Comparison of Insulin Monotherapy and Combination Therapy With Insulin and Metformin or Insulin and Troglitazone in Type 2 Diabetes

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OBJECTIVE — To evaluate the safety and efficacy of treatment with insulin alone, insulin plus metformin, or insulin plus troglitazone in individuals with type 2 diabetes.

RESEARCH DESIGN AND METHODS — A total of 88 type 2 diabetic subjects using insulin monotherapy (baseline HbA_{1c} 8.7%) were randomly assigned to insulin alone ($n = 31$), insulin plus metformin ($n = 27$), or insulin plus troglitazone ($n = 30$) for 4 months. The insulin dose was increased only in the insulin group. Metformin was titrated to a maximum dose of 2,000 mg and troglitazone to 600 mg.

RESULTS — HbA_{1c} levels decreased in all groups, the lowest level occurring in the insulin plus troglitazone group (insulin alone to 7.0%, insulin plus metformin to 7.1%, and insulin plus troglitazone to 6.4%, $P < 0.0001$). The dose of insulin increased by 55 units/day in the insulin alone group ($P < 0.0001$) and decreased by 1.4 units/day in the insulin plus metformin group and 12.8 units/day in the insulin plus troglitazone group (insulin plus metformin versus insulin plus troglitazone, $P = 0.004$). Body weight increased by 0.5 kg in the insulin plus metformin group, whereas the other two groups gained 4.4 kg ($P < 0.0001$ vs. baseline). Triglyceride and VLDL triglyceride levels significantly improved only in the insulin plus troglitazone group. Subjects taking metformin experienced significantly more gastrointestinal side effects and less hypoglycemia.

CONCLUSIONS — Aggressive insulin therapy significantly improved glycemic control in type 2 diabetic subjects to levels comparable with those achieved by adding metformin to insulin therapy. Troglitazone was the most effective in lowering HbA_{1c}, total daily insulin dose, and triglyceride levels. However, treatment with insulin plus metformin was advantageous in avoiding weight gain and hypoglycemia.

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Approximately 15 million Americans have type 2 diabetes. With 625,000 new cases of diabetes each year, diabetes will continue to have a major impact on the health care of the population in the U.S. (1). Estimates suggest that as much as one-half of costs related to diabetes are attributable to the treatment of comorbid conditions and long-term diabetic complications (2,3). As a result, health care providers are concerned with identifying therapies that will effectively treat diabetes and prevent the complications of the disease.

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Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DCCT, Diabetes Control and Complications Trial; 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.

The Diabetes Control and Complications Trial (DCCT) and the U.K. Prospective Diabetes Study (UKPDS) demonstrated the relationship between improved blood glucose control and the prevention of diabetic complications (4,5). However, type 2 diabetes is not only a metabolic disorder associated with hyperglycemia but also a syndrome of cardiovascular risk factors, such as dyslipidemia, hypertension, and obesity (6). More than 50% of deaths in people with diabetes is due to cardiovascular disease (7). Thus, the treatment of type 2 diabetes requires agents that not only lower blood glucose levels but also improve lipoprotein levels and blood pressure and reduce body weight.

The biguanide metformin has been shown to lower blood glucose levels by sensitizing the liver to the effects of insulin, thus suppressing hepatic glucose output. It also has mild effects on promoting glucose utilization. Metformin has also been shown to lower cholesterol and triglyceride levels, to reduce hyperinsulinemia and improve insulin sensitivity, and to assist with weight reduction (8,9). The thiazolidinedione troglitazone improves insulin sensitivity by enhancing insulin-mediated glucose disposal, resulting in reduced plasma insulin concentrations. Troglitazone may also have modest effects on lowering hepatic glucose production (10–12). Beneficial effects on serum lipid profiles (13–15), arterial blood pressure (16,17), and vascular tone (18,19) have also been reported.

Insulin therapy is associated with several metabolic benefits including improved insulin sensitivity, improved insulin secretion, decreased overnight hepatic glucose output, decreased postprandial blood glucose levels, and improved lipid profiles (20–24). However, large doses of insulin are often required to achieve near normal blood glucose levels and are associated with weight gain and the risk of hypoglycemia.

