Insulin Detemir Reduces Weight Gain Due To Reduced Food Intake in Patients with Type 1 Diabetes

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Running Title: Insulin Detemir Reduces Food Intake

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Abstract

Objective: Insulin detemir lacks the usual propensity for insulin to cause weight gain. We investigated whether this effect was due to 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 regime (with insulin aspart as bolus insulin) were randomized to insulin detemir or NPH insulin as basal insulin for 16 weeks, followed by the other basal insulin for 16 weeks. At the end of each 16 weeks, total energy expenditure (TEE), resting EE, diet induced thermogenesis, activity EE, energy intake, weight change, glycemic control, hypoglycemic episodes and hormones that affect satiety/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 (2016± 501 kcal/day) than NPH insulin (2181± 559 kcal/day) (p=0.026). There was no significant difference in any measure of EE, %HbA1c or number of hypoglycemic episodes. Leptin was lower and resistin was higher with insulin detemir compared to NPH insulin (p=0.039, p=0.047). Following the meal, ghrelin and pancreatic polypeptide (p=0.002, p=0.001) were higher with insulin detemir.

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

Exogenous insulin replacement therapy remains the most effective treatment for hyperglycemia in type 1 diabetes and poorly controlled type 2 diabetes patients, but it regularly results in excessive weight gain. The Diabetes Control and Complications trial (DCCT) showed that insulin-associated weight gain (1) was greater in patients receiving intensified intervention than that of 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 UK study of 65 young subjects with type 1 diabetes (2). Thirty percent of the women admitted to having under-dosed insulin to manipulate their weight, while 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 to NPH insulin (3) and lower weight gain in 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 might also 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 UK Medicines and Healthcare Products Regulatory Agency (Eudract 2006-003060-59), the East Kent Research Ethics Committee and University of Surrey Research Ethics Committee. The study was a 32 week, single-centre, open-labeled, randomized, cross-over trial. Twenty three patients with type 1 diabetes on a basal-bolus regime were recruited [male: female 14:9, average age 38.8±2.17 years (mean ±SEM), average weight 81.9±2.21 kg, body mass index 28±3.6 kg/m2, duration of diabetes 19.95±2.09 years, Hba1c 8.2±0.22 %]. One patient did not complete the trial for personal reasons. Patients were randomized to receive either insulin detemir or Neutral Protamine Hagedorn (NPH) insulin as basal insulin. Following 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, according to pre-breakfast and pre-dinner 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. During the trial, subjects attended the hospital for 8 planned visits and the investigator was in contact by telephone at least ten times. Inclusion criteria was type 1 diabetes>12 months, on a basal bolus insulin regimen for >3 months, age>18 years, BMI<40, HbA1c 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 and 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 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 EE (REE) for 30 minutes was measured by indirect calorimetry (Medgraphics CCM Express). A fasting blood sample was taken for the measurement of hormone/adipokines. A fasting urine sample was collected for baseline urine enrichment for the calculation of TEE using double labeled water. Subjects were then given a standard fiber-free liquid mixed meal (600 Kcal, 60 g carbohydrate, 21 g lipid, 19 g protein) and multiple measurements of energy expenditure were made by indirect calorimetry and hormonal responses measured for 3 hours. Blood samples were taken at over 180 minutes for GLP-1, ghrelin, pancreatic polypeptide and peptide YY.

