Insulin Detemir Reduces Weight Gain As a Result of Reduced Food Intake in Patients With Type 1 Diabetes

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OBJECTIVE—Insulin detemir lacks the usual propensity for insulin to cause weight gain. We investigated whether this effect was a result of reduced energy intake and/or increased energy expenditure.

RESEARCH DESIGN AND METHODS—A 32-week, randomized crossover design trial was undertaken in 23 patients with type 1 diabetes. Patients on a basal-bolus regimen (with insulin aspart as the bolus insulin) were randomly assigned to insulin detemir or NPH insulin as a basal insulin for 16 weeks, followed by the other basal insulin for 16 weeks. At the end of each 16-week period, total energy expenditure, resting energy expenditure, diet-induced thermogenesis, activity energy expenditure, energy intake, weight change, glycemic control, hypoglycemic episodes, and hormones that affect satiety and fuel partitioning were measured.

RESULTS—After 16 weeks, weight change was −0.69 ± 1.85 kg with insulin detemir and +1.7 ± 2.46 kg with NPH insulin ($P < 0.001$). Total energy intake was significantly less with insulin detemir (2,016 ± 501 kcal/day) than with NPH insulin (2,181 ± 559 kcal/day) ($P = 0.026$). There was no significant difference in any measure of energy expenditure, HbA_{1c} percentage, or number of hypoglycemic episodes. Leptin was lower and resistin was higher with insulin detemir compared with NPH insulin ($P = 0.039$, $P = 0.047$). After the meal, ghrelin and pancreatic polypeptide levels ($P = 0.002$, $P = 0.001$) were higher with insulin detemir.

CONCLUSIONS—The reduced weight gain with insulin detemir compared with NPH insulin is attributed to reduced energy intake rather than increased energy expenditure. This may be mediated by a direct or indirect effect of insulin detemir on the hormones that control satiety.

Exogenous insulin-replacement therapy remains the most effective treatment for hyperglycemia in type 1 diabetic and poorly controlled type 2 diabetic patients, but it regularly results in excessive weight gain. The Diabetes Control and Complications Trial showed that insulin-associated weight gain (1) was greater in patients receiving intensified intervention than in those receiving conventional intervention (5.1 vs. 3.7 kg, $P < 0.0001$, during first 12 months of therapy).

In type 1 diabetes, adherence to prescribed insulin regimens may be compromised by a desire to avoid weight gain. The problem of insulin omission was confirmed in a U.K. study (2) of 65 young subjects with type 1 diabetes. A total of 30% of the women admitted to having underdosed insulin to manipulate their weight, whereas 45% of women who developed microvascular complications had intentionally misused insulin to prevent weight gain.

Not all types of insulin treatment are equally prone to causing weight gain. Treatment with insulin detemir, a novel basal insulin analog, has been consistently shown to cause no weight gain in patients with type 1 diabetes, compared with NPH insulin (3), and lower weight gain in patients with type 2 diabetes. A myristic fatty-acid chain attached to the B-terminal of the insulin molecule allows reversible albumin binding and prolonged residence time in the subcutaneous depot and in the circulation (4).

The mechanism(s) underlying the apparent weight advantage of insulin detemir has not been identified. Elucidation of this mechanism(s) could provide valuable insights into the ways in which insulin treatment causes weight gain in diabetes. Such knowledge also might enable the future development of insulin analogs with even greater metabolic advantages.

RESEARCH DESIGN AND METHODS

—This study was registered with clinicaltrials.gov (NCT00509925) and was approved by the U.K. Medicines and Healthcare Products Regulatory Agency (Eudract 2006-003060-59), the East Kent Research Ethics Committee, and the University of Surrey Research Ethics Committee. The study was a 32-week, single-center, open-labeled, randomized crossover trial. Twenty-three patients with type 1 diabetes on a basal-bolus regimen were recruited (male-to-female ratio 14-to-9, [means ± SD] average age 38.8 ± 2.17 years, average weight 81.9 ± 2.21 kg, BMI 28 ± 3.6 kg/m^2, duration of diabetes 19.95 ± 2.09 years, and HbA_{1c} 8.2 ± 0.22%). One patient did not complete the trial for personal reasons. Patients were randomly assigned to receive either insulin detemir or NPH insulin as a basal insulin. After 16 weeks of treatment, subjects were switched to the other basal insulin. Insulin aspart was used throughout as the bolus insulin. Both insulin detemir and NPH insulin were administered once or twice daily, according to individual needs and pre-breakfast and predinner glucose targets (aiming for <6.0 mmol/L without significant hypoglycemia). There were 5 patients on twice-daily insulin detemir and 17 patients on once-daily insulin detemir.

