A review of human and analogue insulin trials

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CRD summary
The author concluded that, for both type 1 and 2 diabetes, the most frequently seen benefits of insulin analogue regimens compared with human insulin are reduced hypoglycaemia and post-prandial glucose levels. The conclusions are consistent with the data presented but, owing to limited reporting of review methodology and the lack of a validity assessment, the reliability of these conclusions cannot be evaluated.

Authors' objectives
To assess the effects of rapid-acting insulin analogues and basal insulin analogues, alone and in combination, relative to human insulin in type 1 and type 2 diabetes mellitus.

Searching
PubMed was searched for relevant trials up to December 2005 (references dated 2006 covered publications of abstracts published earlier). The search terms were briefly indicated. In addition, the references of a published meta-analysis were checked and abstracts of the European Association for the Study of Diabetes and the American Diabetes Association (2003 to 2005) were searched. The insulin manufacturers Eli Lilly, Novo Nordisk and Sanofi-Aventis were contacted for abstract information and papers in press.

Study selection

Study designs of evaluations included in the review
Studies were eligible if they were randomised controlled trials. Except for comparisons where only few trials existed, intervention groups had to have at least 50 participants. Treatment duration had to be at least 3 months. Subgroup analyses of trials already included in the review were excluded. Trial durations were generally between 3 months and a year; only one trial lasted longer than a year.

Specific interventions included in the review
Trials were eligible if they compared analogue insulin with human insulin. For type 1 diabetes, trials of basal-bolus therapy were considered; for type 2 diabetes, trials of premixed, basal insulin or basal-bolus therapy were considered. Studies of continuous subcutaneous insulin infusion were not included. The included studies for type 1 diabetes compared rapid-acting insulin (lispro, aspart or glulisine) with human insulin; basal analogue insulin (glargine or detemir) with human basal insulin; or all-analogue insulin regimens (glargine and lispro or detemir and aspart) with all human insulin (NPH insulin and human insulin). The included studies for type 2 diabetes compared premix insulin analogue (aspart or lispro) with human insulin; basal insulin analogues (glargine or detemir) with NPH insulin; or rapid-acting insulin analogues (lispro or glulisine) with human insulin alongside basal-bolus therapy. Treatment duration ranged from 3 to 30 months.

Participants included in the review
Studies were eligible if they included patients with type 1 or type 2 diabetes mellitus. Several of the included studies were conducted on children and adolescents.

Outcomes assessed in the review
Studies were eligible if they reported the following clinical outcomes: glycated haemoglobin (HbA1c), fasting blood glucose (FBG), post-prandial blood glucose (PPG), hypoglycaemia or change in weight.

How were decisions on the relevance of primary studies made?
The author did not state how the studies were selected for the review, or how many reviewers performed the study selection.

Assessment of study quality
The author did not state how validity was assessed, or how many reviewers performed the validity assessment.
Data extraction
The author did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
How were the studies combined?
The data were summarised narratively in the tables and text.

How were differences between studies investigated?
Some differences between the studies were presented in the tables and discussed in the text.

Results of the review
Forty-two studies, and an additional four extension studies of trials already included were included (n=19,005), of which 27 were in type 1 diabetes and 15 in type 2 diabetes. Of the type 1 diabetes studies, eleven (plus two extension studies) investigated rapid-acting analogues (n=6,412), thirteen (plus one extension study) investigated basal analogues (n=5,093) and three investigated all analogue versus all human regimens (n=679). Of the type 2 diabetes studies, four (plus one extension study) investigated premix insulin analogues (n=864), seven investigated basal analogues (n=3,916) and four investigated basal-bolus therapy (n=2,041).

Type 1 diabetes.
When investigating rapid-acting insulin analogues compared with human insulin, the reduction in HbA1c was greater with insulin aspart in most trials (HbA1c lower by 0.12 to 0.16% in favour of aspart; significant for two of the three trials, as well as two extension studies), significant in one of seven trials of insulin lispro (lower by 0.2%, 12 months), and significant for one study of insulin glulisine (0.13%, 12 months). The majority of studies of insulin aspart or insulin lispro reported significantly lower rates of nocturnal hypoglycaemia with the analogues compared with human insulin, and some also reported lower rates of overall hypoglycaemia for insulin lispro. In most studies, significantly lower values of PPG levels were seen with insulin analogues than with human insulin.

