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Lower within-subject variability of fasting blood glucose and reduced weight gain with insulin detemir compared to NPH insulin in patients with type 2 diabetes

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Aim: The aim of this study was to compare the efficacy and safety of a basal-bolus insulin regimen comprising either insulin detemir or neural protamine hagedorn (NPH) insulin in combination with mealtime insulin aspart in patients with type 2 diabetes.

Methods: This was a 26-week, multinational, open-label, parallel group trial with 505 patients with type 2 diabetes (mean age, 60.4 ± 8.6 years; mean BMI, 30.4 ± 5.3 kg/m^2; mean HbA_{1c}, $7.9 \pm 1.3\%$). Patients, randomized 2 : 1 to insulin detemir or NPH insulin, received basal insulin either once or twice daily according to their pretrial insulin treatment and insulin aspart at mealtimes.

Results: After 26 weeks of treatment, significant reductions in HbA_{1c} were observed for insulin detemir (0.2%-points, $p = 0.004$) and NPH insulin (0.4%-points; $p = 0.0001$); HbA_{1c} levels were comparable at study end (insulin detemir, 7.6%; NPH insulin, 7.5%). The number of basal insulin injections administered per day had no effect on HbA_{1c} levels ($p = 0.50$). Nine-point self-measured blood glucose (SMBG) profiles were similar for the two treatment groups ($p = 0.58$), as were reductions in fasting plasma glucose (FPG) (insulin detemir, 0.5 mmol/l; NPH insulin, 0.6 mmol/l). At study end, FPG concentrations were similar for the two treatment groups ($p = 0.66$). By contrast, within-subject day-to-day variation in fasting SMBG was significantly lower with insulin detemir ($p = 0.021$). Moreover, patients receiving insulin detemir gained significantly less body weight than those who were administered NPH insulin (1.0 and 1.8 kg, respectively, $p = 0.017$). The frequency of adverse events and the risk of hypoglycaemia were comparable for the two treatment groups.

Conclusions: Patients with type 2 diabetes, treated for 26 weeks with insulin detemir plus insulin aspart at mealtimes, experienced comparable glycaemic control but significantly lower within-subject variability and less weight gain compared to patients treated with NPH insulin and insulin aspart. Insulin detemir was well tolerated and had a similar safety profile to NPH insulin.

Keywords: basal-bolus, body weight, insulin detemir, type 2 diabetes, variability
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Introduction

Type 2 diabetes is a chronic metabolic disorder, currently affecting 140–150 million people worldwide, which often leads to long-term microvascular and macrovascular complications that substantially increase morbidity and mortality [1].

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Traditionally, oral antidiabetic drugs (OADs) constitute the first line of treatment for type 2 diabetes when diet and exercise fail to provide satisfactory glycaemic control. However, as the disease advances, progressive loss of pancreatic β-cell function necessitates the use of insulin therapy when glycaemic targets cannot be achieved by oral therapy alone [2]. Although insulin has commonly been regarded as a final treatment option, several recent studies have provided evidence that tight glycaemic control, achieved in part through earlier and more intensive use of insulin, can reduce the incidence and delay the progression of a number of long-term complications associated with type 2 diabetes [3–5]. Moreover, evidence suggests that in contrast to sulphonylureas, early insulin treatment in newly diagnosed patients with type 2 diabetes may temporarily prolong endogenous insulin secretion and promote better metabolic control [6].

Usually, insulin therapy is initiated as a daily injection of long-acting basal insulin in combination with OADs. However, when glycaemic control becomes inadequate, a basal-bolus insulin regimen is often adopted [2]. Although the development of short-acting bolus insulin analogues (e.g. insulin aspart and insulin lispro) has improved postprandial glycaemic control, traditional basal insulin preparations [e.g. neural protamine hagedorn (NPH) insulin and Ultralente® insulin] cannot deliver insulin at the constant and reproducible low level that characterizes normal insulin secretion. For example, NPH insulin reaches a peak in plasma concentration approximately 5 h after injection and has an insufficient duration of action to cover night-time requirements [7,8]. Furthermore, inadequate resuspension prior to injection and variations in crystal size make dosing precision and absorption kinetics highly variable, resulting in unpredictable glucose levels [9–11].

