ORIGINAL ARTICLE

Long-acting insulin analogue detemir compared with NPH insulin in type 1 diabetes

A systematic review and meta-analysis

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KEY WORDS

basal-bolus therapy, detemir, fasting plasma glucose, HbA_{1c}, NPH insulin

ABSTRACT

INTRODUCTION Although numerous studies showed an improvement in glycemic control in type 1 diabetic patients treated with long-acting insulin analogue detemir compared with Neutral Protamine Hagedorn (NPH) insulin, the beneficial effects of insulin detemir has not been confirmed by all investigators.

OBJECTIVES The aim of the study was to compare the effect of treatment with detemir insulin vs. NPH insulin on metabolic control, hypoglycemic episodes, and body weight gain in patients with type 1 diabetes by means of a systematic review and a meta-analysis.

METHODS The following electronic databases were searched up to November 2010: MEDLINE, EMBASE, and the Cochrane Library. Additional references were obtained from the reviewed articles. Only randomized controlled trials of at least 12-week duration with basal-bolus regimen therapies using detemir insulin vs. NPH insulin were included.

RESULTS The analysis included 10 studies involving 3825 patients with type 1 diabetes. Combined data from all trials showed a statistically significant reduction in hemoglobin A_{1c} (HbA_{1c}) (weighted mean difference: [WMD] –0.073, 95% CI –0.135 to –0.011, $P = 0.021$) in the detemir group compared with the NPH group. There was also a significant reduction of fasting plasma glucose (FPG) (WMD –0.977 mmol/l, 95% CI –1.395 to –0.558, $P < 0.001$), all-day hypoglycemic episodes (relative risk [RR] 0.978, 95% CI 0.961–0.996), severe hypoglycemic episodes (RR 0.665, 95% CI 0.547–0.810), nocturnal hypoglycemic episodes (RR 0.877, 95% CI 0.816–0.942), as well as smaller body weight gain (WMD –0.779 kg, 95% CI –0.992 to –0.567) in patients using detemir insulin compared with those using NPH insulin.

CONCLUSIONS Basal-bolus treatment with insulin detemir, as compared with NPH insulin, provided a minor benefit in terms of the HbA_{1c} value and significantly reduced FPG in type 1 diabetic patients. Treatment with detemir insulin was also superior to NPH insulin in reducing the risk of all-day, nocturnal, and severe hypoglycemic episodes, with the added benefit of reduced weight gain.

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INTRODUCTION Current strategies for the treatment of type 1 diabetes with insulin involve the use of basal-bolus therapy to maintain near normoglycemia in order to prevent long-term complications.[1,2] The replacement of endogenous basal insulin is difficult to achieve with currently available human insulin preparations such as intermediate-acting Neutral Protamine Hagedorn (NPH) insulin. This insulin formulation is associated with a high day-to-day variation in insulin absorption of 20%–30% and a changing insulin concentration before each administration due to inadequate resuspension.[3] Furthermore, pronounced insulin peaks 5–7 hours after injection increase the risk of nocturnal hypoglycemia and the peak duration is too short to maintain glycemic control throughout the night.[4] These pharmacokinetic properties of NPH insulin may result in an increased risk of nocturnal hypoglycemic episodes and hyperglycemic escape before breakfast.

Intensified insulin regimens designed to maintain near-normoglycemia may be limited by the increased risk of hypoglycemia.[5] The NPH insulin profile may also force patients to increase calorie intake to counter an increased threat to hypoglycemia with resultant weight gain.[6]

Long-acting insulin analogue glargine and detemir more accurately reproduce the physiological basal insulin profile. Although both insulin analogues are safe and efficient in most patients with diabetes, some observations indicated that there are differences in their pharmacokinetics and pharmacodynamics.[7] Insulin detemir is a long-acting basal soluble acylated analogue.[8] Detemir exists predominantly in a hexameric state at the injection site and binds to albumin via the fatty acid chain leading to slow dissociation of the analogue.[9] This stable profile of insulin detemir contrasts with that of insulin glargine, which precipitates from its acidic solution in the subcutaneous tissue.[7] The combination of protracted absorption and delayed action provides a smoother and more protracted action profile than NPH insulin. Therefore, insulin detemir may provide more consistent insulin levels and more predictable glucose control with less day-to-day variation and fewer hypoglycemic episodes than NPH insulin. Moreover, these pharmacological properties have been suggested to be responsible for significantly lower within--subject variability than insulin glargine.[10,11] However, several studies indicated that insulin glargine may produce a flatter glycemic profile than insulin detemir. Some authors showed that in patients with type 1 diabetes insulin detemir had similar effects to those of glargine during the initial 12 hours after administration, but the effects were lower during 12–24 hours.[12] Other studies reported that insulin glargine showed lower post-dinner and bedtime glucose levels in type 1 diabetes than insulin detemir.[13]