Despite the proven benefits of insulin, metformin, and troglitazone, there is progressive deterioration of glycemic control in type 2 diabetes when agents are used as monotherapy. In the UKPDS, mean blood glucose concentrations and HbA_{1c} levels increased steadily, irrespective of treatment with diet, oral agents, or insulin (25). Six years after diagnosis, B-cell function had declined to between 28 and 52% of normal, and the investigators estimated that it would be necessary to add an additional agent every 4 years to maintain fasting glucose levels within the target range (26).

Theoretically, improved insulin sensitivity and lipid profiles associated with metformin and troglitazone therapy should provide an added benefit in subjects with type 2 diabetes who are taking insulin by further improving blood glucose levels and the cardiovascular risk profile. Combination therapy using sulfonylurea agents and metformin and/or troglitazone has been shown to improve blood glucose control compared with monotherapy (27–30). The use of metformin or troglitazone in combination with insulin has also demonstrated improved blood glucose control over insulin therapy alone (31–34). However, a direct comparison of insulin alone compared with insulin in combination with metformin or troglitazone has not been done.

RESEARCH DESIGN AND METHODS

Study patients were required to meet the following criteria: type 2 diabetes, aged 24–70 years, treatment with insulin alone, total daily insulin dose of at least 30 units, an HbA_{1c} level ≥7.0%, and normal renal and hepatic function.

Subjects who met the inclusion criteria were randomly assigned in an unmasked fashion to continue insulin alone or to add metformin or troglitazone to insulin. Random assignment was determined by the sponsor who provided sealed sequentially numbered envelopes. The entire study period was 4 months; all subjects were seen biweekly for 1 month after randomization to treatment and monthly for the subsequent 3 months. Between-visit contact with the study nurse or physician rarely occurred and was only initiated by the patient, usually because of frequent hypoglycemia. Complete medical histories, physical examinations, waist and hip measurements, 3-day food records, fasting lipid and lipoprotein profiles, C-peptide concentrations, and serum chemistries were determined at the beginning and end of the study. Body weight, HbA_{1c} levels, fasting plasma glucose levels, and liver enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) were obtained monthly. Patients were asked to use their meters to check plasma glucose levels at least twice daily. Glycemic control based on at least two daily meter-obtained plasma glucose measurements and tolerance to the assigned treatment were assessed at each office visit. Patients were encouraged to maintain baseline levels of dietary intake and physical activity throughout the study. Informed consent was obtained from all subjects before entry into the study after approval by the university institutional review board.

Intervention

Subjects assigned to take insulin and metformin took a maximum daily dose of 2,000 mg of metformin, titrated as follows: one 500-mg tablet with breakfast and supper from week 0 to week 2, two 500-mg tablets with breakfast, one 500-mg tablet with supper from week 2 to week 4, and two 500-mg tablets with breakfast and supper from week 4 to week 16. Subjects assigned to take insulin and troglitazone took a maximum daily dose of 600 mg of troglitazone titrated as follows: one 200-mg tablet with breakfast from week 0 to week 2, one 400-mg tablet with breakfast from week 2 to week 4, and three 200-mg tablets with breakfast from week 4 to week 16. The dose of metformin or troglitazone was adjusted when necessary to prevent adverse effects. Patients received the maximum dosage tolerated from weeks 4–16.

For subjects taking insulin alone, the dose of insulin as well as the frequency of injections were modified throughout the course of the study to achieve plasma glucose levels as close to normal as possible (HbA_{1c} ≤5.6%). At each office visit the insulin dose for patients on insulin monotherapy was increased at the discretion of the investigator by a minimum of 5% and a maximum of 20% for meter-obtained plasma glucose levels averaging up to150 mg/dl, a maximum of 25% for plasma glucose levels 151–200 mg/dl, a maximum of 30% for plasma glucose levels 201–250 mg/dl, and up to 40% for plasma glucose levels >250 mg/dl.

Plasma glucose data were downloaded from the patient's meter to the computer; all patients used a glucose meter that stored the readings as well as the date and time the readings were obtained. The baseline dose of insulin and frequency of injections were never increased in subjects assigned to take metformin or troglitazone in combination with insulin (combination therapy). A 10–20% decrease in the dosage of insulin in subjects on combination therapy was permitted only if patients experienced frequent hypoglycemia or if the patient's meter-obtained plasma glucose levels were consistently <100 mg/dl. The dose of metformin or troglitazone was not modified in response to plasma glucose levels.