These limitations have therefore prompted the development of new basal insulin analogues (insulin glargine and insulin detemir [12]) of which insulin detemir, a derivative of human insulin soluble at neutral pH [13,14], is the most recent to be developed [15]. The protracted action of insulin detemir largely stems from delayed absorption from the injection site due to self-association and binding, via a covalently attached fatty acid moiety, to albumin in the interstitial fluid [13,14]. This novel mechanism of protraction provides more reproducible insulin absorption and lower within-subject variability than other basal insulins [16].

Comparative studies of insulin detemir and NPH insulin in patients with type 1 diabetes have demonstrated similar glycaemic control but a more extended and smoother time-action profile with insulin detemir, properties that are associated with lower within-subject variability in fasting blood glucose and a reduced risk of hypoglycaemia [17–21]. Furthermore, compared to NPH insulin, patients receiving insulin detemir gain significantly less body weight at comparable metabolic control [17–19,21,22]. These characteristics could be particularly advantageous in the treatment of type 2 diabetes where approximately 80% of newly diagnosed patients are overweight or obese [23]. For patients with type 2 diabetes, fears of weight gain and hypoglycaemia associated with intensive insulin therapy [24] have often resulted in a reluctance to initiate insulin treatment and/or titrate insulin to a dose where near-normal glycaemia is achieved [25].

The present study was conducted to compare the efficacy, safety and weight change associated with a basal-bolus regimen comprising either insulin detemir or NPH insulin in combination with mealtime insulin aspart in patients with type 2 diabetes previously treated with insulin.

Research Design and Methods

Sixty-three sites in five European countries participated in this open-label, parallel-group trial. The trial consisted of a 3-week screening period and a 26-week treatment period. The study was approved by local ethics committees and health authorities according to local regulations and was conducted in accordance with ICH-Good Clinical Practice guidelines [26] and the Declaration of Helsinki [27]. Signed informed consent was provided before any trial-related activities.

Patients

A total of 505 patients with type 2 diabetes of $\geq$12 months duration, aged $\geq$35 years, HbA_{1c} $\leq$12.0% and who had received insulin treatment for at least 2 months (basal insulin dose $\geq$30% of the total daily insulin dose) were included in the trial. Patients were excluded if they had received OADs within 2 months of the trial, were pregnant or breast feeding, suffered from proliferative retinopathy, uncontrolled hypertension, recurrent major hypoglycaemia, impaired renal or hepatic function, cardiac problems, or if they received a total daily basal insulin dose $>$ 100 IU/day.

Study Design

Patients were randomized (2 : 1) to receive either insulin detemir (Levemir™, Novo Nordisk A/S; 100 U/ml) or NPH insulin (isophane human insulin, Novo Nordisk

A/S, Copenhagen, Denmark; 100 IU/ml) as basal insulin for 26 weeks. Patients receiving more than one basal insulin injection per day prior to the trial received twice-daily (before breakfast and at bedtime) injections following randomization. All other patients, including those receiving biphasic (premixed insulin) prior to the trial, received a once-daily basal insulin injection (at bedtime). For all patients, insulin aspart (NovoRapid®, Novo Nordisk A/S, 100 U/ml) was administered immediately prior to each main meal. All insulin preparations were injected subcutaneously (basal insulin, abdomen or thigh; bolus insulin, abdomen) using a NovoPen® 3 device (Novo Nordisk A/S). Throughout the trial, basal insulin doses were optimized according to self-measured blood glucose (SMBG) values. Patients randomized to insulin detemir were initiated on 50% of their pretrial basal insulin dose whereas those randomized to NPH insulin continued with their pretrial basal insulin dose. During the trial, patients were instructed to aim for the following SMBG levels: prebreakfast, 4–7 mmol/l; nocturnal (02 : 00–04 : 00), 4–7 mmol/l; postprandial (90 min after meal), <10 mmol/l. If a patient did not reach these SMBG targets on a once-daily basal insulin regimen (either with insulin detemir or NPH insulin), and further dose escalations were inadvisable, they were transferred to a twice-daily basal insulin regimen with appropriate dose adjustments.