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During the trial, subjects attended the hospital for eight planned visits, and the investigator was in contact with the patients by telephone at least 10 times. Inclusion criteria was type 1 diabetes duration >12 months, on a basal-bolus insulin regimen for >3 months, aged >18 years, BMI <40 kg/m^2, and HbA_{1c} between 7.0 and 11.0%. Exclusion criteria included anticipated change in medications known to interfere with glucose metabolism, proliferative retinopathy, recurrent major hypoglycemia or hypoglycemic unawareness, impaired hepatic or renal functions, pregnancy, and uncontrolled hypertension. Body weight, fat mass, fat-free mass (measured on a Tanita BC-418 segmental body composition analyzer), insulin doses, hypoglycemic episodes, and home blood glucose readings were recorded at baseline and at weeks 8, 14, and 16 of each 16-week treatment period. During week 14 of both treatment periods, patients attended after an overnight fast. Resting energy expenditure for 30 min was measured by indirect calorimetry (Medgraphics CCM Express). A fasting blood sample was taken for the measurement of hormones and adipokines. A fasting urine sample was collected for baseline urine enrichment for the calculation of total energy expenditure, using double-labeled water. Subjects then were given a standard, fiber-free, liquid mixed meal (600 kcal, 60 g carbohydrate, 21 g lipids, and 19 g protein), and multiple measurements of energy expenditure were made by indirect calorimetry and hormonal responses measured for 3 h. Blood samples were taken at over 180 min for glucagon-like peptide-1, ghrelin, pancreatic polypeptide, and peptide YY.

Double-labeled water (0.174 g/kg body wt ^{18}O and 0.07 g/kg body wt ^2H_2O) then was administered orally to measure total energy expenditure. Patients were provided with urine-collection bottles and a log sheet to monitor the time and date of collections for 14 days. To measure appetite, subjects were provided with a large container of a standardized pasta meal (1,230 g, 1,740 kcal) and were asked to eat until they felt comfortably full. The meal was weighed before and after patients had eaten and the calorie intake was calculated. At the end of the visit, an Actiheart monitor (CamNtech, Cambridge, U.K.) was fitted to record their activity energy expenditure for the next 5 days. Patients also were provided with a diary to record their 7-day food intake during the following week. They were taught how to accurately complete a record of everything they ate. During week 16 of each treatment period, patients attended the hospital with their food diaries, Actihearts, and 14-day urine samples.

Analytical methods

For measurement of total energy expenditure, the urine samples were analyzed in duplicate for $H_2{}^{18}O$ and ^2H_2O on a Δ plus XP isotope ratio mass spectrometer (Thermo Scientific, Bremen Germany) with a Gasbench II inlet system and a GCpal auto sampler (CTC Analytics, Presearch, Basingstoke, U.K.). $^2H_2$ enrichment was measured using a platinum catalyst rod. The sample tubes were capped and flushed (100 mL/min) with the equilibration gas, 5% H_2 in helium, and incubated for a minimum of 40 min at 22.5°C. The isotopic enrichment of ^{18}O was determined from carbon dioxide equilibration. Sample tubes were flushed with 0.5% CO_2 in helium and incubated overnight at 22.5°C. Isotopic enrichments were measured relative to laboratory standards that were previously calibrated against the international standards of the Vienna Standard Mean Ocean Water and Standard Light Arctic Precipitation (International Atomic Energy Agency, Vienna, Austria).

Plasma adiponectin, leptin and total ghrelin, total peptide YY, and glucagon-like peptide-1 concentrations were determined by radioimmunoassay (Millipore, Billerica, MA). Plasma IGF-1 concentrations were determined using a nonextraction immunoradiometric assay (Beckman Coulter U.K., High Wycombe, U.K.). Plasma resistin and pancreatic polypeptide were measured using an ELISA (Millipore).

Data analysis

Average 24-h total energy intake was calculated from the food diary assessment by a fully qualified dietitian who was blinded to which basal insulin the patient was taking. Diet-induced thermogenesis was calculated as the area under the energy expenditure curve (3 h) during the standard meal and converted to daily diet-induced thermogenesis using the total daily calorie intake from the food diary.