The frequency of hypoglycemia was determined by the number of plasma glucose readings stored in the patient's meter that were <65 mg/dl. Severe hypoglycemia was defined as any low plasma glucose level that patients were unable to treat themselves, and the patient's symptoms were reversed with oral carbohydrate, glucagon, or intravenous glucose. Edema was determined to be absent or present based on physical examination at the beginning and end of the study or at any time the patient complained of swelling.

Analytical determinations

HbA_{1c} levels were measured by using high-pressure liquid chromatography. An automated glucose oxidase method (Glucose Analyzer 2; Beckman Instruments, Fullerton, CA) was used to measure plasma glucose concentrations. C-peptide concentrations were measured by radioimmunoassay using polyclonal antisera. Fasting lipid and lipoprotein concentrations were assessed by standard laboratory methods.

Statistical analysis

Demographic variables were checked for normality across groups. A log transformation improved normality for all of the variables. A one-factor ANOVA was done for the log of each demographic variable to determine whether the means differed across the three groups. Fisher's exact tests of group by both race and sex were performed. Outcome variables were checked for normality across groups, and log transformations were used for total daily insulin dose, ALT, AST, C-peptide, HDL cholesterol, triglyceride, and VLDL

triglyceride levels. A one-factor ANOVA was done for each of the outcome measures. ANOVA contrasts were obtained for group, time, and group-by-time interaction with Bonferroni correction. The Fisher-Hayter test was used to examine all pairwise comparisons (35).

Difference variables were analyzed using a one-way ANOVA. Where the ANOVA was significant, a multiple-comparisons test was performed to determine which means differed from one another. When variables did not meet the normality requirement, even with a log transformation, these variables were analyzed by the Kruskal-Wallis test. Where the means differed, a Mann-Whitney *U* test was used to examine all pairs, with a Bonferroni adjustment.

Two-tailed tests were performed for the analyses. A *P* value <0.05 was considered statistically significant. All analyses were conducted using SAS software, version 6.12. Results are reported as the mean ± SD unless otherwise indicated.

Table 1—*Demographic parameters of the study population*

	Insulin alone	Insulin plus metformin	Insulin plus troglitazone
N	31	27	30
Age (years)	54.4 ± 9.1	51.8 ± 10.5	51.7 ± 8.0
Sex (M/F)	15/16	15/12	13/17
Ethnicity (*n*)			
Caucasian	17	14	17
African-American	9	4	5
Hispanic	5	8	8
Other		1	
Duration of diabetes (years)	10.5 ± 7.3	7.6 ± 4.1	11.6 ± 6.8
Duration of insulin therapy (years)	4.8 ± 4.7	3.5 ± 3.3	5.1 ± 4.0
C-peptide (ng/ml)	1.9 ± 1.4*	2.5 ± 1.7	2.8 ± 1.9
BMI	36.4 ± 9.0	37.1 ± 6.6	36.4 ± 6.0

Data are means ± SD. *$P < 0.05$ vs. insulin plus troglitazone.

RESULTS — Altogether, 92 subjects met the eligibility criteria and were randomly assigned to receive insulin alone or combination therapy. A total of 31 subjects were assigned to insulin alone, 30 subjects were assigned to insulin plus metformin, and 31 subjects were assigned to insulin plus troglitazone. Two subjects assigned to take insulin plus metformin experienced severe and unrelenting diarrhea on metformin 500 mg daily and withdrew from the study. One subject assigned to take insulin plus metformin achieved <80% compliance with medication administration and was terminated from study participation. One subject assigned to take insulin plus troglitazone withdrew from the study because she was concerned about the negative publicity associated with troglitazone. Thus, 88 subjects remained for analysis.

