Comparative efficacy and safety of long-acting insulin analogs in patients with type 2 diabetes failing on oral therapy: systemic [systematic] review and meta-analyses


CRD summary
Initiating long-acting insulin analogues for people with type 2 diabetes failing on oral agents seemed to provide glycaemic control similar to rapid-acting insulin analogues, NPH insulin or glucagon-like peptide-1 analogues and slightly inferior to biphasic insulin analogues with fewer side effects. The reliability of the conclusions is unclear due to limited evidence.

Authors' objectives
To compare the effectiveness and safety of regimens based on long-acting insulin analogues with other injectable preparations in insulin-naive patients with type 2 diabetes failing on oral agents.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to March 2010 for studies published in English; minimal search terms were reported.

Study selection
Randomised controlled trials (RCTs) that compared long-acting insulin analogue-based regimens with either rapid-acting insulin analogues, biphasic insulin analogues, human neutral protamine Hagedorn (NPH) insulin or glucagon-like peptide-1 (GLP-1) analogues for 12 weeks or more were eligible for inclusion. Participants were insulin-naive adults (>18 years) with type 2 diabetes inadequately controlled with oral agents. Outcomes of interest were HbA1c levels, fasting glucose, postprandial glucose, weight gain, daily insulin dose by body weight, incidence of total, nocturnal and severe hypoglycaemia and incidence of adverse events and withdrawal. Studies were excluded where use of oral agents was unbalanced between study arms and where there was a history of insulin treatment.

Participants in the included studies had a mean age of 58 years, mean body mass index of 30.1kg/m², mean duration of diabetes of nine years and 55.6% were male. Participants had a median HbA1c level of 8.8% and median fasting plasma glucose of 10.9 mmol/L. Long-acting insulin analogues were either detemir or glargine. Rapid-acting and biphasic insulin analogues were either aspart or lispro. GLP-1 analogues were either exenatide or liraglutide. Most studies included oral glucose-lowering medications together with insulin.

The authors did not state how many reviewers selected studies for the review.

Assessment of study quality
Studies were assessed for quality using the Jadad scale of randomisation, blinding and description of withdrawals. An additional point was given for intention-to-treat analysis.

It appeared that two reviewers independently assessed studies for quality with disagreements resolved by consensus and discussion with a third reviewer.

Data extraction
Data were extracted on the outcomes to enable calculation of mean differences (MDs) for continuous data and odds ratios (ORs) for dichotomous data, together with 95% confidence intervals (CIs). Changes between baseline and the endpoint of the trial were used to compare groups for the outcomes, HbA1c, fasting or postprandial glucose and weight gain. The standard deviation of the difference between baseline and the end of study was calculated according to the approach suggested in the Cochrane Handbook. Where RCTs were published in more than one paper, data from each paper were assessed. Data from intention-to-treat studies were recorded according to intention-to-treat principles.

Two reviewers independently extracted data. Disagreements were resolved by consensus and discussion with a third reviewer.
Methods of synthesis
Pooled odds ratios and weighted mean differences (WMDs), together with 95% confidence intervals, were calculated using a random-effects model. Data from parallel and crossover studies were combined in meta-analyses. Heterogeneity was assessed by the $X^2$ test and quantified with the $I^2$ metric. Subgroup analyses were undertaken according to baseline HbA1c (<9%, ≥9%), Jadad quality score (<3 points, ≥3 points), variation in study length, oral agents given as add on therapy (yes, no), the nature of the oral agents used in combination with insulin and long-acting insulin analogue type (glargine, detemir). Sensitivity analyses were undertaken to assess the influence of low quality studies on the results. Funnel plots were used to assess potential for publication bias and small sample size.

Results of the review
Twenty-two RCTs (9,548 participants, range 20 to 2,091 participants) were included in the review. Nineteen studies had a parallel group design. Three studies had a crossover design. Seventeen studies were analysed according to intention-to-treat principles. No studies were double blinded. Overall Jadad scores ranged from 2 to 4 points (median 3). Median follow-up was 34 weeks.

Change in HbA1c levels: Compared to long-acting insulin analogues, biphasic insulin analogues were associated with a significantly greater reduction of HbA1c levels (WMD 0.19, 95% CI 0.04 to 0.34; seven RCTs; $I^2=58.7\%$). There was no evidence of significant differences in HbA1c levels when long-acting insulin analogues were compared with rapid-acting insulin analogues, human NPH insulin and GLP-1 analogues. Heterogeneity in the comparison of long-acting with biphasic insulin was reduced ($I^2=0\%$) with the exclusion of a study with shorter diabetes duration and lower baseline HbA1c levels and was no longer significant.

