Improved Glycemic Control Without Weight Gain Using Triple Therapy in Type 2 Diabetes

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OBJECTIVE — To evaluate the safety and effectiveness of triple therapy using insulin, metformin, and a thiazolidinedione following a course of dual therapy using insulin and metformin or insulin and a thiazolidinedione in type 2 diabetes.

RESEARCH DESIGN AND METHODS — Twenty-eight type 2 diabetic subjects using insulin monotherapy (baseline HbA_{1c} level 8.5%) who had been randomly assigned to insulin (INS) and metformin (MET) (INS + MET, $n = 14$) or INS and the thiazolidinedione troglitazone (TGZ) (INS + TGZ, $n = 14$) (dual therapy) for 4 months were given INS, MET, and TGZ (triple therapy: INS + MET, add TGZ; or INS + TGZ, add MET) for another 4 months. The INS dose was not increased.

RESULTS — HbA_{1c} levels decreased in both groups during dual therapy and improved further during triple therapy (INS + MET 7.0 ± 0.8, INS + TGZ 6.2 ± 0.8, $P < 0.0001$; INS + MET, add TGZ 6.1 ± 0.4%, $P < 0.001$; INS + TGZ, add MET 5.8 ± 0.6%, $P < 0.05$; and INS + TGZ vs. INS + MET, $P = 0.02$). Significant reductions in total daily insulin dose occurred in the INS + TGZ (−14.1 units, $P < 0.0001$), INS + TGZ add MET (−13.7 units, $P < 0.01$), and the INS + MET add TGZ groups (−17.3 units, $P < 0.003$), but not in the INS + MET group (−3.2 units) (INS + TGZ vs. INS + MET $P < 0.05$). Subjects in the INS + TGZ group experienced significant weight gain (4.4 ± 2.7 kg, $P < 0.0005$). No weight gain occurred in the INS + MET, INS + MET add TGZ, and INS + TGZ add MET groups.

CONCLUSIONS — Triple therapy using INS, MET, and TGZ resulted in lower HbA_{1c} levels and total daily insulin dose than during dual therapy. The use of triple therapy resulted in 100% of subjects achieving an HbA_{1c} <7.0%, while decreasing the dose of INS. Weight gain was avoided when MET therapy preceded the addition of TGZ therapy. The addition of TGZ resulted in the greatest reductions in HbA_{1c} levels and insulin dose. Triple therapy using INS, MET, and a thiazolidinedione (such as TGZ) can be a safe and effective treatment in type 2 diabetes.

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Research in the previous decade has conclusively demonstrated the benefit of improved blood glucose control in the prevention of diabetes complications (1,2). Efforts to advance our ability to achieve near normal glycemic control have resulted in an array of pharmaceutical interventions that not only lower blood glucose levels, but also have beneficial effects on comorbid conditions such as hypertension and hyperlipidemia. In the treatment of type 2 diabetes, health care providers have the option of using insulin (INS), sulfonylureas, thiazolidinediones, biguanides such as metformin (MET), and other oral agents to achieve treatment goals (3,4).

MET 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 (5,6). Thiazolidinediones, like troglitazone (TGZ), improve insulin sensitivity by enhancing insulin-mediated glucose disposal, resulting in reduced plasma insulin concentrations. Thiazolidinediones may also have modest effects on lowering hepatic glucose production (7–9). In addition, studies have shown that thiazolidinediones enhance β-cell responsiveness and may prolong β-cell survival (10,11). Several randomized, placebo-controlled studies have demonstrated the effectiveness of dual therapy using oral sulfonylureas or INS in combination with either MET or TGZ in lowering blood glucose levels in type 2 diabetic subjects (12–22). Studies of the combined use of MET plus a thiazolidinedione have also shown improved glycemic control when compared with MET alone (23–26). Thiazolidinediones added to treatment with sulfonylureas and MET resulted in significant improvements in HbA_{1c} levels compared with continued sulfonylurea and MET therapy (27,28). However, no single prospective study has investigated the safety and effectiveness of triple therapy using INS, MET, and a thiazolidinedione compared with the dual therapies of INS and MET or INS and a thiazolidinedione in subjects with type 2 diabetes.