Several studies comparing the effect of basal--bolus insulin detemir or glargine vs. NPH insulin reported an improvement in hemoglobin A_{1c} (HbA_{1c}) in patients with type 1 diabetes using long-acting insulin analogues;[14-16] others did not report any differences.[17-19] In the study by Monami et al.,[20] a meta-analysis comparing insulin glargine and detemir vs. NPH insulin in type 1 diabetes concluded that the effect of long-acting insulin analogues on HbA_{1c} is superior to NPH insulin. However, in a separate analysis only insulin detemir reduced HbA_{1c} levels. The effect was not observed in patients using glargine. The key difference between both analogues is that insulin detemir demonstrated significantly less variability in metabolic effect than insulin glargine, which is of potential clinical relevance.[21] Furthermore, meta-analysis by Monami et al.[20] was based on limited search, omitting such important databases as EMBASE and Cochrane Central. Therefore, we have decided to present the results of our systematic review and meta-analysis of studies that compared insulin detemir and NPH insulin in type 1 diabetes.

METHODS

Inclusion and exclusion criteria

The systematic review and meta-analysis were performed according to Cochrane Collaboration standards.[22] Studies included in the review had to be randomized controlled trials (RCTs) with a duration of at least 12 weeks, comparing the effect of basal-bolus therapy with long-acting insulin analogue detemir and NPH human insulin in patients with type 1 diabetes. All patients had a history of type 1 diabetes ≥1 year. Studies with a shorter disease duration were excluded due to there being no relevant information regarding HbA_{1c} values, which was the principle outcome variable used in assessing improvement in diabetes control.[23] The secondary outcome measures were: changes in fasting plasma glucose (FPG), weight, severe hypoglycemic episodes (as defined by the investigators), all-day hypoglycemic episodes, and nocturnal and severe nocturnal hypoglycemic episodes.

In all trials, basal insulin was combined with prandial insulin (human or short-acting analogue). Studies with different prandial insulins (human regular insulin and short-acting analogue) in treatment arms were excluded. Trials which were a follow-up of a previous study, without new randomization, were also excluded.

Search strategy

A search was performed, collecting all published randomized clinical trials on humans up to November 2010. The following electronic databases were systematically searched for relevant studies: MEDLINE (PubMed), EMBASE (Ovid), the Cochrane Controlled Trials Register, and the Cochrane Database of Systematic Reviews. The text word terms and medical subject headings (MeSH) used were: "diabetes type 1"; "diabetes mellitus", "type 1"; "type 1 diabetes mellitus"; "T1DM"; "basal-bolus"; "intensive insulin therapy*"; "multiple daily injection*"; "long-acting insulin analog*"; "detemir"; "B29-tetradecanoyl-Lys-B30-des-Ala-insulin*"; "tetradecanoyl-Lys(B29)-des-Ala(B30)-insulin"; "tetradecanoyllysyl(B29)-desalanyl (B30)-12C-Lys(B29)-DB30Ides-(B30)-insulin"; "Lys(B29)-tetradecanoyl-NN304"; "NN-304, NN 304"; "NPH"; and "human insulin". Furthermore, reference lists from original studies and review articles were screened. The Novo Nordisk Trial Registry (www.novonordisk trials.com) was searched for unpublished trials.

There was lack of limitation regarding the language of publication; however, some types of article (i.e., abstracts, letters to the editor, minutes of scientific meetings) were excluded from the analysis.

Data extraction

Two reviewers (AS, LG) independently screened the title and abstract of each reference identified by the search strategy. Data from full-length articles of all potentially relevant publications and unpublished trials from the Novo Nordisk Trial Registry website were examined to determine whether they met the inclusion criteria. The subsequent data extraction was