For basal-bolus therapy using insulin detemir or insulin glargine (where doses were titrated to achieve glycaemic targets), no differences in HbA1c values were seen between the insulin analogue and NPH insulin (13 trials). Most phase III trials of glargine or detemir found significant reductions in hypoglycaemia, particularly nocturnal hypoglycaemia, for insulin analogues compared with NPH. Some of the trials of insulin detemir reported reduced within-person variability of FBG compared with NPH. Patients consistently showed less weight gain with insulin detemir than with NPH, and also with glargine in the one study where this outcome was measured.

Comparing all analogue with all human insulin regimens (three trials), a significantly larger decrease in HbA1c was seen in two of the three trials identified with the analogue regimens. Nocturnal hypoglycaemia was significantly lower with insulin glargine/insulin lispro than with NPH/human insulin and, overall, minor and nocturnal hypoglycaemia were significantly reduced with insulin detemir/insulin aspart compared with NPH/human insulin. PPG was significantly lower with the analogue regimens. With insulin detemir/insulin aspart, both within-person variation in blood glucose and weight gain were significantly less than with NPH/human insulin.

Type 2 diabetes.
For patients with type 2 diabetes, treatment with premix insulin analogues generally showed similar results in terms of HbA1c and hypoglycaemia compared with biphasic human insulin (four trials). PPG levels were significantly lower with the premix analogues.

For basal therapy used once or twice daily (seven trials), results for HbA1c were similar when comparing insulin glargine or insulin detemir with NPH insulin, but three trials showed significantly lower rates of hypoglycaemia with the analogues, two trials showed significantly lower PPG, and two trials showed less weight gain.

Four trials comparing rapid-acting analogues with human insulin in basal-bolus regimens gave mixed results with respect to HbA1c and hypoglycaemia, but PPG was significantly lower with the rapid-acting analogues. Two trials
studied basal analogues in basal-bolus therapy. One study compared insulin detemir with NPH, with both groups using insulin aspart, and found no differences in HbA1c, FBG or hypoglycaemia. The other study compared insulin detemir plus insulin aspart with NPH plus human insulin and found that nocturnal hypoglycaemia, weight gain and within-person variation of self-monitored glucose levels were significantly lower with the all-analogue regimen.

Authors' conclusions
In type 1 diabetes, the rapid-acting insulin analogues generally reduced hypoglycaemia and PPG in comparison with human insulin, while the basal analogues tended to reduce hypoglycaemia, particularly nocturnal hypoglycaemia. Weight gain may also be reduced with basal analogues compared with human basal insulin. In type 2 diabetes, premix rapid-acting analogues controlled PPG better than human insulin mixes. Basal analogues used as basal only therapy reduced hypoglycaemia significantly more than NPH insulin.

CRD commentary
This review had clearly stated inclusion criteria for the study design, intervention and outcome. Only PubMed was searched and no other databases, but supplementary searches were carried out and the author made some attempt to identify unpublished studies. The potential for language bias cannot be assessed as language restrictions were not described. In addition, the likelihood of reviewer bias and error cannot be evaluated as details of the methods employed to select studies and extract the data were not given. The quality of the included studies was not reported and only limited details of the studies were presented, making it difficult to judge the appropriateness of using a narrative synthesis. Potential adverse effects or long-term effects were not discussed. While the conclusions appear to be supported by the data presented, owing to the limitations highlighted, the reliability of these results cannot be evaluated and, therefore, should be treated with caution.

Implications of the review for practice and research
Practice: The author did not state any implications for practice.

Research: The author stated that benefits in terms of PPG reduction and potential impact on cardiovascular risk, especially with the rapid analogues (as a premix or as part of an all-analogue basal-bolus regimen), should be investigated further.

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