RESEARCH DESIGN AND METHODS

— Eighty-eight INS-treated type 2 diabetic subjects had been participating in a 4-month study (weeks 0–16) that involved random assignment to INS alone ($n = 31$), INS + MET ($n = 27$), or INS + TGZ ($n = 30$) in an open-label fashion (29). Random assignment was determined by the sponsor, who provided sealed sequentially numbered envelopes that were concealed until the time of randomization. At the final study visit

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Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; INS, insulin; MET, metformin; TGZ, troglitazone.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

(week 16), the subjects who had been assigned to take dual therapy using INS + MET or INS + TGZ were invited to participate in a second 4-month study, during which subjects were given both MET and TGZ in combination with INS (weeks 16–32). Fourteen subjects in each of the two groups assigned to dual therapy agreed to continue the second 4-month study using triple therapy (INS+ MET adding TGZ, INS + TGZ adding MET). Before entry into the initial phase of the study, subjects had to meet the following criteria: 24–70 years of age (1), taking ≥30 units of INS per day (2), having an HbA_{1c} level ≥7.0% (3), and normal renal and hepatic function (4). Subjects were seen in the Diabetes Research Clinic at the University of Texas Southwestern Medical Center between February 1998 and March 2000.

During weeks 16–32, when the third medication was added to the subjects' treatment, subjects were seen at the same frequency they had been seen during weeks 0–16, i.e., biweekly for 1 month and monthly for the subsequent 3 months. 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 both 4-month study periods (weeks 0, 16, and 32). Measures of body weight, HbA_{1c}, fasting plasma glucose, and liver enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) were obtained monthly. Glycemic control based on at least two daily home plasma glucose measurements and tolerance of 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 both study periods after approval by the university institutional review board.

The primary end point was HbA_{1c} level. Secondary end points included weight, INS dose, and frequency of adverse events. We hypothesized that triple therapy would further improve HbA_{1c} levels over dual therapy.

Intervention

From weeks 16–32, subjects continued taking the dose of MET (1,000 mg twice daily) or TGZ (600 mg daily) they were taking at week 16 at the conclusion of the first 4-month study. The dose of MET or TGZ that the patient was taking at week 16 was not changed during weeks 16–32.

Subjects who were taking INS and TGZ at week 16 added MET as follows: one 500-mg tablet with breakfast and supper for weeks 16–18, two 500-mg tablets with breakfast and one 500-mg tablet with supper for weeks 18–20, and two 500-mg tablets with breakfast and supper for weeks 20–32. Subjects who were taking INS and MET at week 16 added TGZ as follows: one 200-mg tablet with breakfast for weeks 16–18, one 400-mg tablet with breakfast for weeks 18–20, and three 200-mg tablets with breakfast for weeks 20–32.

Subjects were advised to check plasma glucose levels twice daily. Plasma glucose data were downloaded from the patient's glucose meter to the computer; all patients used a meter that stored the plasma glucose readings as well as the date and time the readings were obtained. The baseline dose of INS and frequency of injections were not increased in subjects assigned to take MET or TGZ in combination with INS during weeks 0–16, neither was it increased during triple therapy (weeks 16–32). A 10–20% decrease in the dosage of INS was permitted only if patients experienced frequent hypoglycemia or if the patient's self-obtained plasma glucose levels were consistently <100 mg/dl. The dose of MET or TGZ was not modified in response to 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 assessed as absent or present based on physical examination or if the patient complained of swelling.

Analytical determinations

HbA_{1c} levels were measured by using high-pressure liquid chromatography (upper limit for nondiabetic individuals in this assay is 5.6%). 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 between the two groups. Outcome variables were checked for normality across groups, and log transformations were used for total daily INS dose, ALT, AST, C-peptide, HDL cholesterol, triglyceride, and VLDL triglyceride levels. A one-factor–between (group) and one-factor–within (time) ANOVA was performed. The time variable consisted of the variable of interest at baseline, week 16, and week 32. If the interaction term of group by time was statistically significant, contrasts were obtained (30). Fisher's exact test was used to analyze categorical variables.

Difference variables that were normally distributed were analyzed using a one-factor–between (group), one-factor–within (difference) ANOVA. If the interaction term of group by difference was statistically significant, contrasts were obtained. Variables that did not meet the normality requirement were analyzed by the Kruskal-Wallis.

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 means ± SD, unless otherwise indicated.

RESULTS — During weeks 0–16, 27 subjects took INS plus MET and 30 subjects took INS plus TGZ. Seven of the 57 subjects could not participate in the triple-therapy phase (weeks 16–32) of the project because TGZ was withdrawn from the market. Of the remaining 50 subjects, 14 from each group agreed to participate in the second 4-month phase of the study. All 28 subjects tolerated the maximum dose of both oral agents.