Methods

HbA_{1c} (reference range of assay: 4.3–6.1%) was determined in whole blood by high-performance liquid chromatography (HPLC) using a Bio-Rad Variant™ instrument. Clinic fasting plasma glucose (FPG) concentrations were determined by a hexokinase method. These and standard safety determinations (haematology and biochemistry) were performed by a central laboratory (Laboratorium für Klinische Forschung GmbH, Raisdorf, Germany). One Touch Profile® blood glucose meters (LifeScan, Neckargemünd, Germany) calibrated for blood glucose measurements were used for all SMBG assessments. HbA_{1c} and FPG were measured at the screening visit and after 13 and 26 weeks of treatment. Patients performed 9-point SMBG profiles before randomization and after 13 and 26 weeks of treatment. In addition, fasting SMBG levels were measured on each of the final 7 days of treatment.

Adverse events, coded according to the Novo Nordisk Adverse Reaction Dictionary, were monitored throughout the study period and, where necessary, were treated by established methods of care. Treatment emergent adverse events were defined as events occurring from the first day of dosing to 7 days following the final dose. Clinical laboratory assessments (haematology and biochemistry), physical examinations, fundoscopy/fundus photography, 12-lead electrocardiogram (ECG), and measurements of vital signs (blood pressure and pulse) and body weight were performed at screening, randomization and after 13 and 26 weeks of treatment (as appropriate).

Hypoglycaemic episodes were classified as major when a subject was unable to treat him/herself, as minor if blood glucose concentration was <2.8 mmol/l but no assistance was required, and as symptoms only if the episode was not confirmed by a blood glucose measurement. Nocturnal hypoglycaemia was defined as any hypoglycaemic episode that occurred between the hours of 23 : 00 and 06 : 00.

Statistical Analyses

All analyses were based on the intention-to-treat (ITT) analysis set, which included all patients randomized and exposed to at least one dose of study drug. The primary endpoint, HbA_{1c} (%) after 26 weeks of treatment, was evaluated by an analysis of variance (ANOVA) model, with treatment and country as fixed effects and covariate adjustment for baseline values. The study had sufficient power (85%) to detect an average difference of 0.4% in HbA_{1c} between treatment groups. A 95% two-sided confidence interval (CI) was constructed for the difference between the treatment group means (insulin detemir – NPH insulin); insulin detemir was deemed non-inferior if the upper limit of the 95% CI was <0.4% (absolute). Treatments were considered comparable if the non-inferiority criterion was fulfilled.

The influence of the number of basal insulin injections per day on HbA_{1c} levels following 26 weeks of treatment was investigated by including the number of basal injections as a factor in the ANOVA model used for the primary endpoint while successively including and excluding the treatment by number of basal injections interaction term.

Change in body weight (both with and without adjustment for change in HbA_{1c} concentration) and FPG levels following 26 weeks of treatment were analysed using a similar ANOVA model to that used for the primary endpoint. The 9-point SMBG profiles, measured after 26 weeks of treatment, were analysed using a repeated measures ANOVA model. Within-subject day-to-day variation in fasting SMBG levels during the last 7 days of treatment was compared between the two treatment groups using variance component models. To estimate the relative risk of hypoglycaemia, all hypoglycaemic

episodes occurring during the maintenance period were analysed as recurrent events using a gamma frailty model with treatment group as covariate. Nocturnal hypoglycaemic episodes were analysed separately (as above). All results are presented as means ± SD unless otherwise specified. The significance level was 5%.

Results

Overall, the two treatment groups were evenly matched with respect to demographic and baseline characteristics (table 1). Of those receiving treatment, 315 of 341 patients (92.4%) in the insulin detemir group and 156 of 164 patients (95.1%) in the NPH insulin group completed the trial. A similar proportion of patients withdrew from each treatment group due to ineffective therapy, adverse events and non-compliance with the protocol. The overall nature and proportion of different pretrial insulin regimens was similar for the two treatment groups. At the end of the treatment period, the percentage of patients receiving once or twice-daily basal insulin injections was 39 and 61%, respectively, for the insulin detemir group, and 41% and 59%, respectively, for the NPH insulin group.