All three groups were comparable in age, sex, ethnicity, duration of diabetes, duration of insulin therapy, waist-to-hip ratio (average 0.93), and HbA_{1c} level (see Tables 1 and 2). The group treated with insulin alone had a significantly lower mean C-peptide level at baseline than the insulin plus troglitazone group. C-peptide levels did not change in any group throughout the course of the study and were not related to change in HbA_{1c} level. There was no apparent reason for the lower C-peptide level in the insulin alone group, such as ethnicity, sex, or duration of diabetes. The insulin plus troglitazone group weighed less ($P < 0.001$) and took more insulin at baseline ($P < 0.01$) than the other two groups. The average BMI among the groups, however, was similar.

The group assigned to insulin monotherapy had lower baseline triglyceride and VLDL triglyceride levels than the other two groups. Eight subjects in both the insulin alone group and insulin plus metformin group, and thirteen subjects in the insulin plus troglitazone group took lipid-lowering medication at baseline. Three subjects in the insulin plus troglitazone group taking lipid-lowering medication took gemfibrozil or nicotinic acid; the remaining subjects in all three groups using lipid-lowering medication took statin drugs. Two subjects in the insulin alone group and three subjects in both the insulin plus metformin and insulin plus troglitazone groups had triglyceride levels >500 mg/dl. We are unable to ascertain any reason for the lower triglyceride levels in the insulin alone group, and we believe this occurred simply by chance.

Glycemic control

All three groups demonstrated a significant improvement in glycemic control after 4 months of their assigned treatment ($P < 0.0001$) (Table 2). Comparable HbA_{1c} levels were achieved at study end in the insulin alone and insulin plus metformin groups (mean 7.0 ± 1.0% and 7.1 ± 1.0%, respectively). However, the mean HbA_{1c} level in the insulin plus troglitazone group was ~10% lower than in the other two groups (mean 6.4 ± 0.8%, $P < 0.05$ vs. insulin alone and insulin plus metformin). Two subjects in the insulin plus metformin group had no improvement in HbA_{1c} level (HbA_{1c} levels increased 0.1 and 0.3%). All of the subjects taking insulin and troglitazone experienced an improvement in HbA_{1c} level. Four subjects taking insulin plus metformin were unable to tolerate the maximum dose of 2,000 mg/day. Three subjects took 1,000 mg/day, and one subject took 1,500 mg/day. The average reduction in HbA_{1c} level in those taking less than the maximum dose of metformin did not differ from that of the subjects on the maximum dose (−1.8 vs. –1.7). All of the subjects taking insulin plus troglitazone tolerated the maximum dose of 600 mg/day. Mean fasting plasma glucose concentrations significantly decreased in all three groups. Neither the change in fasting plasma glucose from baseline nor the absolute fasting plasma glucose concentrations at week 16 differed among the groups.

Daily insulin requirements

All patients received at least twice daily injections of insulin using either 70/30 insulin or NPH and regular insulin. At baseline, five subjects in each of the insulin alone and insulin plus metformin groups took three to four daily insulin injections of intermediate and short-acting insulin, and six subjects in the insulin plus troglitazone group took multiple daily insulin injections. At the end of 16 weeks of treatment, total daily insulin dosage increased

Table 2—*Clinical parameters before and after 4 months of respective treatment*

	Insulin alone		Insulin plus metformin		Insulin plus troglitazone	
	Before	After	Before	After	Before	After
N	31	31	27	27	30	30
Weight (kg)	107.0 ± 26.7	111.4 ± 28.0§	105.8 ± 22.4	106.3 ± 21.5	101.1 ± 17.8*	105.5 ± 17.4§
Waist-to-hip ratio	0.91 ± 0.10	0.90 ± 0.10	0.96 ± 0.08	0.95 ± 0.07	0.93 ± 0.08	0.92 ± 0.09
Daily insulin dose (units)	80.3 ± 41.7	134.9 ± 82.8§‖	82.9 ± 48.2	81.5 ± 50.1	96.5 ± 52.7†	83.7 ± 39.1
FPG (mg/dl)	192.7 ± 66.6	155.9 ± 57.7¶	192.5 ± 54.8	150.9 ± 49.2¶	185.6 ± 60.6	127.7 ± 41.1#
HbA_{1c} (%)	8.7 ± 1.6	7.0 ± 1.0§	8.8 ± 1.2	7.1 ± 1.0§	8.5 ± 1.2	6.4 ± 0.8§**
Total cholesterol (mg/dl)	190.8 ± 42.3	189.0 ± 40.3	192.9 ± 44.6	194.5 ± 43.4	196.6 ± 45.5	198.8 ± 44.7
HDL cholesterol (mg/dl)	38.3 ± 13.6	39.5 ± 10.6	31.5 ± 7.1	31.8 ± 6.7	34.6 ± 14.4	36.1 ± 9.6
LDL cholesterol (mg/dl)	108.4 ± 29.1	111.4 ± 30.6	110.7 ± 41.3	113.8 ± 35.0	112.4 ± 33.0	121.7 ± 32.7
Triglyceride (mg/dl)	178.3 ± 156.9‡	156.2 ± 114.3	226.8 ± 161.3	233.6 ± 182.4	215.3 ± 146.7	169.0 ± 70.2¶††
VLDL triglyceride (mg/dl)	128.1 ± 148.6‡	115.4 ± 108.5	161.8 ± 135.4	169.3 ± 138.1	161.6 ± 133.4	109.5 ± 65.9¶††