At baseline on INS alone, the two groups of 14 subjects who continued on to triple therapy were comparable in age, sex, ethnicity, C-peptide, weight, BMI, waist-to-hip ratio, INS dose, and duration of INS therapy. C-peptide levels did not

Table 1—*Baseline characteristics (week 0) of the study population*

	INS + MET, add TGZ	INS + TGZ, add MET
n	14	14
Age (years)	52.3 ± 10.5	54.7 ± 5.9
Sex (M/F)	9/5	6/8
Ethnic group		
Caucasian	8	9
African American	3	3
Hispanic	2	2
Other	1	0
Duration of diabetes (years)	7.0 ± 4.0	13.0 ± 7.8*
Duration of INS therapy (years)	2.7 ± 2.2	6.4 ± 4.8
Fasting C-peptide (ng/ml)	3.1 ± 1.7	2.2 ± 1.0
Waist-to-hip ratio	0.96 ± 0.08	0.93 ± 0.09

Data are means ± SD. *$P < 0.03$ vs. INS + MET group

change during the course of the study. The INS + TGZ group had a longer duration of diabetes ($P = 0.03$) (Tables 1 and 2). The 28 subjects who agreed to continue study participation during weeks 16–32 did not differ on any parameters at baseline or week 16 from the 22 eligible subjects who concluded study participation at week 16 (mean values of subjects who continued to triple therapy versus those who did not: HbA_{1c} 6.6 vs. 6.8%, fasting plasma glucose 138 vs. 134 mg/dl, BMI 38 vs. 38 kg/m^2, total daily INS dose 85 vs. 92 units, and total incidence of mild hypoglycemia 6 vs. 4 episodes).

Glycemic control

Glycemic control improved in both groups after 4 months of dual therapy ($P < 0.0001$) and further improved after 4 months of triple therapy ($P < 0.001$ for INS + MET add TGZ; $P < 0.05$ for INS + TGZ add MET). HbA_{1c} levels differed between the groups at week 16 after 4 months of dual therapy (INS + MET 7.0 ± 0.8%, INS + TGZ 6.2 ± 0.8%; $P = 0.02$, for INS + MET vs. INS + TGZ). Fewer subjects in the INS + TGZ group had HbA_{1c} levels >7.0% (INS + TGZ, $n = 2$; INS + MET, $n = 5$) and more achieved HbA_{1c} levels ≤6.0% (INS + TGZ, $n = 7$; INS + MET, $n = 2$) after the first 4 months of the study ($P = 0.057$). However, HbA_{1c} levels were similar between both groups after 4 months (week 32) of triple therapy (INS + MET add TGZ 6.1 ± 0.4%; INS + TGZ add MET 5.8 ± 0.6%). None of the subjects had an HbA_{1c} level >7.0% after 4 months of triple therapy, and 57.1% of all of the subjects had an HbA_{1c} level ≤6.0% after 4 months of triple therapy.

Mean fasting plasma glucose concentrations significantly decreased in both groups at the end of dual therapy (week 16 vs. 0, $P < 0.0001$ for INS + TGZ and $P < 0.02$ for INS + MET). Modest but not significant improvements occurred in fasting plasma glucose levels after 4 months of triple therapy (Table 2). Neither the change in fasting plasma glucose nor the absolute fasting plasma glucose concentrations at weeks 16 and 32 differed between the groups.

Daily insulin requirements

At baseline, all but two subjects in the INS + MET group and all but five subjects in the INS + TGZ group took fixed doses of twice-daily injections of either 70/30 INS or NPH and regular INS. Subjects on multiple injections took three to four daily injections of short- or rapid-acting INS and one to two daily injections of intermediate-acting INS.

At week 16, the INS + MET group experienced a modest decrease in the total daily INS dose of 3.2 units (range 0 to −14). This was followed by a further decrease of 17.3 units (range 0 to −104) at week 32 after the addition of TGZ, resulting in a significantly lower total daily INS dose at week 32 compared with week 16 (INS + MET 68.4 ± 47.1 for week 16 vs. INS + MET add TGZ 51.1 ± 24.9 for week 32; $P < 0.003$).

