F* test (GraphPad Software). Frequencies of hypoglycemia among the groups were compared by using the chi-square test. The data collected at 0 months were used as the

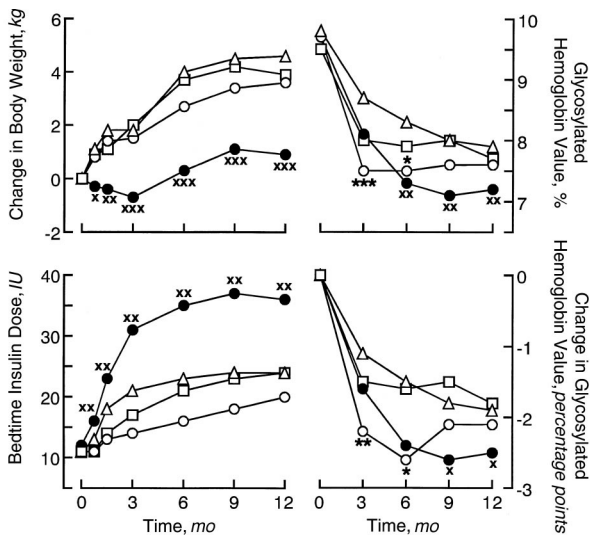


Figure 1. Change in body weight (top left), bedtime insulin dose (bottom left), glycosylated hemoglobin value (top right), and change in the glycosylated hemoglobin value (bottom right) during 12 months of insulin treatment in patients receiving bedtime insulin plus metformin (black circles), those receiving bedtime insulin plus glyburide (squares), those receiving bedtime insulin plus both oral agents (white circles), and those receiving bedtime and morning insulin (triangles). In the top left and bottom left panels, x = $P < 0.05$, xx = $P < 0.01$, and xxx = $P < 0.001$ for bedtime insulin plus metformin compared with all other treatments; in the top right and bottom right panels, xx = $P < 0.05$ and xxx = $P < 0.01$ for bedtime insulin plus metformin compared with bedtime and morning insulin and bedtime insulin plus glyburide. In the top right and bottom right panels, * = $P < 0.05$ and ** = $P < 0.01$ for bedtime insulin plus glyburide and metformin compared with bedtime and morning insulin.

baseline against which changes during insulin therapy were compared. All statistical tests were two-tailed, and all data are given as the mean \pm SE.

Role of the Funding Source

Funding authorities had no role in the analysis or interpretation of the data or in the subsequent decision to submit the report for publication.

Results

Insulin Doses

Initial doses of insulin were similar in all groups (Figure 1). After 12 months, the dosages of bedtime insulin were 24 ± 3 IU/d in patients receiving bedtime insulin plus glyburide, 36 ± 9 IU/d in patients receiving bedtime insulin plus metformin ($P < 0.01$ compared with all other groups), 20 ± 3 IU/d in patients receiving bedtime insulin plus both oral drugs, and 24 ± 3 IU/d in patients receiving bedtime and morning insulin. The dose of bedtime insulin was significantly higher in patients receiving bedtime insulin plus metformin than in other patients at all time points starting 3 weeks after therapy (Figure 1). In patients receiving bedtime and morning insulin, the morning insulin dose averaged 16 ± 1 IU at 3 weeks and 29 ± 3 IU at 12 months.

Serum free insulin levels were similar among the groups at baseline (data not shown) and averaged 12 ± 1 mU/L. At 12 months, the mean serum free insulin levels were significantly increased ($P < 0.05$ for 12 months compared with 0 months); they averaged 17 ± 2 mU/L in patients receiving bedtime insulin plus glyburide, 22 ± 4 mU/L in patients receiving bedtime insulin plus metformin, 16 ± 2 mU/L in patients receiving bedtime insulin plus both oral drugs, and 19 ± 3 mU/L in patients receiving bedtime and morning insulin. Differences among groups were not statistically significant.

Glycemic Control

Glycosylated Hemoglobin

Hemoglobin A_{1c} values were similar among the groups at 6 weeks before therapy and at 0 weeks (Figure 1). Glycosylated hemoglobin values decreased during the 6-week run-in period by $0.2\% \pm 0.1\%$ in all groups ($P < 0.05$), and the groups did not differ. At 3 and 6 months after therapy, patients receiving bedtime insulin plus glyburide and metformin had a significantly lower hemoglobin A_{1c} value than those receiving bedtime insulin plus glyburide and those receiving bedtime and morning insulin (Figure 1). This difference disappeared after 6 months (Figure 1). Unlike the other patients, patients receiving bedtime insulin plus metformin showed a progressive decrease in glycosylated hemoglobin values over time. At 12 months, glycosylated hemoglobin values in this group averaged $7.2\% \pm 0.2\%$; this change and the absolute change (-2.5 ± 0.4 percentage points) differed significantly from that seen in the other groups (Figure 1).