TABLE 1 Characteristics of the included trials

Author	Generation of randomization scheme	Allocation concealment	Blinding (yes/no/not reported)	ITT	Age, y, mean ±SD (range) detemir/NPH	Duration of intervention, mo	Detemir number of patients included (completed the study)	NPH number of patients included (completed the study)
Bartley et al.[24]	adequate (telephone randomization system)	adequate	no	no	35 (18–75) 35 (18–70)	24	331 (279)	164 (144)
Kølendorf et al.[25] (cross-over design)	lack of description	unclear	no	yes	Det/NPH: 38.5 ±12.3 NPH/Det: 39.9 ±12.4	4	Det/NPH: 66 NPH/Det: 64	
Pieber et al.[26]	adequate (central randomization)	adequate	no	yes	$Det_{mor + din}$: 39.0 ±12.4 $Det_{mor + bed}$: 40.4 ±11.4 NPH: 41.1 ±11.9	4	$Det_{mor + din}$: 139 (132) $Det_{mor+bed}$: 132 (122)	129 (125)
Robertson et al.[27]	adequate (block randomization 2:1, telephone randomization system)	adequate	no	yes	11.9 ±2.8 11.7 ±2.8	6	232 (226)	115 (109)
Russell-Jones et al.[28]	adequate (computerized randomization system, randomization 2:1)	adequate	no	yes	40.9 ±12.4 39.8 ±12.3	6	491 (465)	256 (235)
Vague et al.[29]	adequate (telephone randomization system)	adequate	no	no	38.9 ±13.3 41.8 ±14.2	6	301 (284)	146 (141)
Home et al.[30]	adequate (telephone randomization system)	adequate	no	yes	Det_{12h}: 40.9 ±13.0 $Det_{mor + bed}$: 41.3 ±11.4 NPH: 38.3 ±12.4	4	Det_{12h}: 137 $Det_{mor + bed}$: 139	132
NN304-1604[31]	lack of description (randomization 2:1)	unclear	no	no	13.2 (2.5) 14.1 (2.5)	6	57 (55)	29 (27)
NN304-1689[32]	lack of description (randomization 1:1 with age stratification)	unclear	no	yes	not reported	12	177 (164)	171 (160)
NN304-1476[33]	lack of description (randomization 2:1)	unclear	no	yes	42.4 (14.2) 41.8 (13.5)	11	196 (183)	98 (91)

Abbreviations: Det – detemir, ITT – intention-to-treat, NPH – Neutral Protamine Hagedorn, SD – standard deviation

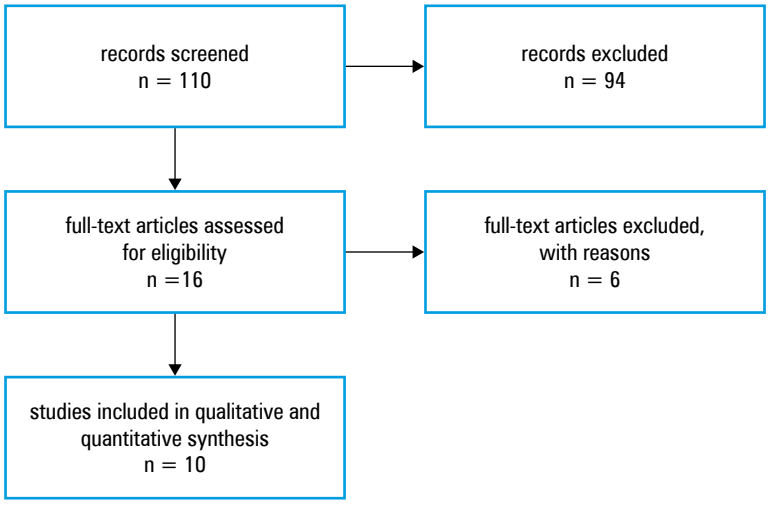

FIGURE 1 Diagram of data extraction

performed independently by 2 reviewers (AS, DG) using standard data extraction forms. Extracted data were compared to eliminate errors. Any differences in opinion were resolved by discussion with a third investigator (EP).

Study quality The quality of the studies that met the inclusion criteria was assessed independently by reviewers without blinding to authorship or journal. We examined the use of the following strategies associated with a good quality trial: 1) generation of allocation scheme; 2) allocation concealment; 3) blinding of participants, outcome assessors and data analysis (yes/no/not reported); 4) intention-to-treat analysis (yes/no); and 5) comprehensive follow-up. Allocation concealment was regarded as adequate when the randomization method used did not allow the investigator or the participant to identify or influence the intervention group before the entry of eligible participants into the study. When randomization was used, but no information about the method of randomization was available, the quality of allocation concealment was considered as unclear, and inadequate when inappropriate methods of randomization (e.g., alternate medical record numbers, unsealed envelopes, coin tossing) were used. In intention-to-treat (ITT) analysis, a "yes" response means that the authors had specifically reported undertaking this type of analysis and/or that our own study confirmed this finding. Conversely, "no" means that the authors did not report the use of ITT analysis and/or that we could not confirm its use in the study assessment. The patient follow-up completeness was assessed by determining the percentage of participants excluded or lost in follow-up. Only studies with >80% follow-up were included.