The INS + TGZ group experienced a

Table 2—*Clinical parameters on INS alone, after 4 months of combination therapy (INS + MET or INS + TGZ), followed by 4 months of triple therapy*

	INS + MET, add TGZ			INS + TGZ, add MET		
	INS	INS + MET (week 16)	INS + MET add TGZ (week 32)	INS	INS + TGZ (week 16)	INS + TGZ add MET (week 32)
Weight (kg)	112.6 ± 26.4	112.4 ± 25.2	112.2 ± 23.2	100.3 ± 13.8	104.7 ± 12.8*	104.0 ± 12.9
BMI (kg/m^2)	38.5 ± 7.8	38.4 ± 7.3	38.4 ± 6.9	36.4 ± 5.7	38.0 ± 5.5*	37.7 ± 5.3
Insulin dose (units/day)	71.6 ± 49.7	68.4 ± 47.1	51.1 ± 24.9†§	98.3 ± 36.7	84.2 ± 28.0*	70.5 ± 22.3†
FPG (mg/dl)#	183.1 ± 54.6	138.8 ± 38.7*	121.1 ± 22.6	187.1 ± 38.5	137.0 ± 41.5*	126.4 ± 22.9
HbA_{1c} (%)	8.5 ± 1.3	7.0 ± 0.8*	6.1 ± 0.4†	8.4 ± 1.0	6.2 ± 0.8*‡	5.8 ± 0.6†
Total cholesterol (mg/dl)¶	177.2 ± 35.7	175.4 ± 35.1	186.6 ± 40.0	187.6 ± 47.8	212.9 ± 45.0	212.3 ± 52.3
HDL cholesterol (mg/dl)	30.2 ± 4.3	31.3 ± 7.7	35.0 ± 8.1	30.1 ± 10.6	35.1 ± 9.1	35.7 ± 6.7*
LDL cholesterol (mg/dl)	103.0 ± 38.4	103.0 ± 34.7	110.9 ± 36.8	103.4 ± 29.2	128.7 ± 26.8*‡	125.3 ± 35.4
Triglycerides (mg/dl)	205.7 ± 149.2	200.0 ± 133.9	160.3 ± 89.1	206.7 ± 141.6	165.3 ± 65.5	178.0 ± 135.9
VLDL triglycerides (mg/dl)	150.1 ± 136.2	162.8 ± 137.3	119.8 ± 87.4	164.7 ± 141.9	133.5 ± 69.3	142.1 ± 137.9

Data are means ± SD. *$P < 0.05$ vs. baseline; †$P < 0.05$ vs. week 16; ‡$P < 0.05$ vs. INS + MET; §$P < 0.05$ vs. INS + MET, add TGZ; #conversion factor for SI units in mmol/l is 0.0555; ¶$n = 13$ for lipid parameters for INS + MET; $n = 12$ for INS + TGZ.

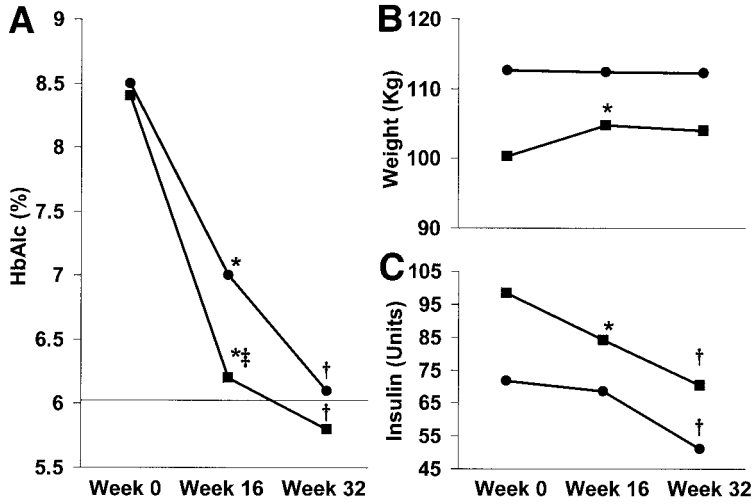

Figure 1—*Change in mean HbA_{1c} level (A), weight (B), and total daily INS dose (C) in INS-treated type 2 diabetic patients after 4 months of dual therapy using INS + MET (●) or INS + TGZ (■) and after 4 months of triple therapy using INS, MET, and TGZ [INS + MET add TGZ (●), INS + TGZ add MET (■)]. *P < 0.05 vs. baseline, †P < 0.05 vs. week 16, ‡P < 0.05 vs. INS + MET group.*

