Long-acting insulin analogue detemir compared with NPH insulin in type 1 diabetes: a systematic review and meta-analysis

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CRD summary
The review found that detemir insulin provided a minor benefit in terms of HbA1c value and significantly reduced fasting plasma glucose in patients with type 1 diabetes compared with Neutral Protamine Hagedorn (NPH) insulin. Low methodological quality of the included studies means the reliability of the results is uncertain.

Authors’ objectives
To compare the effect of treatment with detemir insulin versus Neutral Protamine Hagedorn (NPH) insulin on metabolic control, hypoglycaemic episodes and body weight gain in patients with type 1 diabetes.

Searching
PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Database of Systematic Reviews were searched up to November 2010. Reference lists from original studies and review articles were screened for additional articles. The Novo Nordisk Trial registry (www.novonordisk-trials.com) was searched for unpublished trials. No language restrictions were applied and search terms used were reported.

Study selection
Randomised controlled trials (RCTs) of at least 12 weeks duration with basal bolus regimen therapies that used detemir insulin versus NPH insulin were included. Patients had to have type 1 diabetes for at least one year. Studies that used different prandial insulins (not combined with basal insulin) and also follow-up studies without new randomisation were excluded.

The primary outcome measure was glycated haemoglobin (HbA1c) concentration. Secondary outcomes were changes in fasting plasma glucose, weight, severe hypoglycaemic episodes, all-day hypoglycaemic episodes, and nocturnal or severe nocturnal hypoglycaemic episodes.

Mean participants age ranged from 11.7 to 42.4 years (where reported). Some trials targeted children or adolescents and others targeted adult populations. Duration of the intervention ranged from four to 24 months.

Two reviewers independently screened the studies for inclusion.

Assessment of study quality
Two reviewers independently assessed trial quality using criteria that included sequence generation, allocation concealment, blinding, whether an intention-to-treat analysis was performed and loss to follow-up.

Data extraction
Two reviewers extracted the data with standard data extraction forms and any differences were resolved by discussion with a third reviewer.

Mean differences were calculated for continuous outcomes and relative risk for dichotomous outcomes.

Methods of synthesis
Pooled weighted mean differences (WMD) for continuous data and Relative Risk (RR) for dichotomous data with their corresponding 95% confidence intervals (CI) were calculated. Heterogeneity was assessed using $I^2$; $I^2$ greater than 50% was considered evidence of significant heterogeneity. When heterogeneity was identified, a random-effects model was used and sensitivity analysis was performed.

Results of the review
Ten RCTs (nine parallel and one cross over design) were included in the review (3,825 patients; 3,048 adults and 777 children).
children). In four trials allocation concealment was unclear, and in one trial randomisation was unclear. There was a lack of blinding in all of the studies.

**HbA1c values** (10 RCTs): The meta-analysis showed a significant reduction of HbA1c levels in detemir insulin group compared with NPH insulin (WMD -0.073, 95% CI -0.135 to -0.011, p= 0.021; I² = 0%). Statistically significant effects that favoured detemir insulin were also found in adults, the population of patients with HbA1c above 8% and duration of intervention six months or less.

**Fasting Plasma Glucose** (10 RCTs): The meta-analysis showed a significant reduction in the detemir group compared with the NPH group; with significant heterogeneity (WMD -0.977mmol/l, 95% CI -1.395 to -0.558, p<0.001; I²=66.5%).

**Hypoglycaemic episodes** (eight RCTs): The meta-analysis showed that detemir group had a significant reduction of the number of patients with all-day hypoglycaemic episodes (RR 0.978, 95% CI 0.961 to 0.996, p=0.016), nocturnal hypoglycaemic episodes (RR 0.877, 95% CI 0.816 to 0.942, p<0.001) and severe hypoglycaemic episodes (RR 0.665, 95% CI 0.547 to 0.810, p<0.001). There was no statistically significant difference in severe nocturnal hypoglycaemic episodes between the two groups.

**Body weight** (six RCTs): Pooled results showed significant reduction in body weight gain in the detemir group compared with the NPH group (WMD -0.77kg, 95% CI -0.992 to -0.567, p<0.001).

**Authors' conclusions**

Compared with NPH insulin, detemir insulin provided a minor benefit in terms of HbA1c value and significantly reduced fasting plasma glucose in patients with type 1 diabetes. Treatment with detemir insulin was also superior to NPH insulin in reducing the risk of all-day, nocturnal and severe hypoglycaemic episodes and weight gain.

**CRD commentary**

The review question and inclusion criteria were clear. The authors used broad search terms, which were appropriate. Relevant databases were searched. No language restriction was applied, which reduced potential language bias. Two authors were involved in study selection, data extraction and quality assessment, which minimised potential error and bias.

Study quality was assessed using appropriate criteria. The authors acknowledged limitations of the included trials which meant that they were at high risk of bias. Studies were synthesised in meta-analyses and heterogeneity was explored. It was unclear whether the methods for inclusion of data from crossover trials were appropriate but as only one crossover trial was included it was unlikely that the conclusions were affected by this.

The authors’ conclusions reflect the evidence presented, but limitations in the quality of the included trials made the reliability of the findings uncertain.

**Implications of the review for practice and research**

The authors did not state any implications for practice or further research.

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