Home Glucose Monitoring

Compliance with self-measurement of fasting blood glucose levels averaged 39% (range of group means, 38% to 42%) during the run-in period, 50% (44% to 53%) during the first 6 months of therapy, and 41% (37% to 45%) during the last 6 months of therapy. The groups did not differ significantly.

During the run-in period, fasting glucose levels were 10.5 ± 2.1 mmol/L in patients receiving bedtime insulin plus glyburide, 11.2 ± 2.3 mmol/L in patients receiving bedtime insulin plus metformin, 10.0 ± 2.3 mmol/L in patients receiving bedtime insulin plus both drugs, and 12.1 ± 3.1 mmol/L in patients receiving bedtime and morning insulin; during the last 3 months of therapy, these values were 6.4 ± 0.3 , 6.2 ± 0.2 , 6.4 ± 0.3 , and 6.7 ± 0.3 mmol/L, respectively. The groups did not differ significantly.

Diurnal glucose profiles showed that the greatest decreases (mean during the last 3 months of therapy compared with mean during the run-in period) occurred at 4 a.m. and before breakfast, whereas

the smallest decreases occurred after dinner and at 10 p.m. in each group. During the last 3 months of therapy, when glycemic control was significantly better in patients receiving bedtime insulin plus metformin than in the other groups (**Figure 1**), fasting glucose levels had decreased by 4.6 ± 0.5 mmol/L in patients receiving bedtime insulin plus glyburide, 5.3 ± 0.7 mmol/L in patients receiving bedtime insulin plus metformin ($P < 0.05$ compared with bedtime insulin plus glyburide and metformin), 3.5 ± 0.6 mmol/L in patients receiving bedtime insulin plus both oral drugs, and 5.3 ± 0.7 mmol/L in patients receiving bedtime and morning insulin; after dinner, the values had decreased by 1.8 ± 0.6 , 3.6 ± 0.8 ($P < 0.05$ compared with bedtime insulin plus glyburide), 3.2 ± 0.6 , and 2.8 ± 0.5 mmol/L, respectively. When changes in glucose levels were compared between the groups, no significant differences were seen when the change in fasting glucose was used as a covariate (data not shown).

Changes in Body Weight

During the run-in period, body weight remained unchanged in all groups. At 12 months, the patients receiving bedtime insulin plus metformin had not gained weight compared with body weight at 0 months (mean change, 0.9 ± 1.2 kg during 12 months of therapy) (**Figure 1**). Starting from 3 weeks after therapy, this change was significantly lower than that seen in the other groups: Weight gain during 12 months of therapy averaged 3.9 ± 0.7 kg in patients receiving bedtime insulin plus glyburide ($P < 0.001$ for 12 months compared with 0 months; $P < 0.05$ compared with patients receiving bedtime insulin plus metformin), 3.6 ± 0.8 kg in patients receiving bedtime insulin plus both oral drugs ($P < 0.001$ for 12 months compared with 0 months; $P < 0.05$ compared with patients receiving bedtime insulin plus metformin), and 4.6 ± 1.0 kg in patients receiving bedtime and morning insulin ($P < 0.001$ for 12 months compared with 0 months; $P < 0.01$ compared with patients receiving bedtime insulin and metformin). The waist-to-hip ratio (**Table**) decreased significantly ($P \leq 0.05$) in patients receiving bedtime insulin plus metformin (mean change, -0.002 ± 0.007 at 12 months) compared with the other groups (mean changes, 0.012 ± 0.006 , 0.008 ± 0.004 , and 0.016 ± 0.007 , respectively).

Hypoglycemia

Symptomatic Hypoglycemic Episodes

During 12 months of therapy, the mean number of symptomatic hypoglycemic episodes per patient was 3.4 ± 1.0 in patients receiving bedtime insulin plus glyburide, 1.8 ± 0.4 in patients receiving bedtime insulin plus metformin, 3.3 ± 1.6 in patients receiving bedtime insulin plus both oral drugs, and

3.9 ± 1.6 in patients receiving bedtime and morning insulin. The frequency of hypoglycemic episodes in patients receiving bedtime insulin plus metformin was significantly lower ($P < 0.05$) than that seen in patients receiving bedtime and morning insulin. To analyze whether the frequency of symptomatic hypoglycemic episodes contributed to the inability of patients receiving bedtime insulin plus glyburide to increase their insulin dose as much as patients receiving bedtime insulin plus metformin had, analysis of variance was performed by using the change in insulin dose as the dependent variable, the number of symptomatic hypoglycemic episodes and the mean annual hemoglobin A_{1c} value as covariates, and group as a grouping factor. Symptomatic hypoglycemic episodes ($P < 0.05$), mean annual hemoglobin A_{1c} value ($P < 0.05$), and group ($P < 0.05$) were independent determinants of the change in insulin dose during the treatment period (multiple $r = 0.4$; $P < 0.01$). No severe hypoglycemic episodes requiring treatment assistance from another person occurred.