greater decrease in INS dose (−14.1 units; range 0 to −100) between weeks 0 and 16 than the INS + MET group ($P <$ 0.05 vs. INS + MET), leading to a significant difference in total daily dose in the INS + TGZ group at week 16 vs. baseline (INS + TGZ 98.3 ± 36.7 for week 0 vs. 84.2 ± 28.0 for week 16, $P < 0.0001$). This was followed by a further decrease in INS dose at week 32 after the addition of MET, so that the total daily INS dose at week 32 (INS + TGZ add MET 70.5 ± 22.3) was lower than that at week 16 ($P <$ 0.01). The average change in INS from week 16 to 32 was similar in both groups (INS + TGZ add MET −13.7 units, range 0 to −33).

Body weight and daily caloric intake

Subjects randomized to the INS + TGZ group gained an average of 4.4 ± 2.7 kg of body weight after 4 months of dual treatment ($P = 0.0005$ vs. baseline). No further increase in weight occurred during triple therapy when MET was added. Subjects in the INS + MET group did not experience a change in weight during 4 months of dual therapy (−0.2 ± 3.9 kg, $P < 0.002$ vs. INS + TGZ), neither did they gain weight when TGZ was added during weeks 16–32 (Table 2, Fig. 1). There was no change in waist-to-hip ratio in any of the treatment groups.

Based on the 3-day food records obtained at weeks 0 and 16 and at the end of the study, subjects reported comparable decreases in their total daily caloric intake during the first 4 months of the study (INS + MET −223.5 ± 420.7, INS + TGZ −347.0 ± 666.7). Only modest changes in dietary intake were reported during triple therapy in both groups (INS + MET plus TGZ 13.9 ± 757.3; INS + TGZ add MET −36.5 ± 556.1).

Lipid and lipoprotein levels

There were no significant changes in total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride, or VLDL triglyceride levels in the INS + MET group for weeks 0–16 or for weeks 16–32 after the addition of TGZ. However, there was a trend toward increased total cholesterol, LDL cholesterol, and HDL cholesterol levels as well as decreased triglyceride levels with the addition of TGZ therapy (Table 2). The INS + TGZ group experienced an increase in total cholesterol level ($P =$ 0.053) and LDL cholesterol level ($P <$ 0.05) at the end of the 4 months of INS TGZ therapy, resulting in significantly different total and LDL cholesterol levels from the INS + MET group at week 16 ($P < 0.05$ for INS + MET vs. INS + TGZ). No further change in total and LDL cholesterol levels occurred during weeks 16–32 when MET was added to INS and TGZ therapy. The HDL cholesterol level in the INS + TGZ add MET group was significantly higher at week 32 than at baseline ($P < 0.05$).

Adverse events

MET therapy was associated with more episodes of gastrointestinal side effects, although none were serious enough to result in dose reductions or withdrawal of therapy (INS + MET, $n = 8$; INS + TGZ, $n = 4$; INS + MET add TGZ, $n = 4$; INS + TGZ add MET, $n = 12$; $P = 0.01$ for INS + TGZ add MET vs. INS + MET add TGZ). The incidence of edema was low (three cases during weeks 0–16 in both groups and two vs. four cases in the INS + TGZ add MET and INS + MET add TGZ groups, respectively, during weeks 16–32), and there were no differences between the groups. All of the reported cases were mild, some transient, and only three subjects required treatment for edema with low-dose diuretic medication.

None of the subjects experienced an episode of severe hypoglycemia. Mild hypoglycemia (self-treated blood glucose levels <65 mg/dl) occurred ~3.7 times more often in subjects who were assigned to INS + TGZ during the first 4 months of the study (INS + TGZ, 2.3 episodes per patient per month; INS + MET, 0.6 episodes per patient per month; $P < 0.002$ for INS + TGZ vs. INS + MET). This trend persisted, however, into the second 4 months of the study, so that the INS + TGZ add MET group continued to experience significantly more hypoglycemia than the INS + MET add TGZ group (INS + TGZ add MET 3.7 episodes per patient per month and INS + MET add TGZ 1.0 episode per patient per month; $P < 0.01$). Fewer than 25% of low blood glucose readings in both groups were <50 mg/dl.