Data are means ± SD. *$P < 0.001$ vs. insulin, insulin plus metformin at baseline; †$P < 0.01$ vs. insulin, insulin plus metformin at baseline; ‡$P < 0.05$ vs. insulin plus metformin, insulin plus troglitazone at baseline; §$P < 0.0001$ vs. baseline; ‖$P < 0.001$ vs. insulin plus metformin and insulin plus troglitazone at week 16; ¶$P < 0.05$ vs. baseline; #$P < 0.001$ vs. baseline; **$P < 0.05$ vs. insulin and insulin plus metformin at week 16; ††$P < 0.05$ vs. insulin plus metformin at week 16. FPG, fasting plasma glucose.

by 55 units ($P < 0.0001$) in the group treated with insulin alone, from 0.75 to 1.2 units/kg. The mean total daily insulin dose decreased by 1.4 units/day in the insulin plus metformin group (0.78 units/kg at baseline to 0.77 units/kg at week 16), and decreased by 12.8 units/day in the insulin plus troglitazone group (0.95 units/kg at baseline to 0.79 units/kg at week 16). The changes in total daily insulin dose in the insulin plus metformin and insulin plus troglitazone groups were significantly different from each other ($P = 0.004$) (Fig. 1).

The frequency of injections was increased in the insulin alone group as well. Of the 31 subjects treated with insulin alone, 7 subjects changed from two daily injections of NPH and regular insulin to three or four daily injections of NPH and regular insulin. One subject assigned to insulin monotherapy changed from 70/30 insulin twice daily to mixing NPH and regular insulin twice daily. There was no change from baseline in the frequency of injections or type of insulin used by subjects on combination therapy.

Body weight and daily caloric intake

A comparable increase in body weight occurred in the insulin alone (4.4 ± 4.3 kg) and troglitazone plus insulin (4.4 ± 3.2 kg) groups ($P < 0.0001$ baseline vs. week 16). The increase in weight in these two groups was significantly different from the minimal change in weight (0.49 ± 2.8 kg) that occurred in the insulin plus metformin group ($P < 0.0001$).

Based on the 3-day food records obtained at baseline and at the end of the study, the daily caloric intake increased by ~99 ± 571 calories at the end of the study period in the insulin alone group. Daily caloric intake decreased in those taking either metformin or troglitazone in combination with insulin (−292 ± 442 and –253 ± 625 kcal, respectively, $P < 0.04$ vs. baseline).

Lipid and lipoprotein levels

There were no significant changes in total cholesterol, LDL cholesterol, and HDL cholesterol levels from baseline to the end of the study in any of the three treatment groups. A significant improvement in total triglyceride (−55.3 ± 119.4 mg/dl) and VLDL triglyceride levels (−52.1 ± 114.9 mg/dl) occurred in the group treated with insulin plus troglitazone

