Multiple HbA1c targets and insulin analogues in type 2 diabetes: a systematic review

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CRD summary
The review assessed the role of insulin analogues to reach different optimal glycated haemoglobin (HbA1C) targets in type 2 diabetic patients, concluding that basal-bolus insulin regimens obtained the best results. Given the questionable statistical analyses used and the high levels of variation found across trials, the authors’ conclusions should not be considered reliable.

Authors' objectives
To assess the role of insulin analogues to reach different optimal glycated haemoglobin A1c (HbA1c) targets (from 6.5% to 8%) in type 2 diabetic patients.

Searching
MEDLINE, EMBASE, CINAHL, and The Cochrane Library were searched to August 2010 with no language restrictions.

Study selection
Eligible studies were randomised controlled trials (RCTs) of the effect of different insulin regimens (basal, biphasic, prandial, or basal-bolus) with insulin analogues in adults (>18 years old) with type 2 diabetes. Eligible trials had to report the outcomes of glycated haemoglobin levels and the proportion of diabetic patients who reached the glycated haemoglobin goal of 7% or less. Cross-over trials were included if there was at least 12 weeks of follow-up before and after the cross-over phase. Trials were excluded if the treatment duration was less than 12 weeks or the number of patients in any arm was less than 30.

Four types of insulin regimen were studied in included trials: basal insulin analogues (long-acting insulins glargine, detemir, and lispro NPL); biphasic insulin analogues (pre-mixed lispro 25/75, lispro 50/50, aspart 30/70, aspart 50/50, aspart 70/30); prandial insulin analogues (short-acting insulins lispro, aspart, glulisine); and basal-bolus insulin (any combination of prandial and basal insulin analogues). Metformin was the most commonly used oral anti-diabetic drug. Included patients ages ranged from 51.6 to 64 years.

Two reviewers independently selected studies for inclusion, with disagreements resolved by discussion.

Assessment of study quality
Trial quality was evaluated using the Jadad scale (which assessed randomisation, blinding, and withdrawals/drop-outs). An additional point was given if the trial analysis was of the intention-to-treat population. Trials with scores of 2 or less were considered to be of low quality, and scores of 3 or more high quality (since achieving effective blinding would be difficult when comparing regimens).

The authors did not state how many reviewers evaluated study quality.

Data extraction
The proportion of patients with glycated haemoglobin below 6.5%, below 7.0%, below 7.5%, and below 8.0% was extracted for each trial arm.

Two reviewers independently extracted data, with disagreements resolved by discussion.

Methods of synthesis
It appeared that meta-analyses were performed to pool the proportions derived from single trial arms, using a fixed-effect and a random-effects model. Heterogeneity was assessed using the Q-test and $I^2$. A value of $I^2$ greater than 50% represented substantial heterogeneity.

Results of the review
Fifty-three RCTs were included in the review (32,689 patients). Treatment arm sample sizes ranged from 41 to 2,493 patients. All were open-label studies and most had a parallel design. Follow-up periods ranged from 12 to 134 weeks. Jadad scores ranged from 1 to 4 (out of 6 points).

The proportion of patients with glycated haemoglobin below 7% at the end of treatment was 42% (95% CI 36 to 48; 43 trial arms) for the basal regimen, 44% (95% CI 38 to 50; 28 trial arms) for the biphasic regimen, 39% (95% CI 20 to 58; nine trial arms) for the prandial regimen, and 53% (95% CI 47 to 59; 12 trial arms) for the basal-bolus regimen.

Results were also reported of a linear increase in the proportion of patients who achieved targets as they increased from 6.5% to 8%. High levels of heterogeneity were reported for all regimens. Several of the I² values were above 100%, which suggested there were errors in the I² calculations.

**Authors’ conclusions**

At any glycated haemoglobin target, basal-bolus insulin regimens with insulin analogues obtained the best results (53%), which could be useful for detailing the best treatment effect in individual patients.

**CRD commentary**

The review question and inclusion criteria were clear. Several databases were searched, with no language restrictions, to identify relevant trials. There appeared to be no search explicitly to identify unpublished studies. Publication bias was not assessed, so remained a possibility. Suitable methods (the use of independent duplicate processes) were employed to reduce the risks of reviewer error and bias throughout much of the review, although the process details for trial quality assessment were not reported.

However, the value of the quality assessment was limited since trials were effectively split into cohort studies (trial arms) rather than being evaluated in the context of randomised comparisons. The pooling of data in this way was highly questionable, since the benefit of randomisation in the trials was lost; calculation of the relative effectiveness estimates was not achieved. Some of the methods used to pool the data were not explicit. For example, it was unclear which type of model was used to derive the results. Heterogeneity was reported as being high (some I² estimates appear to have been calculated erroneously, with some values being above 100%), which cast further doubt on the reliability of the pooled estimates.

In light of the questionable statistical analyses used and the high levels of heterogeneity found across included trials, the authors’ conclusions should not be considered reliable.

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

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

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