Biochemical Hypoglycemic Episodes

The mean frequency of biochemical hypoglycemic episodes in fasting blood glucose measurements (glucose level < 3.5 mmol/L) was significantly lower in patients receiving bedtime insulin plus metformin (1.1% [3350 measurements]) and those receiving bedtime and morning insulin (1.2% [3936 measurements]) than in those receiving bedtime insulin plus glyburide (2.2% [3184 measurements]; $P < 0.01$ for comparison with both groups) and those receiving bedtime insulin plus metformin and glyburide (1.8% [3954 measurements]; $P < 0.05$). The frequency of biochemical hypoglycemic episodes was correlated with the mean blood glucose level in a nonlinear fashion (**Figure 2**).

During the run-in phase, the mean frequency of biochemical hypoglycemic episodes seen in the diurnal profiles during the run-in phase was 0.27% (no differences were found among the groups) and 1% during 12 months of insulin therapy. The frequency was significantly lower among patients receiving bedtime insulin plus metformin (0.6%) than in those receiving bedtime insulin plus glyburide (1.0%; $P < 0.05$), those receiving bedtime insulin plus both oral drugs (1.5%; $P < 0.001$), and those receiving bedtime and morning insulin (1.0%; $P < 0.05$). The highest frequency of biochemical hypoglycemic episodes was observed at 4 a.m. in all groups (**Figure 3**).

Serum Lipid and Lipoprotein Levels, Blood Pressure, and Urinary Albumin Excretion Rate

Among all groups, serum triglyceride levels were similar at baseline (**Table**); during therapy, these

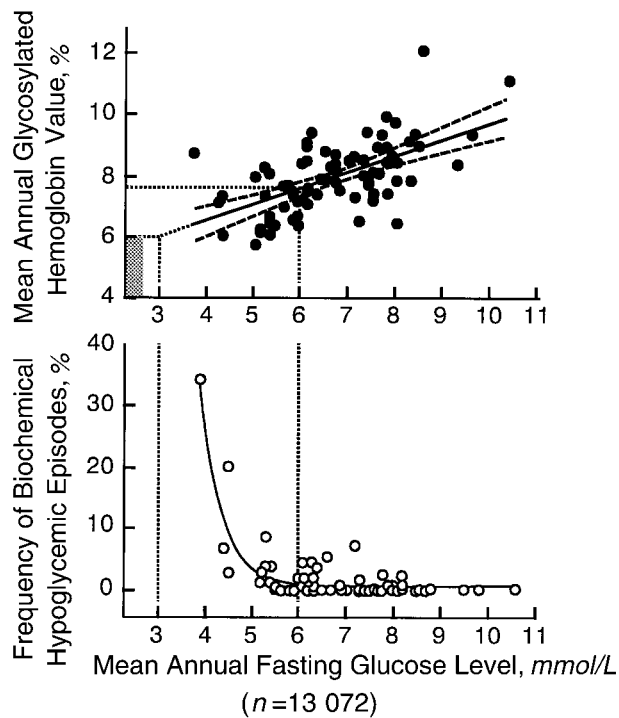


Figure 2. Relation between the mean annual fasting glucose level and the mean annual glycosylated hemoglobin value (top) and the frequency of biochemical hypoglycemic episodes (bottom) (fasting glucose < 3.5 mmol/L [63 mg/dL]) in patients with type 2 diabetes. The regression equation relating fasting glucose and glycosylated hemoglobin was as follows: glycosylated hemoglobin = 4.4 [95% CI, 3.3 to 5.5] + 0.50 [CI, 0.34 to 0.66] × fasting plasma glucose level [measured in mmol/L]. The gray area in the top panel indicates the normal range of glycosylated hemoglobin values. The dotted lines indicate glycosylated hemoglobin values that correspond to fasting glucose levels of 3 and 6 mmol/L (54 and 108 mg/dL).

levels decreased by 0.8 ± 0.3 mmol/L in patients receiving bedtime insulin plus glyburide, 0.7 ± 0.3 mmol/L in patients receiving bedtime insulin plus metformin, 0.4 ± 0.2 mmol/L in patients receiving bedtime insulin plus both oral drugs, and 0.9 ± 0.3 mmol/L in patients receiving bedtime and morning insulin ($P < 0.001$ for change compared with 0 months in all groups). Differences between the groups were not significant. Serum total and high-density lipoprotein cholesterol levels, blood pressure, and the urinary albumin excretion rate remained unchanged during insulin therapy in all groups (data not shown).

