

# Thalidomide Impairs Insulin Action on Glucose Uptake and Glycogen Synthesis in Patients With Type 2 Diabetes

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RESEARCH DESIGN AND  
METHODS

**OBJECTIVE** — To investigate the effect of thalidomide on glucose turnover (glucose production and uptake), on intracellular pathways of glucose utilization (glycogen synthesis [GS], glycolysis [GLS], carbohydrate oxidation, and nonoxidative GLS), and on free fatty acid (FFA) turnover (lipolysis, FFA oxidation, and FFA reesterification).

**RESEARCH DESIGN AND METHODS** — A total of 6 patients with type 2 diabetes were studied with 4-h isoglycemic-hyperinsulinemic clamps (~8 mmol/l and 500–600 pmol/l, respectively) before treatment (Prestudy), after 3 weeks of thalidomide (150 mg orally at bedtime), and after 3 weeks of placebo.

**RESULTS** — Thalidomide reduced insulin-stimulated glucose uptake by 31% (from 27.7 to 19.2  $\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ,  $P < 0.05$ ) compared with the prestudy and by 21% (from 24.2 to 19.2  $\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ,  $P < 0.05$ ) compared with placebo. Thalidomide also reduced insulin-stimulated GS by 48% (from 14.1 to 8.2  $\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ,  $P < 0.05$ ) compared with the prestudy and by 40% (from 13.6 to 8.2  $\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ,  $P < 0.5$ ) compared with placebo. Thalidomide had no effect on rates of GLS, carbohydrate oxidation, nonoxidative GLS, lipolysis, FFA oxidation, and reesterification.

**CONCLUSIONS** — We conclude that thalidomide increased insulin resistance in obese patients with type 2 diabetes by inhibiting insulin-stimulated GS and that patients taking thalidomide should be monitored for possible deterioration in their glucose tolerance.

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Thalidomide, a teratogenic sedative, is currently approved in the U.S. for the treatment of cutaneous manifestations of erythema nodosum leprosum. In addition, the drug has recently shown great promise in the treatment of advanced refractory multiple myeloma (1). Thalidomide has been reported to inhibit tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) production (2,3). This is of interest because TNF- $\alpha$  has been shown to cause insulin resistance and has been proposed to play an important

role in the generation of insulin resistance in obesity and type 2 diabetes (4–9). This suggests the possibility that thalidomide may have beneficial effects on carbohydrate metabolism by increasing insulin sensitivity. To our knowledge, the effect of thalidomide on insulin action has not been examined. The objective of this study was to investigate whether thalidomide, by inhibiting TNF- $\alpha$  production, can improve insulin resistance in obese type 2 diabetic patients.

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**Abbreviations:** EGP, endogenous glucose production; FFA, free fatty acid; GCRC, General Clinical Research Center; GLS, glycolysis; GS, glycogen synthesis; HIV, human immunodeficiency virus; Prestudy, study before thalidomide or placebo treatment; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ .

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

## Subjects

Some characteristics of the 6 patients with type 2 diabetes who were studied 3 times are shown in Table 1. All patients had been treated with oral hypoglycemic agents (sulfonylureas, biguanides, or both), and 1 patient received an additional 10 U of NPH insulin at bedtime. These medications were withheld for 24 h before the studies. The patients' body weights were stable for at least 2 months, and their diets contained a minimum of 250 g/day of carbohydrates for at least 2 days before the studies. Informed written consent was obtained from all subjects after explanation of the nature, purpose, and potential risks of the study. The study protocol was approved by the institutional review board at Temple University Hospital.

## Experimental design

The 6 patients were studied with a single-blind placebo-controlled crossover design. Isoglycemic-hyperinsulinemic clamps (to quantitate insulin action) were performed in the General Clinical Research Center (GCRC) on 3 occasions. The first clamp was performed before thalidomide or placebo treatment (Prestudy). After the Prestudy, the patients were given a 3-week supply of thalidomide or placebo (the sequence of thalidomide and placebo treatment was randomized) and were instructed to take three 50-mg capsules orally every night in addition to their usual antidiabetic medications and to perform glucose monitoring 4 times a day every other day. Three weeks later, the patients were admitted to the GCRC for a second isoglycemic-hyperinsulinemic clamp study and after that were switched to the other test substance (i.e., switched to thalidomide if they started with placebo or to placebo if they started with thalidomide). After another 3 weeks, the subjects were admitted for the third time for a final isoglycemic-hyperinsulinemic clamp study.