Statistical methods We used Comprehensive Meta-analysis ver. 2 software (Biostat; Englewood, New Jersey, United States). The weighted mean difference (WMD) between the treatment and control groups was selected to represent the difference in continuous outcomes.[22] For the dichotomous measures, the relative risk (RR) between the experimental and the control groups with 95% confidence intervals (CIs) was calculated. The weights given to each study are based on the inverse of the variance. For each total, the extent of inconsistency among the results (I^2) was given. In these cases, when significant heterogeneity (I^2 >50%) was observed, a random-effects model was used and the sensitivity analysis was conducted.

RESULTS

Description of studies Sixteen papers underwent further examination and 10 of them met our inclusion criteria: 7 full-text articles and 3 unpublished trials (FIGURE 1).[24-33] The characteristics of the studies included in the meta-analysis are summarized in TABLE 1. Altogether, 3825 patients with type 1 diabetes – 3048 adults[23-25,27-29] and 777 children[26,30,31] – were included in the analysis. All trials contained a sufficient proportion (≥80%) of participants in the final analysis. The duration of the intervention ranged from 4[24,25,29] to 24 months.[23] All included studies were multicenter. One study was crossover,[24] the remainder had a parallel-group

TABLE 2 Characteristics of the excluded trials

Author	Study design, reason(s) for exclusion
Hermansen et al.[14]	randomized controlled trial, different kinds of prandial insulin: aspart and regular
Hermansen et al.[15]	randomized controlled trial, too short a period of observation, different endpoints
Standl et al.[17]	follow-up study of randomized controlled trial of Standl et al.
De Leeuw et al.[18]	follow-up study of randomized controlled trial of Russell-Jones et al.
Sumnik et al.[34]	study without randomization
Braun et al.[35]	study without randomization
Wutte et al.[36]	study to evaluate the dose ratio of insulin detemir and NPH insulin
Bott et al.[37]	study to evaluate the pharmacodynamic and pharmacokinetic effect of insulin detemir
Palmer et al.[38]	study to evaluate the cost-effectiveness of insulin detemir
Dornhorst et al.[39]	study without randomization
Pieber et al.[40]	study to evaluate insulin detemir vs. insulin glargine
Danne et al.[41]	study to evaluate insulin detemir vs. insulin glargine
NN304-1582[42]	unable to perform meta-analysis due to lack of data

TABLE 3 Insulin detemir vs. NPH insulin in patients with type 1 diabetes

Outcome	RCT, n	Detemir, n	NPH, n	Statistical method	Model	I^2	Effect size (95% CI)	*P*
HbA_{1c}, %	10	2413	1345	WMD	fixed	0	–0.073 (–0.135; –0.011)	0.021
FPG, mmol/l	10	2405	1343	WMD	random	66.5	–0.977 (–1.395; –0.558)	<0.001
body weight, kg	6	1694	905	WMD	fixed	0	–0.779 (–0.992; –0.567)	<0.001
hypoglycemic episodes, all	8	1966	1130	RR	fixed	26	0.978 (0.961; 0.996)	0.016
hypoglycemic episodes, major	8	2062	1087	RR	fixed	0	0.665 (0.547; 0.810)	<0.001
nocturnal hypoglycemic episodes, all	8	2103	1201	RR	random	51	0.877 (0.816; 0.942)	<0.001
nocturnal hypoglycemic episodes, major	6	1723	919	RR	fixed	52	0.617 (0.430; 0.883)	0.008
					random		0.687 (0.392; 1.204)	0.189

Abbreviations: CI – confidence interval, FPG – fasting plasma glucose, HbA_{1c} – hemoglobin A_{1c}, RCT – randomized controlled trial, RR – relative risk, WMD – weighted mean difference, others – see TABLE 1

design.[23,25-30] All studies were open-label, as detemir and NPH are visually distinguishable and patients self-administered insulin. A double-dummy technique was considered unnecessary. There was considerable clinical heterogeneity among the trials with regard to the baseline FPG, hypoglycemic episodes (all), nocturnal hypoglycemic episodes (all), and nocturnal hypoglycemic episodes (severe). In all studies except one,[28] aspart insulin was used as prandial insulin.