Change in fasting glucose: Long-acting insulin analogues were associated with a significantly greater reduction in fasting glucose than human NPH insulin (WMD -0.20 mmol/L, 95% CI -0.38 to -0.02; six RCTs; $I^2=0\%$) and GLP-1 analogues (WMD -1.35 mmol/L, 95% CI -1.64 to -1.06; four RCTs; $I^2=0\%$). There was no evidence of significant differences in fasting glucose when long-acting insulin analogues were compared with rapid-acting insulin or biphasic insulin analogues.

Change in postprandial glucose: Compared to long-acting insulin analogues, rapid-acting insulin analogues were associated with a significantly greater reduction in postprandial glucose (WMD 0.78 mmol/L, 95% CI 0.32 to 1.19; three RCTs; $I^2=5.3\%$). There was no evidence of significant differences when long-acting insulin analogues were compared with biphasic insulin analogues. There were insufficient data to make the other comparisons.

Change in weight: Long-acting insulin analogues were associated with a significantly greater reduction in weight when compared to rapid-acting insulin analogues (WMD -1.57kg, 95% CI -3.01 to -0.13; three RCTs; $I^2=73.3\%$) and biphasic insulin analogues (WMD -1.25kg, 95% CI -1.64 to -0.87; four RCTs; $I^2=5.3\%$). By comparison, GLP-1 analogues were more effective than long-acting insulin analogues (WMD 4.12kg, 95% CI 3.25 to 4.99; five RCTs; $I^2=74.8\%$). There was no evidence of significant differences when long-acting insulin analogues were compared with human NPH insulin.

Daily insulin doses by body weight: Long-acting insulin dosages by body weight were significantly lower than biphasic insulin analogues (WMD -0.07 U/kg, 95% CI -0.14 to 0.00; six RCTs; $I^2=87.2\%$) but significantly higher than human NPH insulin (WMD 0.03 U/kg, 95% CI 0.01 to 0.06; five RCTs; $I^2=99.3\%$). There was no evidence of significant differences when long-acting were compared with rapid-acting insulin analogues. There were insufficient data to make comparisons with GLP-1 analogues.

Incidence of total hypoglycaemia: Long-acting insulin analogues were associated with a significantly lower odds of total hypoglycaemic events than biphasic insulin analogues (OR 0.72, 95% CI 0.56 to 0.94; six RCTs; $I^2=61.2\%$) and human NPH insulin (OR 0.57, 95% CI 0.45 to 0.72; six RCTs; $I^2=30.2\%$). There was no evidence of significant differences when long-acting insulin analogues were compared with rapid-acting insulin analogues. There were insufficient data to make comparisons with GLP-1 analogues. Results for incidence of severe hypoglycaemia and nocturnal hypoglycaemia were reported.

Adverse events: Compared to GLP-1 analogues, long-acting insulin analogues were associated with a significantly reduced odds of any adverse events (OR 0.33, 95% CI 0.13 to 0.85; three RCTs; $I^2=84\%$), treatment-related adverse events (OR 0.04, 95% CI 0.03 to 0.06; three RCTs; $I^2=0\%$) and withdrawal due to adverse events (OR 0.19, 95% CI 0.05 to 0.66; four RCTs; $I^2=37.9\%$). There was no evidence of significant differences for the other comparisons.
some cases there were insufficient data to make the comparisons.

Results of sensitivity analyses and subgroup analyses were provided in the paper. It appeared that the authors did not assess publication bias due to the small number of studies.

**Authors’ conclusions**

Initiating long-acting insulin analogues for people with type 2 diabetes failing on oral agents seemed to provide glycaemic control similar to rapid-acting insulin analogues, NPH insulin or glucagon-like peptide 1 analogues and slightly inferior to biphasic insulin analogues with fewer side effects.

**CRD commentary**

The review addressed a clear research question supported by appropriate inclusion criteria. A limited number of electronic databases was searched for studies published in English without any specific attempts to find unpublished studies, so it was possible that some studies may have been missed. Appropriate methods were used to minimise reviewer error and bias during quality assessment and data extraction but the authors did not state how many reviewers selected studies for the review. A valid tool was used for quality assessment; the authors considered that most studies were of low quality.

Synthesis of the study results and assessment of heterogeneity were appropriate. There were many comparisons and two to six studies contributed data for each; for some comparisons there were insufficient data for analyses. Substantial heterogeneity was identified for many analyses. The authors attempted to explore the heterogeneity with subgroup and sensitivity analyses but these were limited by the small number of studies.

The review was generally well conducted but potential for publication bias and a limited and variable evidence base make the reliability of the conclusions unclear.

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

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that more high quality studies were required to assess the long-term effects of insulin preparations on clinical outcomes.

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