**Table 1—Study subjects**

Sex (M/F)	3/3
Age (years)	50 ± 5
Height (cm)	166 ± 2.5
Weight (kg)	100.7 ± 7.9
Lean body mass (kg)	60.7 ± 5.2
Fat (kg)	40.0 ± 3.8
BMI (kg/m <sup>2</sup> )	35.4 ± 2.5
Fasting plasma glucose (mg/dl)	146 ± 27
Duration of disease (years)	6.5 ± 2.4 (range 1–15)

Data are *n* or means ± SEM.

## Procedures

### Isoglycemic-hyperinsulinemic clamps.

Patients were admitted to the Temple University Hospital GCRC on the day before the study. On the morning of the study after an overnight fast, a short polyethylene catheter was inserted into an antecubital vein for infusion of insulin and glucose. A second catheter was placed into the contralateral forearm vein for blood sampling. This arm was wrapped with a heating blanket (~70°C) to arterialize venous blood.

**Regular human insulin.** HumulinR (Eli Lilly) was infused intravenously at a rate of 7 pmol/kg min for 5.5 h starting at -90 min. Glucose concentrations were clamped at the patient's fasting glucose concentration (isoglycemic clamp) by a feedback-controlled glucose infusion with 20% glucose.

**Glucose turnover.** Glucose turnover was determined with 3-[<sup>3</sup>H]glucose. The tracer infusion (40 μCi for 1 min followed by 0.4

μCi/min) was started 90 min before the measurements to ensure isotope equilibration. Glucose was isolated from blood for determination of 3-[<sup>3</sup>H]glucose specific activity as described previously (10). Changes in specific activity during hyperinsulinemia were avoided by adding 3-[<sup>3</sup>H]glucose to the unlabeled glucose that was infused at variable rates to maintain hyperglycemia (11). Rates of whole-body glucose production and uptake were calculated using Steele's equation for steady-state conditions (12).

**Glycolytic flux.** Glycolytic flux was determined according to Rossetti et al. (13). Tritium in the 3-carbon position of glucose is lost in water during glycolysis (GLS), and the rate of tritiated water formation in human plasma reflects the intracellular detritiation of 3-[<sup>3</sup>H]glucose and the rate of GLS (13). The rate of GLS was obtained by dividing the whole-body <sup>3</sup>H<sub>2</sub>O production rate by the specific activity of its precursor (i.e., plasma 3-[<sup>3</sup>H]glucose) (13).

**Glycogen synthesis.** Whole-body glycogen synthesis (GS) rates were obtained by subtracting rates of GLS from rates of glucose uptake.

**Lipid turnover.** Rates of lipolysis were determined by measuring glycerol turnover (lipolysis = glycerol rate of appearance × 3). Glycerol turnover was determined with [<sup>2</sup>H<sub>5</sub>]glycerol by gas chromatography-mass spectrometry as described previously (14). Free fatty acid (FFA) reesterification was calculated as follows: lipolysis - FFA oxidation = FFA reesterification. Fat oxidation was obtained by indirect calorimetry.

**Indirect calorimetry.** Indirect calorimetry was determined at 30-min intervals with a

metabolic measurement cart (Beckman, Palo Alto, CA) as described (15,16).

**Body composition.** Body composition was determined by bioelectrical impedance analysis (17) and by determination of skinfold thickness.

**Biochemical analyses.** Plasma levels of TNF-α were determined using a commercially available kit (BioSource International, Camarillo, CA), and sensitivity was 0.1 pg/ml. Plasma glucose, FFA, triglycerides, ketone bodies, insulin, C-peptide, and urinary nitrogen were determined as described (18).

## Statistical analysis

Data are means ± SEM. Analysis of variance with repeated measures was used to determine differences in measurements across all time points. Comparisons between baseline and study intervals were performed using the paired *t* test or Wilcoxon's signed-rank test as appropriate.