The ^{18}O and ^2H elimination rates (k_O and k_H) were determined from the slope of the natural logarithm of isotope enrichment as a function of time calculated by linear regression. Total body water was calculated as the average of the dilution space for $H_2{}^{18}O$ corrected by 1.01 and ^2H_2O corrected by 1.04. Total daily CO_2 production rate (rCO_2) was calculated as $rCO_2 = 0.4554$ total body water $(1.01\,k_O - 1.04\,k_H)$. Total energy expenditure was calculated from rCO_2 and RQ, using the equation of de Weir (5). The jackknife technique was used to correct for bias and to evaluate experimental and analytical error. Total energy expenditure could only be calculated in 17 paired samples because of the insufficient urine-sample collection in five patients.

The Actiheart data were downloaded at the end of each 5-day period, and activity energy expenditure was calculated using a branched chain equation model (6,7). For postprandial hormone measurements, the areas under the hormone time curves were calculated using the trapezoidal rule and corrected for baseline concentration.

Statistical analysis

Results are presented as means ± SE. The primary analysis was a comparison of the insulin detemir and the NPH insulin treatments, with respect to total energy expenditure (including components of energy expenditure, hormones, and body composition), and separately, with respect to 7-day food intake. In each case, the data were analyzed with a general linear mixed model, with the subject as the random effect and the study period and treatment as fixed effects, including a treatment–by–study period fixed-effect interaction. For the comparison of the same two treatments, using the hormone response to a meal, measured at several time points on each subject in each of the two periods, the above analysis was modified to additionally include a repeated-measure effect for the times of measurement. The software used for these analyses was the PROC MIXED procedure of SAS version 9.1 (SAS Institute, Cary, NC). Structural equation modeling also was performed, using SAS PROC CALIS, to explore the relationships between food and weight and the hormones measured in the study.

RESULTS

Body weight

After 16 weeks of treatment, mean body weight (Fig. 1) and fat-free mass were significantly lower with insulin detemir than with NPH insulin ($P = 0.0006$; $P = 0.0001$). Fat mass was not significantly different between treatments (Table 1).

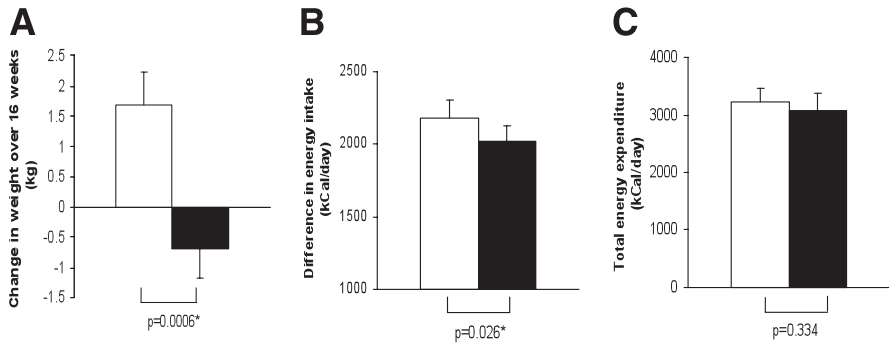

Figure 1—A: *Changes in body weight after 16 weeks of treatment*. B: *Change in energy intake after 16 weeks*. C: *Change in total energy expenditure after 16 weeks*. □, *NPH insulin*; ■, *insulin detemir*.

Glycemic control

HbA_{1c} at the end of 16 weeks of treatment was not different between the two treatments (Table 1). Statistical analysis showed that glycemic control during the two treatments could not explain the significant difference in weight (P = 0.617). There was no significant difference in the number of hypoglycemic episodes (<3.1 mmol/L) between the two treatments. There were no major hypoglycemic episodes (defined as patients unable to treat themselves) in the trial.

Insulin requirements

The total daily dose of insulin aspart did not significantly change in the insulin detemir arm compared with the NPH arm (35.8 ± 3.66 vs. 34.3 ± 3.11 IU/day; P = 0.32). The total daily dose of basal insulin did not significantly change with the insulin detemir arm compared with the NPH arm (27.9 ± 3.2 vs. 26.7 ± 2.76 IU/day; P = 0.33)

Energy intake and expenditure

Average daily food intake, measured using a 7-day food diary, was significantly lower with detemir compared with NPH insulin (P = 0.026). This was attributed to lower fat (P = 0.006) and protein (P = 0.01) intake, with no difference in carbohydrate intake. Calorie intake during the unlimited meal was not different between detemir and NPH insulin.

Total, activity, and resting energy expenditure and diet-induced thermogenesis were not significantly different between insulin detemir and NPH insulin (Table 1). Resting energy expenditure was negatively related to HbA_{1c} (P = 0.023).