Glycaemic Control

Significant reductions from baseline in HbA_{1c} levels were observed for insulin detemir (0.2%-points; $p = 0.004$) and NPH insulin (0.4%-points; $p = 0.0001$) following 26 weeks of treatment, with mean HbA_{1c} concentrations comparable for the two basal insulin regimens at the end of the trial (insulin detemir, 7.6%; NPH insulin, 7.5%) (table 2). The number of basal insulin injections administered per day (1 or 2) did not significantly affect HbA_{1c} levels in either treatment group ($p = 0.50$).

After 26 weeks of treatment, mean FPG levels were significantly reduced from baseline by insulin detemir (by 0.5 mmol/l; $p = 0.027$) and NPH insulin (by 0.6 mmol/l; $p = 0.026$); mean FPG concentrations did not differ significantly between the two treatment groups at the end of the treatment period ($p = 0.66$) (table 2). Moreover, no significant difference was observed in the overall shapes of the 9-point SMBG profiles for the two treatments, measured after 26 weeks of treatment ($p = 0.58$) (figure 1). By contrast, within-subject day-to-day variation in fasting blood glucose concentrations, based on measurements (SMBG) recorded during the final week of the 26-week treatment period, was significantly lower for insulin detemir than for NPH insulin (SD: insulin detemir, 1.3 mmol/l; NPH insulin, 1.4 mmol/l; $p = 0.021$) (table 3).

Insulin Doses

Mean doses of basal and total insulin during the 26-week treatment period are shown in figure 2. After 26 weeks of

Table 1 Demographics and baseline characteristics of patients with type 2 diabetes exposed to trial medication

	Insulin detemir	NPH insulin
Number of patients exposed	341	164
Ethnic origin		
Caucasian	338	162
Asian-Pacific islander	3	2
Gender (male/female)	165/176	93/71
Age (years)	60.6 ± 8.7	60.0 ± 8.4
Weight (kg)	85.7 ± 14.9	89.3 ± 17.5
BMI (kg/m^2)	30.1 ± 5.0	31.1 ± 5.8
Duration of type 2 diabetes (years)	12.9 ± 7.4	13.7 ± 8.0
HbA_{1c} (%)	7.9 ± 1.3	7.8 ± 1.3
FPG (mmol/l)	10.1 ± 3.32	10.4 ± 3.42
Pretrial insulin regimen (%)		
Basal-bolus	86	88
Biphasic (premixed)	14	12
Mean daily pretrial insulin dose‡		
Basal	27.8 ± 14.7*	28.0 ± 15.4†
Bolus	33.6 ± 19.2*	34.8 ± 19.9*

Values are absolute numbers, percentages or means ± SD. NPH, neural protamine hagedorn.
*Units (U).
†International units (IU).
‡Does not include patients treated with premixed insulin formulations.

Table 2 Glycaemic control after 26 weeks of treatment

	Insulin detemir	NPH insulin	Insulin detemir − NPH insulin, mean difference [95% CI]	Significance
HbA_{1c} (%)	7.6 ± 0.1 (n = 315)	7.5 ± 0.1 (n = 155)	0.16 [0.003; 0.312]	Insulin detemir non-inferior*
FPG (mM)	9.7 ± 0.2 (n = 309)	9.6 ± 0.3 (n = 152)	0.11 [−0.400; 0.630]	p = 0.66†

Values are estimated (least square) means ± SE. NPH, neural protamine hagedorn.
*Non-inferiority criterion: upper limit of 95% CI < 0.4% HbA_{1c}.
†ANOVA with treatment and country as fixed effects and covariate adjustment for baseline.

treatment, mean daily doses of insulin detemir and NPH insulin were 36.4 U and 35.3 IU, respectively. Mean daily doses of bolus insulin (insulin aspart) after 26 weeks of treatment were 40.2 U for the insulin detemir group and 35.8 U for NPH insulin group.