## RESULTS

### Substrate and hormone levels

No statistically significant differences were evident among the Pre, the thalidomide, and the placebo study plasma levels of FFA, ketone bodies, glycerol, lactate, triglyceride, alanine, glutamic acid, glutamine, insulin, C-peptide, and glucagon before and after hyperinsulinemia (Table 2).

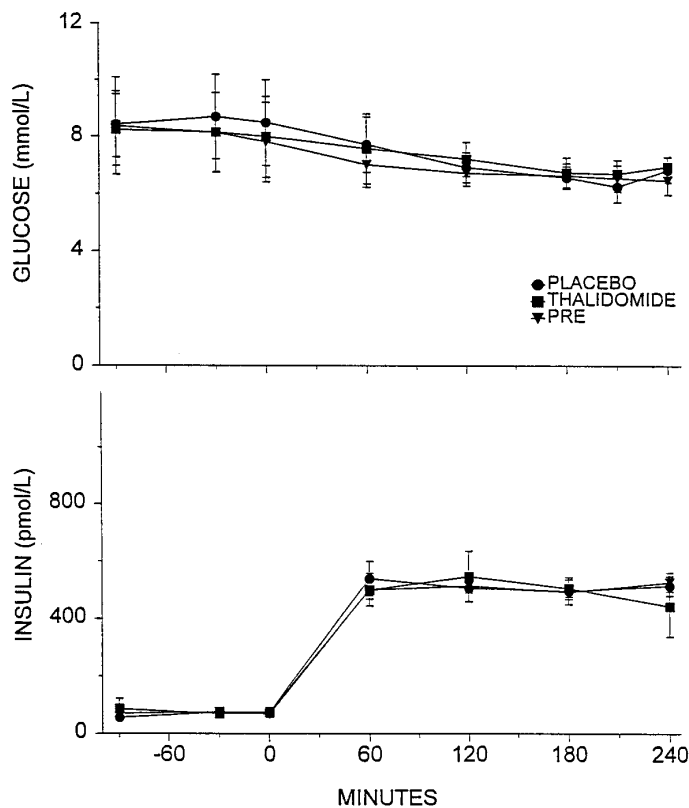
### Glucose and insulin clamp levels

Plasma glucose concentrations were similar in all 3 tests before (basal) and throughout the clamps (Fig. 1). Serum insulin levels rose similarly during insulin infusions in

**Table 2—Substrates and hormones**

	Prestudy		Thalidomide study		Placebo study	
	0 min	240 min	0 min	240 min	0 min	240 min
<b>Substrates</b>						
FFA (μmol/l)	622 ± 41	52 ± 13	651 ± 82	94 ± 25	669 ± 78	68 ± 18
Ketone bodies (μmol/l)	134 ± 30	60 ± 16	256 ± 54	82 ± 26	217 ± 31	90 ± 29
Glycerol (μmol/l)	91 ± 1	42 ± 3	98 ± 9	47 ± 4	93 ± 13	39 ± 5
Lactate (μmol/l)	917 ± 147	885 ± 127	1,085 ± 190	960 ± 104	1,051 ± 126	951 ± 66
Triglycerides (μmol/l)	225 ± 37	191 ± 45	208 ± 60	165 ± 45	178 ± 49	181 ± 44
Alanine (μmol/l)	390 ± 50	315 ± 28	431 ± 98	361 ± 87	358 ± 21	292 ± 8
Glutamine (μmol/l)	425 ± 39	356 ± 26	440 ± 44	344 ± 22	436 ± 17	382 ± 28
<b>Hormones</b>						
Insulin (pmol/l)	68 ± 14	581 ± 59	74 ± 19	545 ± 133	74 ± 8	608 ± 97
C-peptide (ng/ml)	2.25 ± 0.34	1.57 ± 0.22	2.77 ± 0.52	2.06 ± 0.41	2.98 ± 0.47	1.86 ± 0.39
Glucagon (pg/ml)	68 ± 9	42 ± 7	80 ± 9	55 ± 8	85 ± 11	53 ± 5

Data are means ± SEM.