There was unclear allocation concealment in 1 full-length article[21] and in all 3 unpublished studies.[30-32] In 7 papers, the authors used ITT analysis of categorical data.[24-27,29,31,32] In 2 other studies[23,28] the analysis of continuous data was based on the available case analysis. Per protocol analysis was performed in 1 clinical trial.[30] In all unpublished studies,[30-32] there was no description of randomization. Withdrawals and dropouts were described adequately in all full-length studies,[23-29] but there was no description of withdrawals in the clinical trial reports.[30-32] The excluded trials[34-41] and the reasons for exclusion are summarized in TABLE 2.

HbA_{1c} In 5 studies, detemir was significantly better than NPH insulin,[23-26,29] and in 5 studies it was not inferior to NPH insulin,[27,28,30-32] in terms of HbA_{1c} improvement. A meta-analysis of data from 3758 participants showed a significant reduction in HbA_{1c} levels (WMD –0.073, 95% CI –0.135 to –0.011, $P = 0.021$) for patients managed with insulin detemir compared with patients treated with NPH insulin (TABLE 3, FIGURE 2). The included studies were homogenous ($I^2 = 0\%$). Statistically significant effect was noticed in adults (7 RCTs; WMD –0.084, 95% CI –0.150 to –0.019, $P = 0.011$), but not in children (3 RCTs; $P = 0.792$); in patients with baseline HbA_{1c} ≥8 mg% (7 RCTs; WMD –0.102, 95% CI –0.172 to –0.032, $P = 0.004$), but not in patients with a better baseline glycemic control (3 RCTs; $P = 0.684$);

Study	Sample size		Statistics for each study			
	detemir	NPH	difference in means	lower limit	upper limit	*P*
Bartley et al.[24]	320	159	–0.220	–0.408	–0.032	0.022
Home et al.[30]	267	125	–0.180	–0.348	–0.012	0.035
Kolendorf et al.[25]	125	127	0.000	–0.215	0.215	1.000
NN304-1476[33]	195	98	0.040	–0.128	0.208	0.641
NN304-1604[31]	55	27	0.100	–0.646	0.846	0.793
NN304-1689[32]	177	170	0.120	–0.360	0.600	0.624
Pieber et al.[26]	271	129	–0.060	–0.248	0.128	0.531
Robertson et al.[27]	232	115	–0.000	–0.218	0.218	1.000
Russel-Jones et al.[28]	491	256	–0.120	–0.272	–0.032	0.122
Vague et al.[29]	280	139	–0.040	–0.194	0.114	0.610
total	2413	1345	–0.073	–0.135	–0.011	0.021

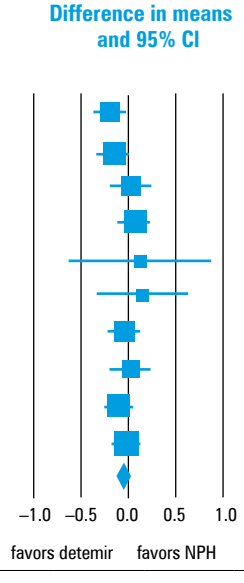

FIGURE 2 Detemir vs. NPH insulin: HbA_{1c}

Study	Sample size		difference in means	Statistics for each study		P
	detemir	NPH		lower limit	upper limit	
Bartley et al.[24]	318	158	–1.080	–1.979	–0.181	0.019
Home et al.[30]	267	125	–1.900	–3.023	–0.777	0.001
Kolendorf et al.[25]	125	127	–0.270	–0.439	–0.101	0.002
NN304-1476[33]	195	98	–0.580	–1.090	–0.070	0.026
NN304-1604[31]	55	27	–1.120	–2.529	0.289	0.119
NN304-1689[32]	177	170	–0.630	–2.510	1.250	0.511
Pieber et al.[26]	271	129	–1.530	–2.422	–0.638	0.001
Robertson et al.[27]	232	115	–1.300	–2.360	–0.240	0.016
Russel-Jones et al.[28]	491	256	–1.460	–2.390	–0.530	0.002
Vague et al.[29]	274	138	–0.760	–1.637	0.117	0.089
total	2405	1343	–0.977	–1.395	–0.558	0.000