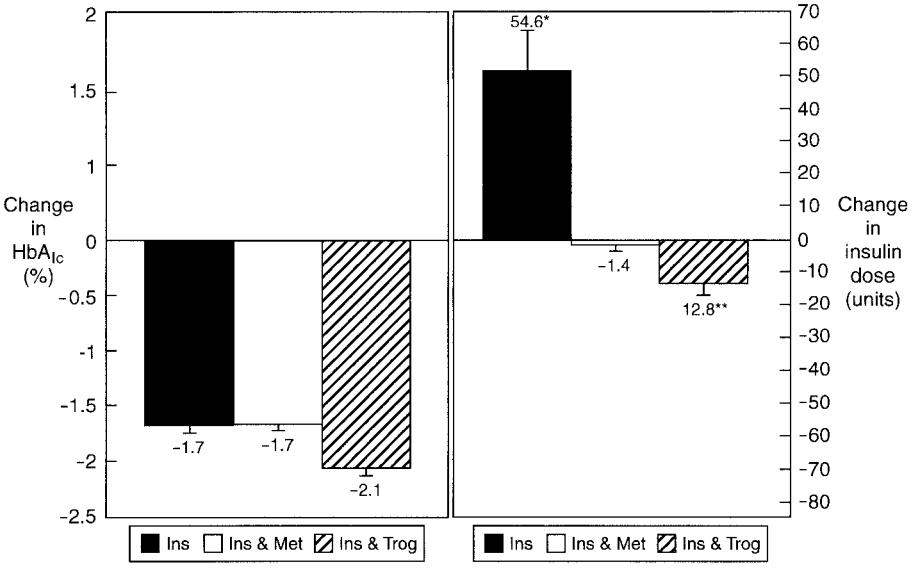

Figure 1—*Change in HbA_{1c} levels and total daily insulin dose in insulin-treated type 2 diabetic patients after 4 months of insulin monotherapy (■) or combination therapy with either insulin and metformin (□) or insulin and troglitazone (▨). *P < 0.0001 for insulin vs. insulin plus metformin and insulin plus troglitazone; **P = 0.004 for insulin plus metoformin vs. insulin plus troglitazone.*

($P < 0.05$). This improvement resulted in a significant difference in triglyceride and VLDL triglyceride levels between the insulin plus troglitazone group and the insulin plus metformin group at the end of the study ($P < 0.05$).

Adverse events

Compared with 36.7% of the subjects taking insulin plus troglitazone and 13% of the subjects taking insulin alone, 67% of subjects taking metformin plus insulin experienced gastrointestinal side effects ($P < 0.01$). Four of the 27 subjects were unable to take the maximum dose of metformin due to persistent gastrointestinal problems.

Mild hypoglycemia (self-treated plasma glucose levels <65 mg/dl) was infrequent but occurred about three times more often in subjects taking insulin plus troglitazone and insulin alone (insulin alone: average of two episodes per patient per month; insulin plus troglitazone: 1.7 episodes per patient per month) compared with subjects taking metformin plus insulin (average of 0.6 episodes per patient per month, $P < 0.01$). Fewer than 30% of low plasma glucose readings in all groups were <50 mg/dl (insulin alone 27%, insulin plus metformin 26%, and insulin plus troglitazone 29%). One subject taking insulin alone experienced six episodes of hypoglycemia severe enough to require assistance to treat, including emergency medical treatment.

None of the subjects taking insulin plus troglitazone experienced any abnormality in liver function tests. In fact, ALT (-6.5 ± 7.3, $P < 0.0001$) and AST (-2.83 ± 5.2) levels decreased in the troglitazone plus insulin–treated group. The incidence of edema was low (insulin alone 5 cases, insulin plus metformin 1 case, and insulin plus troglitazone 3 cases), and there were no differences among the three groups. All but one case in the insulin monotherapy group were mild and easily treated with low-dose diuretic medication. The one subject on insulin monotherapy who developed severe edema was treated for congestive heart failure.

CONCLUSIONS — These results demonstrate that insulin monotherapy as well as insulin in combination with insulin sensitizers, such as metformin and troglitazone, are effective in improving glycemic control. There are important differences among the therapies, however.

Insulin as monotherapy resulted in a reduction in the HbA_{1c} level from 8.7 ± 1.6 to 7.0 ± 1.0%. Patients required ~69% more insulin from baseline to achieve these results. They also required a more complicated insulin regimen in ~25% of the cases, necessitating more time and effort on the part of the patient and the health care team. Subjects on insulin monotherapy also gained a significant amount of weight (4.4 kg). These results suggest that patients who cannot tolerate or cannot afford insulin sensitizers can be effectively controlled on insulin therapy alone.