**Figure 1**—Isoglycemic-hyperinsulinemic clamps (the blood glucose was clamped at the patient's basal glucose concentration) in 6 patients with type 2 diabetes (3 men and 3 women) before (PRE) and after 3 weeks of thalidomide or placebo treatment. Data are means  $\pm$  SEM.

the 3 tests from  $68 \pm 14$  to  $581 \pm 59$  pmol/l (Prestudy), from  $74 \pm 19$  to  $545 \pm 133$  pmol/l (thalidomide study), and from  $74 \pm 8$  to  $608 \pm 97$  pmol/l (placebo study).

**Glucose uptake, GS, and GLS**

Basal rates of glucose uptake, GS, and GLS were not different when comparing the Pre, thalidomide, and placebo studies (Fig. 2).

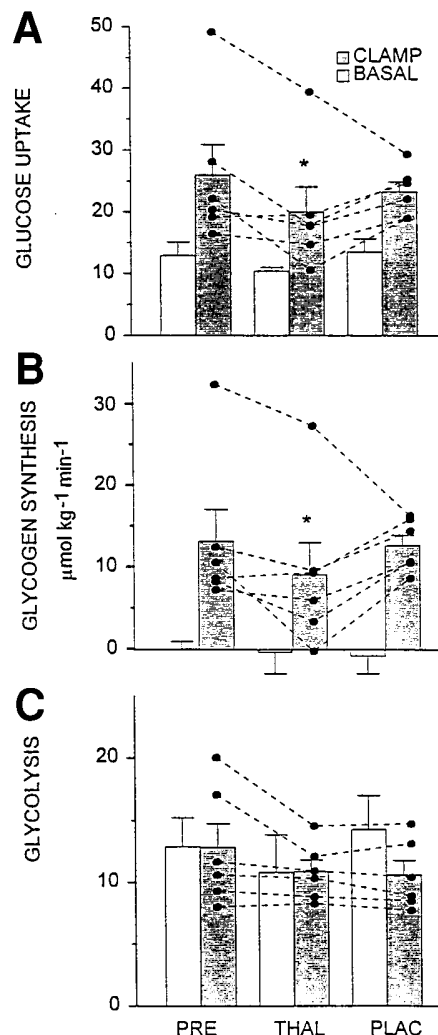
During the last hour of hyperinsulinemic clamping, insulin-stimulated glucose uptake, GS, and GLS were similar between the prestudy and placebo studies. In contrast, in the thalidomide study, rates of glucose uptake ( $19.2 \pm 3.7 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) were significantly lower compared with the prestudy ( $27.7 \pm 4.8 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) and placebo ( $24.2 \pm 1.7 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) studies ( $P < 0.05$ ).

Similarly, in the thalidomide study, rates of GS ( $8.2 \pm 3.8 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) were significantly lower compared with the prestudy ( $14.1 \pm 3.6 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) and placebo ( $13.6 \pm 1.6 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) studies ( $P < 0.05$ ).

The thalidomide-associated decrease in glucose uptake occurred in all 6 patients, whereas the decrease in GS was evident in 5 of 6 patients. In 1 patient, however, glucose uptake and GS decreased not only during the thalidomide study but also during the placebo study (i.e., this patient's insulin sensitivity decreased for unexplained reasons even without thalidomide treatment). The same patient also had the highest glucose uptake. This could be explained by the fact that glucose was clamped at a higher level ( $\sim 8.6$  mmol/l) in that patient than in the other patients. No significant differences were evident in rates of GLS during all 3 experimental periods.

**Carbohydrate oxidation and nonoxidative GLS (lactate/alanine production)**

Thalidomide also had no significant effects on rates of carbohydrate oxidation, which increased in response to insulin (Table 3). It also did not have significant effects on rates of lactate/alanine production (nonoxidative GLS), which decreased in response to insulin.



**Figure 2**—Rates of glucose uptake (A), GS (B), and GLS (C), all determined with  $3\text{-}^3\text{H}$ glucose, in 6 patients with type 2 diabetes after an overnight fast (BASAL) and after 4 h of hyperinsulinemic-isoglycemic clamp studies (CLAMP) before (PRE) and after 3 weeks of treatment with thalidomide (THAL) or placebo (PLAC). \* $P < 0.05$ , thalidomide study vs. prestudy or placebo studies.

