Long-acting insulin analogues NPH human insulin in type 1 diabetes: a meta-analysis
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CRD summary
The authors concluded that long-acting insulin analogues had a small effect on glycated haemoglobin and reduced the risk of severe and nocturnal hypoglycaemia compared with neutral protamine Hagedorn human insulin. In view of the limited search and differences in results between trials evaluating glycated haemoglobin, the authors' conclusions may not be reliable.

Authors' objectives
To compare the impact of long-acting insulin analogues and neutral protamine Hagedorn (NPH) human insulin on glycated haemoglobin (HbA1c), weight gain and incidence of hypoglycaemia in participants with type 1 diabetes.

Searching
MEDLINE was searched up to April 2008. Search terms were reported. A search for unpublished trials was carried out on ClinicalTrials.gov.

Study selection
Randomised controlled trials (RCTs) that compared long-acting insulin analogues plus prandial insulin with neutral protamine Hagedorn human insulin plus prandial insulin in patients with type 1 diabetes were eligible for inclusion. Included trials had to last at least 12 weeks. To be eligible, prandial insulin had to be comparable between both treatment arms. Outcomes eligible for inclusion were glycated haemoglobin (HbA1c) and body mass index (BMI) at the end of the trial, and incidence of hypoglycaemia (symptomatic, severe, nocturnal or all).

Included trials compared detemir or glargine insulin analogues, administered once or twice daily, with neutral protamine Hagedorn human insulin. Included trials duration ranged from 12 to 104 weeks. Where reported, the mean age of participants ranged from 11 to 42.9 years, duration of diabetes ranged from 0.3 to 18.5 years, baseline HbA1c ranged from 6.8 to 8.8%, and baseline BMI ranged from 15.4 to 27kg/m². The definition of a hypoglycaemic episode ranged from less than 2.0mmol/l to less than 4.0mmol/l. Both single and multi-centre trials were included.

Two authors independently selected the studies for review, with disagreements resolved through consultation with a third reviewer.

Assessment of study quality
The methodological quality of the included trials was assessed using the Jadad scale, a three item checklist assessing randomisation, blinding and withdrawals.

The authors did not state how the validity assessment was performed.

Data extraction
For continuous data, the post-intervention data for each group were extracted. For dichotomous data, the number of patients with at least one hypoglycaemic episode were extracted and used to calculate odds ratios (OR) with 95% confidence intervals (CI).

Two reviewers independently extracted the data, with conflicts resolved through discussion with a third reviewer.

Methods of synthesis
For continuous outcomes, pooled standardised mean differences (SMD) with 95% confidence intervals were calculated using a random-effects model. For dichotomous outcomes pooled odds ratios with 95% confidence intervals were calculated using the Mantel-Haenszel method. Separate analyses were carried out for the different types of long-acting
insulin analogues.

**Results of the review**
Twenty trials were included in the review (n=5,981 patients listed in individual trials but reported as totalling 6,178 in text and table). Eighteen trials were parallel design (n=5,601 patients) and two were crossover design (n=380 patients). Ten trials had adequate randomisation, 18 trials had adequate levels of drop-outs and 15 trials used intention-to-treat analyses.

Long-acting insulin analogues significantly reduced glycated haemoglobin (HbA\textsubscript{1c}) compared with neutral protamine Hagedorn human insulin (SMD -0.07, 95% CI -0.13 to -0.01%; 18 trials). Detemir and glargine insulin analogues did not significantly differ in their effect on HbA\textsubscript{1c}.

Detemir was associated with a significantly smaller increase in BMI trial endpoint compared with neutral protamine Hagedorn human insulin (SMD 0.26 kg/m\textsuperscript{2}, 95% CI 0.06 to 0.47; nine trials). Analyses could not be carried out for the impact of glargine on BMI.

Long-acting insulin analogues significantly reduced the risk of severe hypoglycaemia (OR 0.73, 95% CI 0.60 to 0.89; 15 trials) and nocturnal hypoglycaemia (OR 0.69, 95% CI 0.55 to 0.86; 13 trials), but not overall hypoglycaemic events, compared with neutral protamine Hagedorn human insulin.

**Authors' conclusions**
Long-acting insulin analogues had a small effect on glycated haemoglobin and reduced the risk of severe and nocturnal hypoglycaemia compared with neutral protamine Hagedorn human insulin.

**CRD commentary**
The review addressed a clear question with well-defined inclusion criteria. Only two databases were searched, so relevant data may have been missed. A search was conducted for unpublished data, minimising the risk of publication bias. However, it was unclear whether the search was restricted by language, so language bias could not be ruled out. Appropriate steps were taken in the study selection and data extraction processes to minimise the risk of reviewer error and bias. However, it was unclear whether these steps were also taken in the validity assessment process, so reviewer error and bias could not be definitively ruled out.

An appropriate validity assessment was carried out. However, information was not reported on blinding or the level of drop-out considered adequate. Therefore it was not possible to fully determine the quality of included trials. Also, the majority of the trials were industry funded (the authors disclosed that 18 out of 20 trials included in the review were funded by long-acting insulin analogue manufacturers). Statistical heterogeneity was not assessed. However, the forest plot for glycated haemoglobin indicated different directions of treatment. Therefore, it was unclear whether data were sufficiently homogenous to reliably pool.

In view of the limited search and differences in results between trials evaluating glycated haemoglobin, the authors' conclusions may not be reliable.

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

**Practice:** The authors stated that decisions to use the more expensive long-acting insulin analogues should take into account the costs of these drugs and the clinical benefits.

**Research:** The authors stated that further research is needed to determine whether the impact of long-acting insulin analogues on BMI is maintained in the long term.

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