Side Effects and Withdrawal

Of the 96 randomly assigned patients, 88 completed the study. Four patients (8% [3 receiving bedtime insulin plus metformin and 1 receiving bedtime insulin plus metformin and glyburide]) developed side effects associated with metformin (severe diarrhea, metallic taste, abdominal discomfort, and a rash). Four other patients dropped out for reasons that seemed unrelated to treatment (among patients receiving bedtime insulin plus glyburide, 1 had hepatocellular carcinoma and 1 had normoglycemia at

the visit 3 weeks before the start of therapy; among patients receiving bedtime insulin plus metformin, 1 committed suicide and 1 had severe infection).

Discussion

In this randomized, placebo-controlled trial, we compared four bedtime insulin regimens in patients with poorly controlled type 2 diabetes. On the basis of analysis of predictors of treatment responses in previous studies (3, 7, 13) and data from monotherapy trials of metformin (14, 15), we hypothesized that self-adjustment of the insulin dose and use of metformin in addition to insulin might offer therapeutic benefits. We found that the combination of bedtime insulin and metformin effectively prevented weight gain during insulin therapy. This combination also resulted in the best overall glycemic control and was associated with the lowest frequency of hypoglycemic episodes.

Previous long-term data comparing the effects of various insulin regimens on glycemic control are sparse (1–5, 8, 16, 17). In patients with newly diagnosed type 2 diabetes in the UKPDS 33 and 34, glycemic control progressively deteriorated over 10 years regardless of whether the patients had received insulin, sulfonylurea, metformin, or diet therapy (1, 2). However, these two UKPDS reports did not compare different insulin treatment regimens, and insulin doses were adjusted only every 3 months (1, 2). In a study by the Department of Veterans Affairs Implantable Insulin Pump Study Group (8), implantable insulin pumps were compared with mul-

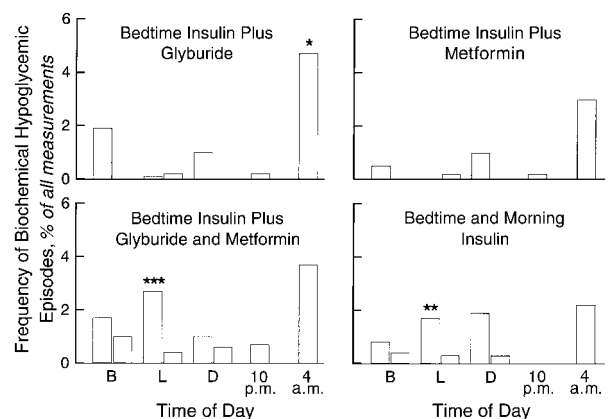


Figure 3. Frequency (percentage of all measurements at a given time point) of biochemical hypoglycemic episodes (blood glucose level < 3.5 mmol/L [63 mg/dL]) during home glucose monitoring of diurnal glucose profiles. These frequencies differed significantly among the groups before lunch (2.7% of 648 measurements before lunch in patients receiving bedtime insulin plus glyburide and metformin compared with 0% in patients receiving bedtime insulin plus metformin [*** $P < 0.001$]) and 0.1% in patients receiving bedtime insulin plus glyburide [*** $P < 0.001$]) and at 4 a.m. (4.7% of 603 measurements at 4 a.m. in patients receiving bedtime insulin plus glyburide compared with 2.2% in patients receiving bedtime and morning insulin; * $P < 0.05$). The frequency of hypoglycemia was also higher before lunch in the bedtime and morning insulin groups than in the bedtime insulin and glyburide or metformin groups (** $P < 0.01$). B = breakfast; D = dinner; L = lunch.

multiple daily injections for 1 year. Hemoglobin A_{1c} values decreased by 1.4 percentage points in the implantable insulin pump group and 1.3 percentage points in the multiple daily injection group and stabilized at 7.3% and 7.4%, respectively, at the end of 1 year. This demonstrates that progressive deterioration of glycemic control can be prevented by intensive treatment, an observation also made in our study (**Figure 1**) and the Veterans Affairs Cooperative Study (18). Glycemic control was better maintained in this study than in our first multicenter study (6, 7).