Hormone responses

Fasting plasma leptin was lower and resistin was higher with insulin detemir than with NPH insulin (P = 0.039; P = 0.047). There was no significant difference in fasting adiponectin and IGF-1. In response to a standard meal, ghrelin and pancreatic polypeptide were higher with insulin detemir than with NPH insulin (P = 0.002; P = 0.001). There was no significant difference in glucagon-like peptide-1 and peptide YY levels (Table 2).

Structured equational modeling

The model showed a positive relationship between weight and leptin, between weight and fat-free mass, and between weight and pancreatic polypeptide (Fig. 2). Additional negative relationships were observed between food intake and leptin, between resistin and leptin, between pancreatic polypeptide and fat-free mass, and between ghrelin and fat-free mass.

Table 1—*Weight changes, energy expenditure, energy intake, and hypoglycemic episodes during and at the end of the treatment periods with insulin detemir and NPH insulin*

	NPH insulin	Insulin detemir	P
Weight change over 16 weeks (kg)	1.7 ± 0.52	−0.69 ± 0.39	**<0.001**
Fat mass change over 16 weeks (kg)	0.42 ± 0.380	0.16 ± 0.45	0.562
Fat-free mass change over 16 weeks (kg)	1.26 ± 0.31	−0.9 ± 0.25	**<0.001**
Energy intake (kcal/day)	2,181 ± 122.1	2,018 ± 109.4	**0.02**
Carbohydrate (g/day)	237.43 ± 15.02	225.2 ± 15.69	0.203
Fat (g/day)	82.59 ± 5.3	69.04 ± 4.45	**0.006**
Protein (g/day)	85.11 ± 5.57	76.6 ± 4.11	**0.01**
Calorie intake during unlimited meal (kcal)	871 ± 74.6	823 ± 85.5	0.523
Total energy expenditure (kcal/day)	3,233 ± 236.9	3,074 ± 301.5	0.334
Resting energy expenditure (kcal/day)	2,034 ± 78.6	1,932 ± 94.5	0.312
Resting energy expenditure (kcal/day/kg)	24.4 ± 0.99	23.6 ± 1.21	0.522
Activity energy expenditure (kcal/day)	542.7 ± 61.4	588.5 ± 76.4	0.566
Diet-induced thermogenesis (kcal/day)	74.2 ± 7.22	73 ± 7.4	0.777
HbA_{1c} (%)	7.5 ± 0.26	7.8 ± 0.23	0.061
Hypoglycemic episodes	4.9 ± 1.53	4.6 ± 1.58	0.586

Data are means ± SE.

CONCLUSIONS—The current study is consistent with previous studies that showed treatment with insulin detemir to be associated with less weight gain than treatment with NPH insulin. There was a significant difference in energy intake, as assessed by a 7-day food diary. This corresponded to an ~160 kcal/day difference between detemir and NPH insulin and could explain the observed weight difference between treatments during this study. Total energy expenditure, as well as its components, showed no differences between insulin detemir and NPH insulin. It is widely recognized that energy expenditure decreases with weight loss. Although the average difference in weight between treatments at the end of the two interventions was ~2.4 kg, total energy expenditure was not different. Thus, a small effect of detemir on total energy expenditure cannot be excluded. Thus, insulin detemir seems to mediate its weight-sparing effects by altering energy intake rather than energy expenditure.

It is well recognized that in patients with diabetes (8), there is a significant underestimation of self-reported food intake, and this also was the case in this study. However, because this was a crossover study, this would be expected to be similar with both insulins. Macronutrient composition analysis showed that the decrease in food intake was a result of a significant reduction in protein and fat intake. It is notable that a decrease in protein intake also was shown in a study investigating the acute effects of insulin detemir on food intake (9).

Various hypotheses have been put forward to explain the weight-sparing effects of insulin detemir. Treatment with insulin detemir has been shown to be associated with reduced blood glucose variability and a reduced risk of hypoglycemia

Table 2—*Fasting hormone concentrations and postprandial hormone AUCs after treatment with insulin detemir and NPH insulin*

	NPH insulin	Insulin detemir	*P*
Adiponectin (ng/mL)	13,650.2 ± 1,749.8	13,680.4 ± 1,620.0	0.953
Leptin (ng/mL)	10.83 ± 1.99	9.45 ± 1.59	**0.039**
Resistin (ng/mL)	9.46 ± 0.90	11.83 ± 2.05	**0.047**
IGF-1 (ng/mL)	182.02 ± 21.85	193.01 ± 20.88	0.307
Glucagon-like peptide-1 (pmol/L)	8.18 ± 0.3	8.8 ± 0.41	0.390
Ghrelin AUC (pg/mL per min)	528.39 ± 19.52	610.92 ± 30.2	**0.002**
Peptide YY AUC (pg/mL per min)	135.2 ± 15.1	139.8 ± 14.4	0.432
Pancreatic polypeptide AUC (pg/mL per min)	777.1 ± 16.3	813.4 ± 16.9	**0.001**