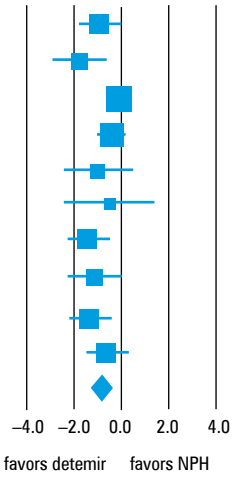

FIGURE 3 Detemir vs. NPH insulin: fasting plasma glucose

Study	Events/Total		risk ratio	Statistics for each study		P
	detemir	NPH		lower limit	upper limit	
Bartley et al.[24]	49/331	42/164	0.578	0.400	0.853	0.003
Home et al.[30]	17/273	10/127	0.791	0.373	1.678	0.541
Pieber et al.[26]	10/271	4/129	1.190	0.380	3.723	0.765
Russel-Jones et al.[28]	31/491	22/256	0.735	0.435	1.242	0.250
Vague et al.[29]	24/284	21/141	0.567	0.327	0.983	0.043
Kolendorf et al.[25]	19/125	33/128	0.590	0.355	0.980	0.041
Robertson et al.[27]	37/232	23/115	0.797	0.498	1.276	0.345
NN304-1604[31]	5/55	3/27	0.818	0.211	3.173	0.772
total	192/2062	158/1087	0.665	0.547	0.810	0.000

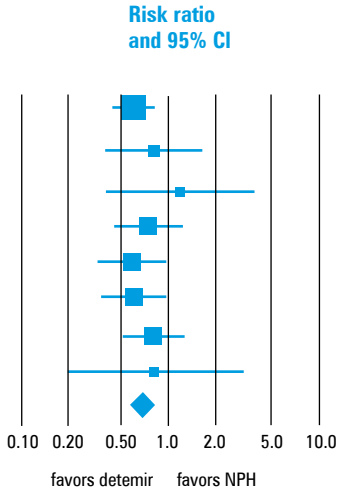

FIGURE 4 Detemir vs. NPH insulin: major hypoglycemias

in studies lasting not more than 6 months (7 RCTs; WMD –0.076, 95% CI –0.148 to –0.004, $P = 0.037$), but not in longer studies (3 RCTs, $P = 0.603$).

Fasting plasma glucose In 7 studies FPG was significantly lower in the detemir group,[23-27,29,32] in 3 other trials[28,30,31] treatment with insulin detemir was no inferior to NPH insulin. Meta-analysis of 10 studies[23-32] (n = 3748) showed a statistically significant reduction of FPG in the detemir group compared with the NPH group (WMD –0.977 mmol/l, 95% CI –1.395 to –0.558, $P < 0.001$; FIGURE 3). The included trials were significantly heterogeneous ($I^2 = 66.5\%$) and the data were pooled in a random-effects model. We have searched for reasons of heterogeneity between studies, but were not able to identify them.

Hypoglycemic episodes All of the studies except 2 reported the number of patients with all-day hypoglycemic episodes[23-28,30,31] and nocturnal hypoglycemic episodes.[23-28,31,32] Meta-analysis of data from 3096 participants showed significant reduction of the number of patients with all-day hypoglycemic episodes in the detemir group compared with the NPH group (RR 0.978, 95% CI 0.961–0.996, $P = 0.016$), with an estimated risk difference (RD) of –0.02 (95% CI –0.037–0.003, $P = 0.02$). Pooled results from 3304 patients showed that lower number of participants managed with detemir had nocturnal hypoglycemic episodes, compared with participants treated with NPH (RR 0.877, 95% CI 0.816–0.942, $P < 0.001$), with an estimated RD of –0.076 (95% CI –0.116 to –0.036, $P < 0.001$).

Severe hypoglycemic episodes Data regarding hypoglycemic episodes (24 hours/diurnal) requiring assistance from another person was available from 8 studies.[23-30] A meta-analysis of data from 3149 participants showed 34% relative risk

Study	Sample size		Statistics for each study				Difference in means and 95% CI
	detemir	NPH	difference in means	lower limit	upper limit	P	
Bartley et al.[24]	320	159	–0.990	–1.847	–0.133	0.024	
Home et al.[30]	267	125	–0.730	–1.039	–0.421	0.000	
NN304-1476[33]	195	98	–0.920	–1.497	–0.343	0.002	
Pieber et al.[26]	139	129	–1.300	–2.066	–0.534	0.001	
Russel-Jones et al.[28]	491	256	–0.540	–0.978	–0.102	0.116	
Vague et al.[29]	282	138	–1.200	–2.763	0.363	0.132	
total	1694	905	–0.779	–0.992	–0.567	0.000	

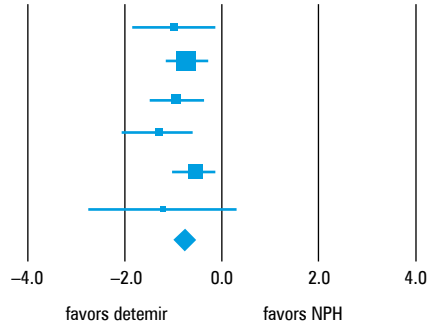

FIGURE 5 Detemir vs. NPH insulin: body weight

reduction of severe hypoglycemic episodes in patients managed with detemir compared with patients treated with NPH (RR 0.665, 95% CI 0.547–0.810, P <0.001; FIGURE 4), with an estimated RD of –0.028 (95% CI –0.049 to –0.007, P = 0.008).