We believe that better maintenance of glycemic control in all treatment groups (**Figure 1**) can be mainly attributed to a new aspect of the education program: teaching the patients to adjust the insulin dose. The individual bedtime insulin doses in our study ranged from 8 to 168 IU/d. If the insulin dose had been increased by 4 IU at each outpatient visit, an increment of only 24 U would have been achieved in 1 year. Thus, even a conservative recommendation to increase the bedtime insulin dose on the basis of fasting blood glucose measurements every 3 days by 2 IU/d would allow an insulin dose of 250 IU/d to be reached in 1 year.

In the present study, we expected patients receiving only one oral drug (glyburide or metformin) in addition to bedtime insulin to require greater increases in their insulin doses than those receiving bedtime insulin plus both oral drugs. This expectation was fulfilled in patients receiving bedtime insulin plus metformin but not in those receiving bedtime insulin plus glyburide. The reasons for this remain uncertain, but statistical analysis implied that the higher frequency of symptomatic hypoglycemic episodes among patients receiving bedtime insulin plus glyburide was responsible (**Figure 3**). It could be argued that it is inappropriate to compare measures of glycemic control among the different groups given the different insulin doses. On the other hand, the dose adjustments were made by the patients and were the result of a randomized trial.

Our data demonstrate, perhaps for the first time, that metformin prevents weight gain during insulin therapy. This beneficial effect of metformin is consistent with previous data from such studies as that of the Multicenter Metformin Study Group (14) and the UKPDS 28 (19). The mechanism underlying the beneficial effect of metformin on body weight is unclear. Recent data on causes of weight gain in patients using insulin alone and those using insulin and metformin suggest, however, that the weight gain-sparing effect of metformin is due to reduced energy intake (20).

The frequency of symptomatic and biochemical hypoglycemic episodes (glucose level < 3.5 mmol/L [63 mg/dL]) was approximately twofold lower in

patients receiving bedtime insulin plus metformin than in the other groups (**Figure 3**). These data are consistent with those of the UKPDS 13, in which the frequency of any hypoglycemia was fourfold lower and major hypoglycemia was threefold lower than the values seen in patients with equally well-controlled type 2 diabetes who received glyburide (15). The frequency of biochemical hypoglycemia was similar to that found previously (glucose level < 4 mmol/L [72 mg/dL] in 2% of all measurements) during comparison of combination therapy with insulin to therapy with insulin alone in patients with type 2 diabetes (6). In the latter study, glycemic control was similar regardless of the treatment regimen and no differences in the frequency of hypoglycemic episodes were seen between patients treated with insulin plus glyburide and metformin and those treated with insulin alone. This was also true in our present study and suggests that metformin combined with glyburide does not reduce hypoglycemic episodes.

As was the case in patients with type 1 diabetes mellitus (21), the frequency of hypoglycemic episodes was closely correlated with mean fasting glycemia. Although no severe hypoglycemic episodes occurred, the frequency of biochemical hypoglycemic episodes increased markedly when the mean annual fasting glucose level was less than 6 mmol/L (**Figure 2**). The latter glucose level corresponded to a mean annual hemoglobin A_{1c} value of 7.4% (**Figure 2**). These data imply that normoglycemia is not necessarily a safe target during insulin therapy and that it is not realistic to achieve normoglycemia by using bedtime insulin combined with metformin, glyburide, or a second injection of insulin. Our previous experience also suggests that an increase in the number or type of insulin injections does not help in this regard (6). The results of the current study encourage exploration of whether the weight gain observed with multiple compared with bedtime insulin injections also could be prevented by using metformin.

A total of 8% of the patients assigned to receive metformin discontinued treatment because of metformin-related side effects (severe diarrhea, nausea, metallic taste, or rash). This percentage is identical to the frequency of severe side effects of metformin reported by the Multicenter Metformin Study Group (14) and is not dissimilar to the 15% frequency of side effects of metformin in the UKPDS 28 (19).

In conclusion, good glycemic control for 1 year was achieved by using simple bedtime insulin regimens in patients whose disease is poorly controlled with sulfonylurea therapy. We attribute this to teaching the patients to self-adjust the insulin dose on the basis of home glucose monitoring of the

fasting glucose level; we hope this approach will be used in clinical practice. In addition, the combination of bedtime insulin and metformin gave better glycemic control, prevented weight gain, and induced less hypoglycemia compared with the other regimens that we tested. Such a regimen could be recommended for treatment of patients with type 2 diabetes whose disease cannot be controlled with oral agents alone, provided that patients tolerate metformin.

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