Efficacy of insulin analogs in achieving the hemoglobin A1c target of <7% in type 2 diabetes: meta-analysis of randomized controlled trials
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CRD summary
This review concluded that a greater proportion of type 2 diabetic patients can achieve the haemoglobin A1c target of below 7% with biphasic insulin compared with basal insulin, but the basal bolus regimen was best for the attainment of the target. The methodological quality and small number of trials for some comparisons limits the reliability of these conclusions.

Authors' objectives
To compare the effects of basal, biphasic, prandial and basal-bolus insulin regimens with insulin analogues to reach the haemoglobin A1c target of below 7% in people with type 2 diabetes.

Searching
MEDLINE, EMBASE, CINAHL and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from inception to January 2010 with specified search terms. United States Food and Drug Administration, European Medicines Agency, ClinicalTrials.gov, Clinical Study Results Database web sites and bibliographies of included articles were also searched. There were no language restrictions on searches.

Study selection
Eligible randomised controlled trials recruited patients (over 18 years old) with diabetes and compared different insulin regimens (basal, biphasic, prandial or basal-bolus) using insulin analogues. The primary outcome was proportion of patients that reached the haemoglobin A1c target of below 7%. Hypoglycaemic events and weight gain were secondary outcomes. Crossover trials were eligible provided there was at least 12 weeks follow-up before and after the crossover phase. Trials were excluded where intervention time was less than three months and the number of patients in any arm was fewer than 30 patients.

Patients had a mean age of 58 years and there were slightly more males than females (56%). There was a mix of insulin-naive and insulin-treated individuals. The majority of trials used an oral drug (predominantly metformin, a sulfonylurea or a glitazone) combined with insulin and measured short-term end points. Details of the four insulin regimens were provided in the paper.

Two reviewers assessed study eligibility with disagreements resolved by consensus.

Assessment of study quality
Trial quality was assessed with a modified Jadad score (a five point scale with points for randomisation, blinding, reasons for withdrawal and use of intention-to-treat analysis).

Two reviewers assessed study validity with disagreements resolved by consensus

Data extraction
Proportions of patients that reached the haemoglobin A1c target of below 7% and hypoglycaemic events were extracted for comparisons to enable odds ratios (OR) and associated 95% confidence intervals (CI) to be calculated. Mean and standard deviations of weight gain were extracted to enable mean difference effect sizes to be calculated. Where a variance measure was unreported, it was estimated based on the worst (largest) ratio between mean and standard deviation amongst other studies.

Methods of synthesis
Mixed models were used to pool effects. Between study heterogeneity was tested using $X^2$ and quantified using $I^2$. Funnel plots were used to explore differences between large and small trials.
Results of the review
Sixteen randomised trials (7,759 patients), three of which were cross-over, were included. Trial quality was generally moderate-to-poor (median score 2.5 out of 5). None of the studies were double-blind due to the visibly different properties of the comparators. Only 11 trials used intention-to-treat.

Patients treated with biphasic insulin had a greater chance of reaching a haemoglobin A1c target of below 7% than those on basal insulin (OR 1.88, 95% CI 1.38 to 2.55; 10 trials) but was also associated with more hypoglycaemic events (OR 0.34, 95% CI 0 to 0.69; 10 trials) and weight gain (OR 1.0 kg, 95% CI 0.28 to 1.73 kg; 10 trials). There was substantial heterogeneity in all analyses, but no evidence of a statistically significant difference between large and small trials in the primary analysis.

Use of basal-bolus insulin as a comparator had a substantial impact, as patients treated with basal-bolus insulin had a greater chance of achieving a haemoglobin target of below 7% (OR 1.75, 95% CI 1.11 to 2.77) than those on biphasic insulin. Furthermore, there was no significant difference in incidence of hypoglycaemia or weight gain, although these results were generated by pooling only three trials.

Three trials allowed head-to-head comparison of biphasic versus prandial insulin and four trials compared prandial and basal but the pooled effects of these analyses were non-significant irrespective of outcome.

Authors’ conclusions
A greater proportion of type 2 diabetic patients can achieve the haemoglobin A1c target of below 7% with biphasic or prandial insulin compared with basal insulin, but the basal bolus regimen was best for the attainment of the target.

CRD commentary
This review used appropriate methods to search for relevant studies, assess eligibility and validity, and to extract information for synthesis whilst minimising potential biases. The method of synthesis appeared appropriate but in the absence of a fully specified model it was assumed that the mixed model retained a random effect for treatment and a fixed effect intercept. If fixed treatment effects were used, the confidence intervals and statistical significance of the pooled effects may not be generalisable to the variable clinical setting encompassed by the inclusion criteria.

The author’s conclusions reflected the evidence but conclusions regarding prandial insulin do not reflect the lack of statistical significance of the pooled effects. The small number of trials for some comparisons and high heterogeneity make generalisability unclear. These limitations of the evidence-base were exacerbated by moderate-to-low trial quality which introduced potential for bias. Thus, there was some uncertainty surrounding the reliability of the conclusions as reflected in the author's judicious implication for research.

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

Research: The authors state that more studies were needed to understand the long-term effects of insulin analogues on patients with diabetes.

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