Insulin in combination with metformin resulted in a comparable average reduction in HbA_{1c}, as with insulin monotherapy (from 8.8 ± 1.2 to 7.1 ± 1.0%). However, this improvement was achieved without an increase in the total daily dose (average of −1.4 units) or complexity of the insulin regimen and with essentially no weight gain (0.5 kg) or hypoglycemia (0.6 episodes per patient per month). The disadvantage is that two-thirds of the subjects taking metformin experienced gastrointestinal side effects. Although the gastrointestinal side effects were usually mild and transient, 2 of 30 subjects could not tolerate metformin at all, and 4 of 30 were unable to tolerate the maximum dose of 2 g per day.

The lowest HbA_{1c} was achieved by subjects taking insulin plus troglitazone (8.5 ± 1.2 to 6.4 ± 0.8%). This occurred despite the fact that the average total daily insulin dose was reduced from 0.95 to 0.79 units/kg, a significantly greater reduction in total daily dose than occurred in subjects taking insulin plus metformin. The reduction in insulin dose occurred despite a weight gain of nearly 4.5 kg. By chance, subjects assigned to take insulin and troglitazone were less insulin sensitive at baseline than the other two groups, taking a significantly larger dose of insulin to achieve comparable baseline HbA_{1c} levels. The baseline dose of insulin of 0.78 units/kg in subjects treated with insulin and metformin remained essentially unchanged.

These results suggest that troglitazone may be a more effective insulin sensitizer than metformin and are consistent with the findings by Yu et al. (32) who demonstrated a 29% improvement in insulin sensitivity in subjects on CSII and troglitazone compared with no significant improvement in subjects on CSII and metformin. Yu et al. further showed that insulin requirements decreased by 53% in subjects taking troglitazone compared with 31% in subjects taking metformin ($P < 0.005$).

Treatment with insulin plus troglitazone also resulted in significant reductions in total triglyceride and VLDL triglyceride levels. However, the frequency of hypoglycemia, albeit low (two episodes per patient per month), was about three times greater than that which occurred with the combination of insulin and metformin. There were no abnormalities in liver function tests in the group that received troglitazone.

The results in the insulin plus troglitazone group compare with those of Schwartz et al. (33) who reported a significant improvement in HbA_{1c} levels, an increase in weight, and a decrease in insulin requirements in type 2 diabetic subjects taking 600 mg of troglitazone in combination with insulin. The improved HbA_{1c} levels reached a nadir after 16 weeks of treatment. Schwartz et al. reported somewhat less weight gain (3.6 kg) and a greater reduction in insulin dosage (29%), however, than that observed in this study. This is likely related to the fact that the HbA_{1c} levels decreased by 1.4% in the study by Schwartz et al. versus 2.4% in this study.

Troglitazone is no longer available, and we can only speculate that other thiazolidinedione compounds will produce similar results. Studies have shown that rosiglitazone and pioglitazone improve insulin sensitivity (36,37) and glycemic control (38,39) to levels that are similar to those achieved with troglitazone.

Although the HbA_{1c} levels were comparable in the insulin alone and insulin plus metformin groups at the end of the study, it is likely that lower HbA_{1c} levels could have been achieved in subjects taking combination therapy if the study design had allowed for increases in the insulin dose in these subjects. In the study by Avilés-Santa (31), in which subjects were masked to treatment with insulin plus a placebo or insulin plus metformin, the dose of insulin was increased as needed in both groups to achieve a normal HbA_{1c} level. The outcome revealed a 1.0% greater decline in HbA_{1c} in subjects who were taking insulin plus metformin compared with those taking insulin plus placebo. Subjects in Avilés-Santa's study who took insulin alone achieved an over-

all lowering of the HbA_{1c} level of 1.5%, a result consistent with the findings of subjects in this study who received insulin monotherapy.