Data for severe nocturnal hypoglycemia were available from 7 studies[23-27,29] and included 2642 participants. Results regarding severe nocturnal hypoglycemic episodes in 1 study[26] were not consistent with the outcomes from other studies, which resulted in significant heterogeneity (I^2 = 52%). Changing the data model from fixed (RR 0.617, 95% CI 0.430–0.883, P = 0.008) to random effect resulted in a statistically nonsignificant result (RR 0.687, 05% CI 0.392–1.204, P = 0.189).

Body weight Pooled results from 6 trials[23,25,27-29,32] including 2599 participants showed significantly lower weight gain in the detemir group compared with the NPH group (WMD –0.779 kg, 95% CI –0.992 to –0.567, P <0.001; FIGURE 5).

DISCUSSION

The meta-analysis resulted in a statistically significant decrease in HbA_{1c} levels and a significant reduction in FPG in the detemir group compared with the NPH group. Our analysis also showed a significant reduction in all hypoglycemic episodes, severe hypoglycemic episodes, and nocturnal hypoglycemic episodes.

Several limitations of our review must be addressed: some of the trials included had limitations in their methodology; in one full-length paper the allocation concealment was not clear;[24] and there was a lack of blinding in all of the studies. In all 3 clinical trial reports, there were no details regarding randomization and unclear allocation concealment. We incorporated 1 crossover study,[24] the others had a parallel design. In a crossover trial, treatment is assessed on the same patients allowing for comparison at the individual rather than the group level, and fewer patients are required to achieve a similar precision to a parallel group trial. In the interpretation of the analysis, the limitations of a crossover trial should be considered.

The analyses presented are in general agreement with the results of Monami et al.[20] Although our analysis and that by Monami et al.[20] seem to be similar, there are important differences: 1) Monami et al.[20] summarized the results of treatment with both long-acting insulin analogues – insulin detemir and insulin glargine; 2) our search was more systematic (not only MEDLINE, but also EMBASE and Cochrane databases); 3) we have included studies published up to November 2010; 4) we excluded trials,[17,18] which were follow-ups of previous studies[43,44] without new randomization; 5) we did not include the unpublished trial NN304-158 2[42] as we were unable to perform a meta-analysis due to lack of data; 6) we analyzed FPG as one of the principal endpoints.

The analysis of FPG is exclusively required when assessing the efficacy of basal insulin in basal-bolus therapy. The HbA_{1c} value is a metabolic outcome, related to many factors such as the kind of prandial and basal insulin, the method of insulin therapy, the method of insulin delivery, patient's adherence to a diabetes regime, blood glucose self-control etc. Moreover, it is well known that HbA_{1c} is clearly influenced by glucose tolerance indices such as FPG and postprandial plasma glucose, but a decrease in postprandial plasma glucose is influenced much more by an improvement in HbA_{1c} levels than a decrease in FPG. Compared to NPH insulin, detemir has a more prolonged and consistent duration of action. Bedtime dosing of NPH insulin may be associated with a waning effect in the early hours of the morning when hepatic gluconeogenesis and FPG levels are increased.[21]

Tight glycemic control is of great importance in diabetes management.[45] Diabetes duration and long-term HbA_{1c} are significant independent risk factors for long-term diabetic complications.[46-48] The Diabetes Control and Complications Trial showed that 1% HbA_{1c} increase causes 30% rise in the risk of new microvascular complications or the progression of the existing ones.[49] Moreover, it was confirmed that the higher the HbA_{1c},

the greater the absolute benefit of HbA_{1c} reduction.[50] The advantage of about 0.1% reduction in HbA_{1c}, observed in our meta-analysis in the group treated with insulin detemir, probably cannot be noticed in individual patient, but may influence the incidence and prevalence of late complications in the whole population of diabetic patients.