Hypoglycaemic Episodes

The percentage of patients who experienced hypoglycaemic episodes during the final 22 weeks of treatment was comparable for the two treatment groups (table 4). Very few patients (<2%) in either treatment group experienced a major hypoglycaemic episode. The relative risks of experiencing hypoglycaemic episodes over a 24-h period or a nocturnal hypoglycaemic episode were also similar for the two treatments (table 4). The relative risk of experiencing a major hypoglycaemic episode was not calculated in the present study due to a very low number of episodes.

Body Weight

Patients treated with insulin detemir gained significantly less weight during the 26-week treatment period compared with those receiving NPH insulin [mean difference in body weight (adjusted for body weight at baseline): −0.79 kg (−1.44; −0.14), p = 0.017, see figure 3]. This difference in weight gain was not due to individual changes in HbA_{1c} levels; with adjustment for change from baseline in HbA_{1c}, the mean difference in body weight (insulin detemir − NPH insulin) was −0.77 kg (−1.41; −0.12) (p = 0.020).

Evaluation of Safety

Insulin detemir and NPH insulin were generally well tolerated, with the overall incidence, pattern and severity of adverse events similar for the two treatment groups. For both treatments, the majority (>90%) of adverse events were of mild or moderate severity. Only a small proportion of adverse events (5% of patients on insulin detemir and 3% of patients on NPH insulin) were considered possibly or probably related to the trial product. Of these, gastro-intestinal disorders (pain, nausea and vomiting) were most common in patients receiving insulin detemir (1.5% of patients), whereas skin and appendage disorders (pruritus, rash erythematous and urticaria) were most frequent in patients receiving NPH insulin (1.8% of patients). Only one serious adverse event (hypoglycaemia), experienced by

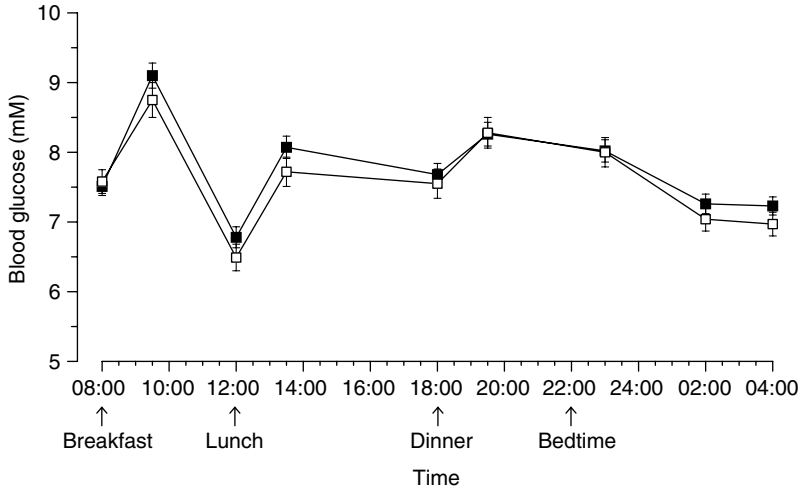

Fig. 1 Mean 9-point blood glucose profiles measured during the final week of treatment with insulin detemir (■) or neural protamine hagedorn (NPH) insulin (□). Bars indicate SEM.

Table 3 Within-subject day-to-day variation in self-measured fasting blood glucose

	Insulin detemir (n = 308)	NPH insulin (n = 152)	p-value
SD (CV%)	1.3 (17.6%)	1.4 (18.5%)	0.021

Mean self-measured fasting blood glucose concentrations during the final 7 days of treatment: Insulin detemir (7.5 mmol/l) and NPH insulin (7.6 mmol/l). NPH, neural protamine hagedorn.

a subject receiving NPH insulin, was considered related to trial product. One death occurred during the trial (a subject in the insulin detemir group with a history of coronary heart disease), but this was not considered related to the trial product.

No clinically relevant findings in clinical laboratory tests, physical examinations, vital signs, fundoscopy/fundusphotograpy or 12-lead ECG examinations were observed for either treatment group.