Double labeled water (0.174 g/kg body weight $^{18}$O and 0.07 g/kg body weight $^{2}$H$_2$O) was then administered orally, to measure TEE. Patients were provided with urine collection bottles and a log sheet to monitor the time/date of collections for 14 days. To measure appetite subjects were provided with a large container of a standardized pasta meal (1230 gm, 1740 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 calculated. At the end of the visit an Actiheart monitor (CamNtech Ltd, Cambridge, UK) was fitted to record their activity EE (AEE) for the next 5 days. Patients were also provided with a diary to record 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 TEE, the urine samples were analysed in duplicate for H$_2^{18}$O and $^2$H$_2$O on a Delta plus XP isotope ratio mass spectrometer (Thermo Scientific, Bremen Germany) with a Gasbench II inlet system and a GCpal auto sampler (CTC analytics, Presearch Ltd Basingstoke, UK). $^2$H$_2$ enrichment was measured using a platinum catalyst rod. The sample tubes were capped and flushed (100ml/min) with the equilibration gas, 5% H$_2$ in helium, and incubated for a minimum of 40 mins at 22.5$^\circ$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$^\circ$C. Isotopic enrichments were measured relative to laboratory standards previously calibrated against international standards 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 (PYY) and glucagon-like peptide-1 (GLP-1) concentrations were determined by radioimmunoassay (Millipore Corporate Headquarters, Billerica, MA). Plasma IGF-1 concentration was determined using a non extraction immunoradiometric assay (IRMA) (Beckman Coulter UK Ltd, High Wycombe, UK). Plasma resistin and pancreatic polypeptide were measured using an enzyme linked immunosorbant assay (ELISA) (Millipore Corporate Headquarters, Billerica, MA).

Data analysis

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

The $^{18}$O and $^2$H 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 (TBW) was calculated as the average of the dilution space for $H_2^{18}$O corrected by 1.01 and $^2$H$_2$O corrected by 1.04. Total daily CO$_2$ production rate ($rCO_2$) was calculated as $rCO_2=0.4554TBW (1.01 k_O -1.04 k_H)$. TEE 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. TEE could only be calculated in 17 paired samples due to insufficient urine sample collection in 5 patients.

The Actiheart data was downloaded at the end of each 5 day period and AEE 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±SEM. 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, body composition) and separately with respect to 7-day food intake. In each case the data were analysed with a general linear mixed model, with subject as random effect and study period as well as treatment as fixed effects, including a treatment by study
period fixed effect interaction. For the comparison of the same 2 treatments, using the hormone response to a meal, measured at several time points on each subject in each of the 2 periods, the above analysis was modified to include additionally a repeated measure effect for the times of measurement. The software used for these analyses was the PROC MIXED procedure of the SAS® statistical analysis package version 9.1 (SAS Institute, Cary, North Carolina, USA). Structural equation modelling was also performed, using SAS® PROC CALIS, to explore the relationships between food, and weight and the hormones measured in the study.
RESULTS

Body Weight (Table 1)

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

Glycaemic control

HbA1c at end of 16 weeks of treatment was not different between the two treatments (Table 1). Statistical analysis showed that glycaemic 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 hypoglycaemic episodes (<3.1 mmol/l) between the two treatments. There were no major hypoglycaemic 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 to 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 insulin detemir arm compared with NPH arm (27.9±3.2 vs 26.7±2.76 IU/day, p=0.33).

Energy Intake and Expenditure (Table 1)

Average daily intake measured using a 7 day food diary, was significantly lower with detemir compared to NPH insulin (p=0.026). This was due to lower fat (p=0.006) and protein intake (p=0.01), with no difference in carbohydrate intake. Calorie intake during the unlimited meal was not different between detemir and NPH insulin.
TEE, AEE, REE and DIT were not significantly different between insulin detemir and NPH insulin (Table 1). REE was negatively related to HbA1c (p=0.023).

**Hormone responses (Table 2)**

Fasting plasma leptin was lower and resistin was higher with insulin detemir than 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 GLP-1 and Peptide YY levels.

**Structured equational modelling (figure 2)**

The model showed a positive relationship between weight and leptin, between weight and FFM, and between weight and pancreatic polypeptide. 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.
DISCUSSION

The present study is consistent with previous studies that showed treatment with insulin detemir to be associated with less weight gain than NPH insulin. There was a significant difference in energy intake as assessed by 7 day food diary. This corresponded to approximately 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 approximately 2.4 kg, TEE was not different. Thus a small effect of detemir on TEE cannot be excluded. Thus insulin detemir appears 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 was also the case in this study. However as this was a crossover study this would be expected to be similar with both insulins. Macronutrient composition analysis showed the decrease in food intake was due to a significant reduction in protein and fat intake. It is notable that a decrease in protein intake was also noted 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 compared to
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 that have reported weight data do not show reduced weight gain with this analog (11,12). In the current study additional statistical analysis showed that the weight difference could not be explained by a difference in glycaemic 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 to 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 due to 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
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.