None of the subjects taking INS + TGZ experienced any abnormality in liver function tests. In fact, ALT (−7.9 ± 8.7, $P < 0.001$ for week 0 vs. 16) and AST levels (−3.3 ± 4.3, $P < 0.02$ for week 0 vs. 16) decreased in the INS + TGZ group, as well as in the INS + MET group when TGZ was added (ALT −7.9 ± 12.7, $P < 0.04$ for week 16 vs. 32; AST −4.1 ± 7.6).

CONCLUSIONS — Dual therapy using MET or TGZ in combination with INS resulted in significant improvements in glycemic control. Triple therapy using INS, MET, and TGZ led to even further improvements in glycemic control. While decreasing the dose of INS, all 28 subjects achieved an HbA_{1c} level <7.0% after 4 months of triple therapy, and >57% of

subjects achieved an HbA_{1c} level ≤6.0%. In comparison, 25% of all of the subjects had HbA_{1c} levels >7.0%, and ~33% of subjects had HbA_{1c} levels ≤6.0% after 4 months of dual therapy. Although all of the treatments were effective in improving blood glucose control, there were differences between MET and TGZ when used in combination with INS as dual therapy. In addition, the order in which the INS sensitizers were added to achieve triple therapy resulted in different outcomes.

Insulin in combination with TGZ resulted in a significantly lower HbA_{1c} level (INS + TGZ vs. INS + MET, 6.2 vs. 7.0%), greater reduction in INS dose (−14.1 vs. −3.2 units), more frequent hypoglycemia (2.3 vs. 0.6 episodes/patient/month), and greater weight gain (4.4 vs. −0.2 kg) after 4 months of dual therapy compared with INS + MET. Adding MET to TGZ and INS resulted in a significantly greater reduction in INS dosage than that which occurred when MET was added to INS during the first 4 months of the study. The administration of TGZ during dual therapy as well as triple therapy, irrespective of the order in which it was used, resulted in a trend toward decreased triglyceride levels and increased LDL and HDL cholesterol levels, consistent with previous reports (14,19,21,31,32).

When TGZ was added to INS + MET therapy (triple therapy), the HbA_{1c} level improved to the level that had been achieved with INS + TGZ therapy (dual therapy), and the reduction in the total daily dose approached that achieved with INS + TGZ treatment, suggesting that TGZ is a more effective INS sensitizer. This is consistent with the findings by Yu et al. (18), who demonstrated a 29% improvement in INS sensitivity in subjects on continuous subcutaneous insulin infusion pump therapy and TGZ compared with no significant improvement in subjects on continuous subcutaneous insulin infusion pump therapy and MET. Yu et al. further showed that INS requirements decreased by 53% in subjects taking TGZ compared with 31% in subjects taking MET ($P < 0.005$).

The advantage of MET over INS, sulfonylureas, and thiazolidinediones is the absence of weight gain despite improvements in glycemic control, although investigators have shown that weight gain can be avoided with thiazolidinediones when aggressive lifestyle interventions are implemented (33). Of interest is that subjects in this study did not gain weight when TGZ was added to dual treatment with INS + MET, even though the HbA_{1c} level improved from 7.0 to 6.1%. This was in stark contrast to the 4.4-kg weight gain that subjects taking INS + TGZ experienced during the first 4 months of this study. In addition, subjects who had been taking TGZ and INS experienced no further weight gain when MET was added, despite further improvement in HbA_{1c} levels.

These findings might be explained by the fact that MET has anorexic properties and is associated with an increase in gastrointestinal side effects. Our subjects reported an increase in the incidence of gastrointestinal side effects when MET was added to their treatment, although their complaints were not serious enough to warrant a reduction in the dose of MET. The food records do not support the notion that subjects taking MET experienced a greater loss of appetite compared with subjects taking TGZ since comparable reductions in caloric intake were reported by both groups. The large standard deviation in reported caloric intake, however, makes it difficult to ascertain the importance of this finding. Other studies in which MET was combined with a thiazolidinedione also resulted in negligible, if any, amounts of weight gain despite improved glycemic control (24,25).

Fluid retention and edema (3,4) have been associated with TGZ therapy and have been proposed as possible reasons for weight gain in patients who take TGZ. The incidence of edema in this group was low, however, and did not differ between groups. Furthermore, the group in which TGZ was added to INS + MET therapy did not gain weight.