Data are means ± SE. AUC, area under the curve.

compared with treatment with NPH insulin (10). This might imply that patients are avoiding weight gain by reducing their "defensive snacking." The basal analog insulin glargine has consistently reduced hypoglycemia compared with NPH insulin, but most trials (11,12) that have reported weight data do not show reduced weight gain with this analog. In the current study, additional statistical analysis showed that the weight difference could not be explained by a difference in glycemic control or hypoglycemic episodes.

Another putative mechanism for the weight-lowering effect of insulin detemir concerns the blood glucose–lowering action of this analog (13). A relatively greater percentage of the total blood glucose–lowering effect of insulin detemir is derived from its hepatic action, compared with that of exogenous human insulin delivered into the subcutaneous and systemic circulation (14,15). This could result in a relative reduction of peripheral lipogenesis, preventing weight gain (14). It has been suggested that the reversible albumin-binding property of insulin detemir limits access to peripheral tissues through the endothelial barrier, while allowing full access to hepatocytes via the large sinusoidal fenestrae in hepatic capillary membranes. The slight hepatoselective effect seen with insulin detemir may thus reduce free fatty acid deposition and glucose uptake into peripheral tissues. It has been demonstrated that the partitioning of fuels among different tissues and between metabolic pathways has significant effects on food intake (16). This may be via ATP production or may be caused by changes in satiety factors, such as leptin and ghrelin. Although there was a decrease in fasting leptin, an increase in resistin, and an increase in the ghrelin response to a meal, these changes could be a consequence rather than a cause of weight loss (17). In humans, an infusion of PP was shown to reduce acute food intake at a buffet meal 2 h after the infusion and reduce food intake for the following 24 h (18). PP-binding sites have been demonstrated in the area postrema, and the activation of neurons in the area postrema after PP administration suggests that PP has a central effect on satiety (19). The observed increase of PP in the insulin detemir–treated patients is of considerable interest, and the mechanism is unknown.

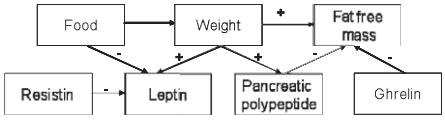

Figure 2—*Mathematical model showing the relationships between changes in measured variables. +, Significant positive relationship; −, Significant negative relationship.*

An alternative mechanism that has been proposed is that insulin detemir may act directly on the brain to affect appetite. Insulin receptors are abundant in parts of the brain, including the hypothalamus (20), where insulin is involved in the regulation of satiety and appetite (21). Preliminary studies (22,23) have reported that the effect of human insulin on cerebrocortical activity is compromised in obese patients, whereas the effect of insulin detemir is enhanced. Insulin detemir may have a tissue-selective action, with a relative preference for brain compared with peripheral tissues. A recent study (9) showed that while inducing comparable peripheral effects, insulin detemir, compared with human insulin, had an enhanced anorexigenic impact on the central nervous system that controls nutrient uptake.

The design of this crossover study allowed a statistical exploration of the relationships between changes in the measured variables using structural equation modeling. The mathematical model that was developed confirms known physiological relationships between food intake, weight, and leptin and between weight and fat-free mass. The negative relationship between ghrelin and fat-free mass also confirms previous studies (24,25). A negative relationship between pancreatic polypeptide and fat-free mass has not previously been reported.

A limitation of the study is that it was an open-label design and the fact that test subjects knew they were on insulin detemir, which has been widely advertised to cause less weight gain, might be a confounding factor.

In conclusion, this study shows that a relative reduction in weight gain associated with insulin detemir therapy versus NPH insulin is attributed to a reduction in calorie consumption. This effect might be mediated by a direct effect on the brain or by an indirect effect on satiety as a result of the hepatoselective effect of insulin detemir modulating orexigenic and anorexigenic hormones.

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S.Z. undertook the clinical research study and wrote the manuscript. B.S. assisted with the clinical studies. F.S.-M. and N.C.J. analyzed the samples. K.B., an independent dietician, assessed the food diaries. S.J. helped with statistical analysis. R.H.J. helped write the manuscript. A.M.U. designed and supervised the study, researched data, and helped write the manuscript. D.L.R.-J. was the principal investigator and designed and supervised the study, researched data, and helped write the manuscript.

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