Metformin is advantageous and unique in avoiding the weight gain associated with other pharmacological treatments of type 2 diabetes. Avilés-Santa reported a 0.5-kg weight gain in subjects taking insulin plus metformin despite a reduction in HbA_{1c} level of 2.5%. The insulin plus placebo subjects in her study gained an average of 3.2 kg. Others have also reported this (40,41). Although metformin has anorexic properties, the precise reason metformin-treated diabetic patients do not gain weight is unclear. In this study, subjects taking insulin plus metformin reported ingesting an average of nearly 300 fewer calories per day at the end of 4 months of treatment. On the other hand, subjects taking insulin plus troglitazone also reported eating an average of 250 fewer calories per day despite gaining nearly 4.5 kg. The large standard deviation in reported caloric intake, however, places the reliability of the food records into question, and makes it difficult to draw any firm conclusions regarding change in dietary intake.

Although weight gain is undesirable, is a weight gain of 4.5 kg harmful relative to the benefits of improved glycemic control? In the DCCT, the intensively treated type 1 diabetic patients gained an average of 4.5 kg while lowering HbA_{1c} levels by nearly 2%, similar to what was observed in this study. Yet, intensive treatment in the DCCT resulted in a significantly lower risk for the development and progression of retinopathy, nephropathy, and neuropathy as well as significantly lower cholesterol and triglyceride levels and fewer macrovascular events (4,42). In the UKPDS of over 4,500 type 2 diabetic patients, each 1% reduction in updated mean HbA_{1c} level was associated with reductions in risk of 37% for microvascular complications and 14% for macrovascular complications (43). In the UKPDS, intensively treated subjects also gained an average of 3–4 kg (5).

On the other hand, the weight gain in the DCCT and UKPDS occurred over several years; the weight gain in this study occurred over several months. Because trogolitazone is associated with fluid retention and edema (9), we cannot exclude the possibility that weight gain in this group was at least partially due to fluid retention, even though we did not observe a significant increase in edema in subjects treated with insulin plus troglitazone. The potential for fluid retention is potentially dangerous, especially in patients who have heart disease.

Studies have shown that troglitazone treatment is associated with a shift of adipose tissue from more metabolically active and perhaps harmful central fat depots to less metabolically active and less harmful peripheral sites (44,45). Troglitazone's effect on improving insulin sensitivity may be related to an increase in the amount of brown adipose tissue, which dissipates energy via oxidation of fatty acids (46,47). Thus, the potential for detrimental effects from weight gain seen with the combination of insulin and troglitazone is unclear. Patients should be counseled to modify dietary intake to minimize weight gain when thiazolidinediones are initiated, and health care providers should carefully assess for signs of fluid retention.

In general, hypoglycemia occurred infrequently, was mild and self-treated, and was not a deterrent to continued participation in the study or to increasing the dose or modifying the insulin regimen in patients treated with insulin alone. Insulin monotherapy and insulin in combination with troglitazone were associated with comparable amounts of hypoglycemia (1.75 episodes per patient per month). Insulin plus metformin was associated with the least amount of hypoglycemia. Treatment with metformin has not been associated with hypoglycemia (48). The reason for this is unknown.

Only one subject experienced episodes of severe hypoglycemia. He was randomized to insulin alone and had reported several episodes of severe hypoglycemia before entering the study. Diabetic patients should be well educated about the symptoms, prevention, and treatment of hypoglycemia, and blood glucose monitoring should be encouraged with all intensified treatment regimens.

Subjects in this study were unmasked to treatment, introducing the possibility for bias. There were also baseline differences among the groups for triglyceride and C-peptide levels (lower for the insulin alone group) and total daily dose (higher in the insulin plus troglitazone group). However, the investigators closely adhered to the guidelines for insulin adjustment, and we do not believe that the baseline differences significantly influenced the outcome of the study or negate the interpretation of the data.

Over one-third of type 2 diabetic individuals in the U.S. are estimated to have an HbA_{1c} level >8.0%, including 51.5% of those who take insulin (49). This study demonstrates that near normal glycemic control can be achieved with insulin monotherapy or insulin in combination with insulin sensitizers. Although weight gain is undesirable, avoiding weight gain should not be pursued at the expense of improving glycemic control. The overwhelming evidence regarding the impact of improved glycemic control on lowering the risk for the development and progression of microvascular complications of diabetes mandates early and aggressive treatment of type 2 diabetes that results in blood glucose levels as close to normal as possible. Pharmacological advances in the management of diabetes, including insulin sensitizers, help make normoglycemia an eminently achievable goal.

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