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 have reported that the effect of human insulin on cerebrocortical activity is compromised in obese patients, while 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 [22, 23]. A recent study [9] showed that while inducing comparable peripheral effects, insulin detemir had an enhanced anorexigenic impact on the central nervous system that controls nutrient uptake compared to human insulin.

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 which 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 due 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 due to the hepatoselective effect of insulin detemir modulating orexigenic and anorexigenic hormones.

**Author Contributions**

SZ undertook the clinical research study and wrote the manuscript. BS assisted with the clinical studies. FSM and NJ analysed the samples, KB, an independent dietician, assessed the food diaries. SJ helped with statistical analysis. RJ helped write the manuscript. MU designed and supervised the study, researched data and helped write the manuscript. DRJ, principal investigator, designed and supervised the study researched data and helped write the manuscript.

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**Figure legends**

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)

Figure 2. Mathematical model showing the relationships between changes in measured variables. +indicates a significant positive relationship and – indicates a significant negative relationship.
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16. Hopkins DF, Williams G: Insulin receptors are widely distributed in human brain and bind human and porcine insulin with equal affinity. Diabet Med 1997;14:1044-1050


<table>
<thead>
<tr>
<th></th>
<th>NPH insulin</th>
<th>Insulin detemir</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight change over 16 weeks (kg)</td>
<td>1.7±0.52</td>
<td>-0.69±0.39</td>
<td>&lt;0.001</td>
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<td>Fat mass change over 16 weeks (kg)</td>
<td>0.42±0.380</td>
<td>0.16±0.45</td>
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<td>Fat free mass change over 16 weeks (kg)</td>
<td>1.26±0.31</td>
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<td>237.43±15.02</td>
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<td>82.59±5.3</td>
<td>69.04±4.45</td>
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<td>Protein (gm/day)</td>
<td>85.11±5.57</td>
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<td>Total EE (kcal/day)</td>
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<td>3074±301.5</td>
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<td>Resting EE (kcal/day)</td>
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<td>Resting EE (kcal/day/kg)</td>
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<td>Activity EE (kcal/day)</td>
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<td>73±7.4</td>
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<td>HbA1c (%)</td>
<td>7.5±0.26</td>
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<td>Hypoglycaemic episodes</td>
<td>4.9±1.53</td>
<td>4.6±1.58</td>
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**Table 1:** Weight changes, energy expenditure, energy intake and hypoglycaemic episodes during and at the end of treatment periods with insulin detemir and NPH insulin
Table 2: Fasting hormone concentrations and postprandial hormone AUCs following treatment with insulin detemir and NPH insulin

<table>
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<th>Insulin detemir</th>
<th>P values</th>
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<tr>
<td>Adiponectin (ng/ml)</td>
<td>13650.2±1749.8</td>
<td>13680.4±1620.0</td>
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<td>Leptin (ng/ml)</td>
<td>10.83±1.99</td>
<td>9.45±1.59</td>
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<td>Resistin (ng/ml)</td>
<td>9.46±0.90</td>
<td>11.83±2.05</td>
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<td>IGF-1 (ng/ml)</td>
<td>182.02±21.85</td>
<td>193.01±20.88</td>
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<td>GLP-1 (pmol/l)</td>
<td>8.18±0.3</td>
<td>8.8±0.41</td>
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<td>Ghrelin AUC (pg/ml.min)</td>
<td>528.39±19.52</td>
<td>610.92±30.2</td>
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<td>PYY AUC (pg/ml.min)</td>
<td>135.2±15.1</td>
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<td>Pancreatic polypeptide AUC (pg/ml.min)</td>
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