Discussion

The present study in patients with type 2 diabetes compared the efficacy and safety of a basal-bolus insulin regimen comprising either insulin detemir or NPH insulin in combination with mealtime insulin aspart.

Following 26 weeks of treatment, comparable glycaemic control was observed for the two treatment regimens; insulin detemir and NPH insulin reduced HbA_{1c} and FPG levels by a similar extent and had closely matched self-measured 9-point blood glucose profiles.

Consistent with studies in patients with type 1 diabetes [17–21], a notable difference between insulin detemir and NPH insulin was the significantly lower within-subject day-to-day variation in fasting blood glucose levels associated with insulin detemir. Glycaemic variability could arise from erratic compliance to insulin treatment or could, for example, be due to recurrent lapses of coexisting illnesses or drug–drug interactions. However, the reduced within-subject variability associated with insulin detemir is thought to be due to a more consistent release of insulin from the subcutaneous depot because, in contrast to NPH insulin, insulin detemir remains in solution [13]. This characteristic also circumvents the inconsistency in administered dose that arises from inadequate resuspension of insulin preparations (e.g. NPH insulin) prior to injection [11]. To our knowledge, insulin detemir is the first basal insulin to demonstrate a within-subject variability in fasting blood glucose that is significantly lower than NPH insulin in patients with type 2 diabetes. This attribute may be of particular benefit in the treatment of type 2 diabetes because long-term glucose instability, rather than the severity of hyperglycaemia or progression to high or low FPG levels over time, is a predictor of cardiovascular-related mortality in elderly (>75 years) patients [28]. Furthermore, the lower day-to-day variation and hence more predictable glycaemic response to insulin detemir should increase confidence in titrating insulin doses to achieve more ambitious blood glucose targets due to a reduced fear of hypoglycaemia [29].

The lower within-subject variability associated with insulin detemir is anticipated to reduce the frequency by which blood glucose levels fall into the hypoglycaemic

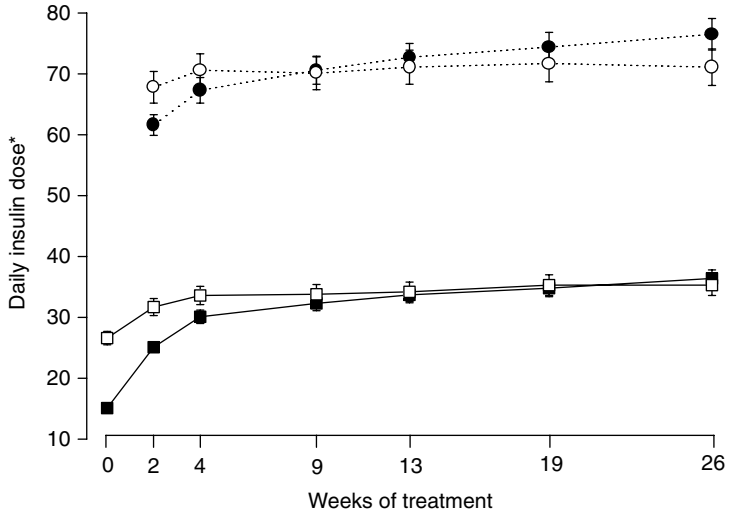

Fig. 2 Mean insulin detemir (■), neural protamine hagedorn (NPH) insulin (□) and total insulin doses [insulin detemir + insulin aspart (●), NPH insulin + insulin aspart ( )] over the 26-week treatment period. Bars indicate SEM. *U (insulin detemir and insulin aspart) and IU (NPH insulin).