The group taking INS and TGZ during the first 4 months of the study experienced significantly more hypoglycemia (recorded plasma glucose readings <65 mg/dl) than the group taking INS and MET, consistent with previous reports regarding the relative absence of hypoglycemia associated with MET therapy. However, the addition of MET to INS + TGZ in this study did not result in any reduction in the incidence of hypoglycemia, whereas subjects taking INS and MET who added TGZ to their treatment experienced only a modest increase in the incidence of hypoglycemia.

An intriguing explanation for these findings may be related to different effects of MET and TGZ on endogenous glucose production and glucose disposal. Inzucchi et al. (25) studied 29 subjects who were randomly assigned to receive MET or TGZ for 3 months as monotherapy, followed by 3 months of both MET and TGZ. They showed that endogenous glucose production decreased by 19% in subjects using MET, whereas there was no significant change in those taking TGZ. On the other hand, the mean glucose disposal rate increased in the TGZ group by 54%, in contrast to an increase of 13% in the MET group. These findings were expected and consistent with the known action of these agents. Of greater interest is the finding that no further decrease in endogenous glucose production was observed when MET was added to TGZ therapy or when TGZ was added to MET therapy. However, the rate of glucose disposal increased not only when TGZ was added to MET therapy, but also when MET was added to TGZ therapy, resulting in an overall mean increase in the glucose disposal rate of 40% in subjects who received MET first and 77% in subjects who received TGZ first (25).

TGZ 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 INS sensitivity (34,35) and, when used in combination with INS, improve glycemic control (36,37) to levels that are similar to those achieved with TGZ and INS. When pioglitazone or rosiglitazone replaced TGZ as monotherapy, no change in HbA_{1c} levels was observed (38).

Poulsen et al. (39) randomized 16 type 2 diabetic subjects taking twice-daily INS to either continue their baseline INS dose or to take triple therapy using MET, rosiglitazone, and premeal rapid-acting INS. Without changing the total daily INS dose, subjects using triple therapy experienced a 2% reduction in HbA_{1c} level and a significant gain in weight of 3–4 kg (39). This compares with the ~2.5% improvement in HbA_{1c} level experienced by our subjects after 4 months of dual therapy followed by 4 months of triple therapy. Poulsen's triple-therapy subjects, however, altered their INS regimen while adding MET and rosiglitazone, making it difficult to ascertain how much of the improvement in glycemic control was related to a different INS regimen or to the

addition of INS sensitizers. The weight gain experienced by Poulsen's subjects was comparable with that experienced by our subjects after 4 months of INS + TGZ therapy but in contradiction to the lack of weight gain in our subjects after 4 months of triple therapy. This may suggest that adding a thiazolidinedione after several months of treatment with INS + MET rather than initiating INS, MET, and thiazolidinedione therapy simultaneously may be advantageous in avoiding weight gain. These results need to be confirmed with additional studies of longer duration.

Subjects in this study were unmasked to treatment, introducing the possibility for bias, although the investigators closely adhered to the protocol for INS adjustment. The INS regimen was not changed, and the dose of INS was not increased, allowing for an assessment of the effect of the INS sensitizers in this relatively small sample of type 2 diabetic subjects.

This study demonstrates that triple therapy using INS, MET, and a thiazolidinedione can be a safe and effective treatment approach to achieving near normal glycemic control in type 2 diabetes. Furthermore, triple therapy can improve glycemic control with relative ease; we did not need to intensify INS regimens to accomplish mean HbA_{1c} levels at or below 6.2%. The increased economic cost of INS in combination with two INS sensitizers, however, may be prohibitive for some patients.

These results suggest that weight gain and possibly hypoglycemia can be minimized if INS and MET are administered before the addition of a thiazolidinedione compound if further improvement in glycemic control is desired. Larger reductions in INS dosage are also likely when both classes of INS sensitizers are added to INS therapy. However, the addition of TGZ resulted in the greatest reduction in HbA_{1c} level and INS dosage, with the largest reduction occurring when TGZ was used first with MET added later. Other thiazolidinedione compounds may yield similar results. Although there were no abnormalities in liver function tests and the incidence of edema was low and mild in nature, these remain potentially serious side effects of thiazolidinedione compounds and should be closely monitored. With more than one-third of type 2 diabetic individuals in the U.S. having HbA_{1c} levels >8.0% (40), triple therapy using INS and both classes of INS sensitizers provide a pharmacologic alternative in the pursuit of improved glycemic control.

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