**Endogenous glucose production**

Suppression of endogenous glucose production (EGP) after 4 h of hyperinsulinemia was  $68 \pm 14\%$  (from  $13.3 \pm 2.2$  to  $4.3 \pm 2.1 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) during the Prestudy,  $100 \pm 12\%$  (from  $10.9 \pm 0.6$  to  $0.0 \pm 1.2 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) during the thalidomide study, and  $93 \pm 12\%$  (from  $14.5 \pm 2.0$  to  $1.0 \pm 1.8 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) during the placebo study. These differences were not statistically significant.

**Lipolysis, FFA oxidation, and reesterification**

Basal rates of lipolysis ( $5.5 \pm 0.9$ ,  $4.8 \pm 1.1$ , and  $6.8 \pm 1.7 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , respec-

**Table 3—Carbohydrate oxidation and nonoxidative GLS**

	Prestudy	Thalidomide study	Placebo study
Carbohydrate oxidation	4.0 ± 0.9	4.3 ± 1.1	4.6 ± 1.4
0 min	<i>P</i> < 0.002	<i>P</i> < 0.01	NS
240 min	8.0 ± 1.3	8.0 ± 1.8	6.9 ± 1.5
Nonoxidative GLS	7.4 ± 2.9	5.8 ± 4.3	9.9 ± 3.8
0 min	NS	NS	NS
240 min	5.2 ± 1.8	3.5 ± 1.5	3.7 ± 1.7

Data are means ± SEM in micromoles per kilogram per minute.

tively), FFA oxidation ( $0.8 \pm 0.1$ ,  $0.8 \pm 0.2$ , and  $0.7 \pm 0.2 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , respectively), and FFA reesterification ( $4.7 \pm 1.1$ ,  $4.1 \pm 1.1$ , and  $6.1 \pm 1.6 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , respectively) were not different when comparing the Pre, thalidomide, and placebo studies (Table 4). Similarly, insulin-inhibited rates of lipolysis ( $3.6 \pm 0.7$ ,  $2.3 \pm 0.6$ , and  $3.0 \pm 0.6 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , respectively), FFA oxidation ( $0.6 \pm 0.2$ ,  $0.6 \pm 0.2$ , and  $0.5 \pm 0.1 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , respectively), and FFA reesterification ( $3.0 \pm 0.7$ ,  $1.7 \pm 0.6$ , and  $2.5 \pm 0.6 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , respectively) also were not different from each other when comparing the 3 studies.

### Body composition

Thalidomide treatment did not result in significant changes in body weight ( $100.7 \pm 7.9$ ,  $101.5 \pm 7.5$ , and  $100.2 \pm 7.8 \text{ kg}$  during the Pre, thalidomide, and placebo periods, respectively) or body fat ( $40.0 \pm 3.8$ ,  $38.2 \pm 2.6$ , and  $40.0 \pm 3.9 \text{ kg}$ , respectively). However, trends were evident toward a decrease in urinary nitrogen excretion ( $447 \pm 107$  vs.  $601 \pm 78 \mu\text{mol}/\text{min}$ , respectively; NS) and an increase in lean body mass ( $63.3 \pm 6.0$  vs.  $60.1 \pm 5.4 \text{ kg}$ , respectively; NS) when comparing the thalidomide study with the prestudy and placebo studies.

**CONCLUSIONS**—The objective of this study was to investigate whether thalidomide, by lowering TNF- $\alpha$  production, improves insulin action on carbohydrate and fat metabolism in obese type 2 diabetic patients.

Instead of the expected improvement, we found that thalidomide treatment was associated with a 20–25% decrease in the already-compromised insulin-stimulated glucose uptake in these diabetic patients. This decrease in insulin sensitivity was not seen after placebo treatment but occurred in all thalidomide-treated patients. No sig-

nificant increases were evident in plasma levels of FFA or in several diabetogenic hormones (including glucagon, cortisol, and epinephrine), which may have increased insulin resistance. Moreover, the thalidomide-induced inhibition in glucose uptake was completely accounted for by a decrease in insulin-stimulated GS (Fig. 2). This suggested that thalidomide had produced a defect in the GS pathway that resulted in a secondary decrease in insulin-stimulated glucose uptake. We believe that this was the most likely sequence of events because, had thalidomide produced a primary defect in glucose uptake, GS and GLS should have decreased proportionally. This, however, did not happen; rather, the glycolytic flux remained unchanged, and the rate of GS decreased. Therefore, thalidomide apparently inhibited GS perhaps by reducing the activity of glycogen synthase, which is the rate-limiting enzyme of the glycogen synthetic pathway.