Table 4 Hypoglycaemic episodes during the final 22 weeks of treatment

	Insulin detemir (n = 341)			NPH insulin (n = 164)			Insulin detemir/NPH insulin	
Hypoglycaemic episodes	**N**	**(%)**	**E**	**N**	**(%)**	**E**	**Relative risk [95% CI]**	**p-value**
Nocturnal	52	(15.8)	166	38	(23.6)	80	1.02 [0.55; 1.89]	0.95
Total	152	(46.2)	1218	80	(49.7)	708	0.84 [0.52; 1.36]	0.48

NPH, neural protamine hagedorn; N, number of patients experiencing at least one hypoglycaemic episode; %, proportion of patients experiencing a hypoglycaemic episode; E, number of episodes.

range (<2.8 mmol/l). In keeping with this, a lower proportion of patients experienced episodes of hypoglycaemia in the insulin detemir group. However, the risks of overall and nocturnal hypoglycaemia were not significantly different for insulin detemir and NPH insulin. This may be related to the generally lower overall incidence of hypoglycaemia in type 2 diabetes (compared to type 1 diabetes [30]) and the fact that the study was powered to detect differences between treatment groups in HbA_{1c} rather than hypoglycaemia.

Despite comparable levels of glycaemic control, patients administering insulin detemir gained significantly less body weight than those receiving NPH insulin, corroborating previous findings for patients with type 1 diabetes [17–19,21]. The mechanism(s) behind this reduced weight gain are currently unknown. Because reductions in both weight gain and hypoglycaemic risk are a regular finding of clinical studies with insulin detemir [17–19,21], we have proposed that the lower weight gain associated with insulin detemir may result from a decreased need to counteract hypoglycaemia through defensive, between-meal snacking, although recognize that other yet unknown factors may also contribute. In the current study, the risk of hypoglycaemia was not significantly different between the two treatment groups. However, a lower proportion of patients experienced hypoglycaemic episodes in the insulin detemir group. It could therefore be speculated that the reduced weight gain observed for insulin detemir resulted, at least in part, from a reduction in defensive, between-meal snacking. However, further studies are required to confirm or refute this hypothesis.

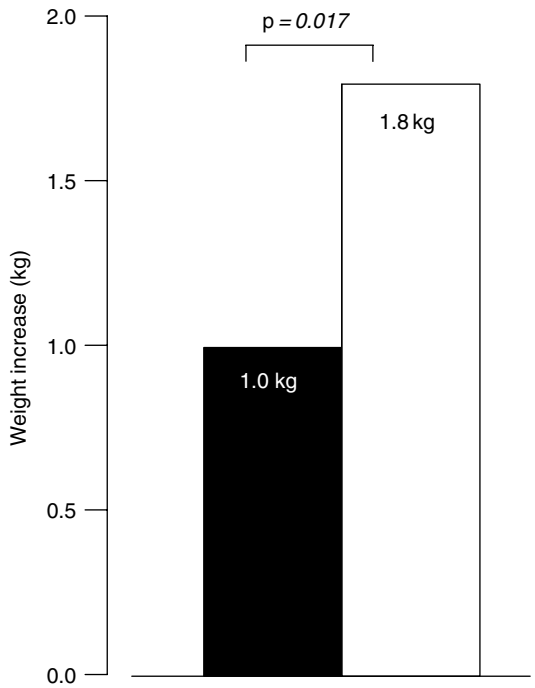

Fig. 3 Mean change in body weight following 26 weeks of treatment with insulin detemir (■) or neural protamine hagedorn (NPH) insulin (□). Mean weight changes are adjusted for baseline and country.

Weight gain can be a major drawback of long-term intensive insulin therapy [24] as the accumulation of visceral fat (central obesity), for example, is closely associated with insulin resistance, hypertension and dyslipidaemia [31–33]. Weight-induced changes in lipid profile and blood pressure increase the risk of coronary artery disease [34,35]. Moreover, studies indicate a higher prevalence of a number of complications associated with type 2 diabetes in obese vs. non-obese patients [36]. Accordingly, a basal insulin, such as insulin detemir, that is associated with less weight gain could offer an important advantage in the management of type 2 diabetes.

In summary, patients with type 2 diabetes receiving 26 weeks of once- or twice-daily basal injections with insulin detemir plus insulin aspart at mealtimes experienced comparable glycaemic control but significantly lower within-subject variability in fasting blood glucose and less weight gain compared to patients treated with NPH insulin and insulin aspart. Insulin detemir was well tolerated and had a similar safety profile to NPH insulin. Thus, insulin detemir represents a promising new basal insulin that could offer distinct advantages over NPH insulin in the treatment of patients with type 2 diabetes.

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