Hypoglycemia remains a major barrier to optimal glycemic control in diabetic patients. In contrast to Monami et al.,[20] our meta-analysis confirmed that treatment with insulin detemir was associated with a significant reduction in all hypoglycemic episodes in comparison with NPH insulin. Thus, it may be due to the difference in inclusion criteria. Furthermore, we showed that 34% fewer patients that were managed with detemir had severe hypoglycemic episodes compared with patients treated with NPH. Fear of nocturnal hypoglycemia especially represents an obstacle to achieving ambitious glucose targets. Moreover, we found statistically significant benefits of insulin detemir over NPH insulin in terms of nocturnal hypoglycemia. The present study confirms that insulin detemir offers improved overnight control, with better FPG levels and less nocturnal hypoglycemia rates, than NPH insulin.

Our meta-analysis of body weight showed significant less weight gain in patients treated with insulin detemir. This finding is of clinical significance because the consequences of an unwanted body weight gain (a common complication of long-term intensive insulin therapy in patients with type 1 diabetes) are the development of central obesity and insulin resistance.[51]

In conclusion, compared with NPH insulin, the long-acting insulin analogue detemir used as basal insulin in basal-bolus therapy, provides a minor benefit in terms of the HbA_{1c} value and significantly reduces FPG in patients with type 1 diabetes. Moreover, treatment with detemir insulin decreases the risk of all-day, nocturnal, and severe hypoglycemic episodes, and also reduces weight gain.

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ARTYKUŁ ORYGINALNY

Zastosowanie długo działającego analogu insuliny detemir w porównaniu z insuliną NPH u pacjentów z cukrzycą typu 1

Przegląd systematyczny i metaanaliza

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SŁOWA KLUCZOWE

detemir, glikemia na czczo, HbA_{1c}, insulina NPH, terapia *basal-bolus*

STRESZCZENIE

WPROWADZENIE Wiele badań wskazuje na poprawę kontroli glikemii u pacjentów z cukrzycą typu 1 leczonych długo działającym analogiem insuliny detemir w porównaniu z insuliną Neutral Protamine Hagedorn (NPH), jednak korzystne działanie insuliny detemir nie zostało potwierdzone przez wszystkich badaczy.

CELE Celem pracy było porównanie wpływu leczenia insuliną detemir z wpływem leczenia insuliną NPH na kontrolę metaboliczną, epizody hipoglikemii i przyrost masy ciała u pacjentów z cukrzycą typu 1, z zastosowaniem przeglądu systematycznego i metaanalizy.

METODY Przeszukano następujące bazy danych do listopada 2010: MEDLINE, EMBASE oraz Cochrane Library. Dodatkowe informacje uzyskano z artykułów poglądowych. Do analizy włączano jedynie badania kliniczne z randomizacją, w których porównywano efekty stosowania przez co najmniej 12 tygodni insulin bazowych detemir *vs* NPH w schemacie wstrzyknięć *basal-bolus*.

WYNIKI Analiza objęła 10 badań z udziałem 3825 pacjentów z cukrzycą typu 1. Połączone dane ze wszystkich badań klinicznych wykazały statystycznie istotną redukcję hemoglobiny A_{1c} (HbA_{1c}) (średnia ważona różnic [*weighted mean difference* – WMD] –0,073; 95% CI od –0,135 do –0,011; $p = 0,021$) w grupie leczonej insuliną detemir w porównaniu z NPH. Ponadto u pacjentów leczonych insuliną detemir w porównaniu z grupą otrzymującą insulinę NPH stwierdzono istotne zmniejszenie: glikemii na czczo (WMD –0,977 mmol/l, 95% CI od –1,395 do –0,558, $p < 0,001$), wszystkich hipoglikemii w ciągu całego dnia (RR 0,978, 95% CI 0,961–0,996), epizodów ciężkiej hipoglikemii (RR 0,665, 95% CI 0,547–0,810), nocnych hipoglikemii (RR 0,877, 95% CI 0,816–0,942), jak również mniejszy przyrost masy ciała (WMD –0,779 kg, 95% CI od –0,992 do –0,567).

WNIOSKI Stosowanie u pacjentów z cukrzycą typu 1 insuliny detemir w schemacie *basal-bolus*, w porównaniu ze stosowaniem insuliny NPH, wiązało się z nieznacznym korzystnym wpływem na HbA_{1c} oraz istotnie zmniejszało glikemię na czczo. Ponadto leczenie insuliną detemir w porównaniu z insuliną NPH wpływało na redukcję ryzyka hipoglikemii ogółem, nocnych i ciężkich; u pacjentów leczonych insuliną detemir zaobserwowano również mniejszy przyrost masy ciała.

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