Thalidomide was found to inhibit only insulin-stimulated glucose uptake but had no discernable effect on basal glucose level. This result can best be explained by the inhibitory action of thalidomide on GS. Basal rates of GS were 0 and thus could not be further reduced by thalidomide. However, after a carbohydrate-rich meal, the

thalidomide-induced insulin resistance would likely decrease glucose tolerance and increase postprandial glucose levels.

In general, thalidomide has been reported to decrease TNF- $\alpha$  production (2,3), but at least 2 reports showed that thalidomide increased TNF- $\alpha$  production (19,20). To determine whether the thalidomide-induced metabolic changes observed in our study were related to changes in circulating TNF- $\alpha$ , we measured serum TNF- $\alpha$  levels. They were found to be very low ( $<2 \text{ pg/ml}$ ) to unmeasurably low ( $<0.1 \text{ pg/ml}$ ) in most of our study subjects during all 3 studies. Undetectably low blood TNF- $\alpha$  levels have been reported previously (4). On the other hand, our TNF- $\alpha$  values may have been artificially low because the serum samples had been frozen and thawed several times before TNF- $\alpha$  was assayed. Hence, we were unable to determine whether thalidomide had altered TNF- $\alpha$  production.

We found no evidence that thalidomide interfered with insulin action on EGP or on FFA turnover (lipolysis, FFA oxidation, reesterification). Two possible reasons exist for this. First, thalidomide may specifically inhibit glycogen synthase activity. Second, a reduction in insulin action on EGP and lipolysis was not detected because the clamp insulin concentrations were too high. Both processes are known to be more sensitive to insulin than glucose uptake, and our clamp insulin concentrations were several times higher than the  $\text{IC}_{50}$  for lipolysis and EGP (21). Thus, the question of whether thalidomide inhibits insulin action on liver and fat metabolism must be further explored.

Thalidomide treatment has been reported to result in an increase in body weight in human immunodeficiency virus (HIV)-positive patients with and without tuberculosis (22,23). The results of this

**Table 4—FFA turnover**

	Prestudy	Thalidomide study	Placebo study
Lipolysis	5.5 ± 0.9	4.8 ± 1.1	6.8 ± 1.7
0 min	<i>P</i> < 0.05	<i>P</i> < 0.05	<i>P</i> < 0.04
240 min	3.6 ± 0.7	2.3 ± 0.6	3.0 ± 0.6
FFA oxidation	0.8 ± 0.2	0.8 ± 0.2	0.7 ± 0.2
0 min	NS	NS	NS
240 min	0.6 ± 0.2	0.6 ± 0.2	0.6 ± 0.1
FFA reesterification	4.7 ± 1.1	4.1 ± 1.1	6.1 ± 1.6
0 min	NS	<i>P</i> < 0.05	<i>P</i> < 0.04
240 min	3.0 ± 0.7	1.7 ± 0.6	2.5 ± 0.6

Data are means ± SEM in micromoles per kilogram per minute.

study suggest that these effects of thalidomide may not be restricted to patients with HIV. Our thalidomide-treated diabetic patients showed a trend toward a gain in body weight and lean body mass and a decrease in urinary nitrogen excretion. The latter suggests that the weight gain was at least partially caused by an increase in lean body mass. Probably because of the small number of patients studied, none of these effects reached statistical significance.

In summary, 3 weeks of treatment with thalidomide caused a 20–30% decrease in insulin-stimulated glucose uptake (i.e., increased peripheral insulin resistance) in obese patients with type 2 diabetes. This result was because of a decrease in insulin-stimulated GS. Basal GS rates were 0 and were unaffected by thalidomide. Thalidomide also did not affect basal glucose uptake and production and basal plasma blood glucose levels, nor did it affect basal or insulin-inhibited fat metabolism. A trend was evident toward a decrease in urinary nitrogen excretion and an increase in lean body mass. Whether these results are also applicable to less obese and less insulin-resistant subjects remains to be determined. Nevertheless, all patients treated with thalidomide should be monitored for possible deterioration in their glucose tolerance.

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