Risk of adverse effects of intensified treatment in insulin-dependent diabetes mellitus: a meta-analysis
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Authors' objectives
To examine the risk of severe hypoglycaemia, ketoacidosis and death from the intensified treatment of insulin-dependent (type 1) diabetes mellitus, using a meta-analysis of randomised controlled trials (RCTs).

Searching
MEDLINE (search dates unclear) was searched. Additional articles were identified by examining the reference lists from research and review articles in the field and an earlier meta-analysis. Two specialist journals were handsearched: Diabetes, Diabetologia and Diabetes Care (from 1975 to 1995) and Diabetic Medicine (from 1985 to 1995).

Study selection
Study designs of evaluations included in the review
Randomised studies comparing intensified insulin treatment regimens with conventional treatments were included in the review. The studies had to incorporate at least one outcome event, and have at least 6 months of follow-up involving blood glucose control monitoring by measurements of glycosylated haemoglobin Al or Alc. Crossover trials were considered if the patients were randomly allocated to groups and switched to the other treatment regimen after a minimum period of 6 months. The first period was then included in the analysis.

Specific interventions included in the review
The following interventions were included in the review: continuous subcutaneous insulin infusion, multiple daily injections of insulin (number not stated), and individual daily injections of insulin (1 to 6 injections per day).

Participants included in the review
Participants with insulin-dependent diabetes mellitus were included in the review. Pregnant patients, and patients with endstage diabetic complications or renal transplants, were excluded from the review. The average age of the participants ranged from 18.0 to 42.4 years, and the average duration of their diabetes ranged from 2.6 to 20.0 years.

Outcomes assessed in the review
The main outcome measures were the number of patients experiencing at least one episode of severe hypoglycaemia or ketoacidosis, and the number of deaths. Episodes of severe hypoglycaemia or ketoacidosis were defined as episodes with typical signs requiring intervention by a third party. For hypoglycaemia, the interventions by a third party were defined as either treatment in a health care facility, parenteral glucose or glucagon, medical attention, or attention by another person. For ketoacidosis, the interventions included hospitalisation or treatment in an out-patient clinic. Other outcomes included the progression of chronic complications including changes in retinal morphology, retinal function, renal function, nerve function, kidney size, changes in glycaemic control, glomerular charge selectivity, and the presence of albuminuria.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
Each study was graded and awarded points for its methodological quality in terms of the control of selection bias at entry and after entry. Selection bias at entry was considered and excluded if randomisation had been organised centrally (3 points). Studies in which sealed envelopes were used for randomisation were given intermediate credit (2 points), while studies without a clearly stated method for masking treatment allocation were given one point. Studies whose final analysis included all of the patients initially randomised (i.e. an intention to treat analysis) were judged as
adequately controlled for selection bias after entry. These studies were awarded 3 points. Studies where a strict intention to treat analysis could not be performed, but in which withdrawals occurred but were judged to have been too few to produce substantial bias, were given 2 points. All other studies were given one point. The mean quality score for the fourteen included studies was 4 (range: 2 to 6).

The authors do not state how the papers were assessed for quality, or how many of the authors performed the quality assessment.

**Data extraction**

Relevant data were extracted onto a standardised form. This was sent to principal investigators who were asked to check the data and to supply missing information. After completion of the data collection process, the investigators were sent another copy to finally check for inaccuracies. As a result of this procedure, additional unpublished data were obtained for 11 of the 14 studies.

**Methods of synthesis**

How were the studies combined?

The studies were combined using the fixed-effect model. Estimates of the combined odds ratio (OR) with 95% confidence intervals (CIs) and probability values were calculated from logistic regression models. The basic model included dummy variables to designate trials and treatment groups. Covariate-by-treatment interaction terms were included to examine the influence of the following variables: mean glycosylated haemoglobin in conventionally treated patients (expressed as a percentage of the mean in an non-diabetic reference population); the percentage reduction in glycosylated haemoglobin in the intensified treatment group; the type of intensified treatment used; the length of follow-up; quality score; the mean age of the participants; gender distribution; and the duration of diabetes. In the case of zero cells the value of 0.5 was added to event cells.

A linear regression of the log of the OR for severe hypoglycaemia was fitted against the percentage reduction in glycosylated haemoglobin as the explanatory variable, using the variance of the observed minus expected (O-E) statistic as weights. A cumulative meta-analysis, in which the analysis was repeated each time a new trial appeared, was also performed. The analysis included all trials contributing at least one end point. A sensitivity analysis was performed to examine the robustness of the results. This included repeating the analyses excluding the Diabetes Control and Complications Trial, excluding studies with low quality scores, including trials with zero events, and using the random-effects model described by DerSimonian and Laird (see Other Publications of Related Interest).

How were differences between studies investigated?

Heterogeneity between studies was calculated from the basic logistic regression model, by treating the residual deviance as a chi-squared value with the degrees of freedom equal to the number of trials minus one. The authors based evidence of heterogeneity on a p-value of less than 0.1 because of the low statistical power of this test.

**Results of the review**

Fourteen studies involving 2,069 participants were included in the review: 12 RCTs and 2 crossover studies. Details of 5 of the excluded trials were provided.

The intensified treatment always included frequent self-monitoring of blood glucose. The conventional treatment typically consisted of twice-daily injection regimens without frequent blood glucose self-monitoring. The mean glycosylated haemoglobin in conventional treatment groups ranged from 41 to 88% (mean: 67%) above the mean of a non-diabetic reference population. In most of the trials, the glycosylated haemoglobin levels were lowered among the intensively treated patients with reductions ranging from 0 to 22%.

Incidence of severe hypoglycaemia: this ranged from 0 to 66.6 (median: 7.9) episodes per 100 person-years in intensively treated patients, and from 0 to 33.3 (median: 4.6) episodes per 100 person-years in conventionally treated patients. The combined OR (2.99) indicated a substantial and statistically significant (p<0.0001) increase in the risk of suffering one or more episodes of severe hypoglycaemia. The test for heterogeneity was significant (p=0.06). The risk of hypoglycaemia was determined by the degree of normalisation of glycaemia achieved (p=0.005 for interaction term).
Incidence of ketoacidosis: this ranged from 0 to 37.5 (median: 2.9) episodes per 100 person-years in intensively treated patients, and from 0 to 0.3 (median: 0) episodes per 100 person-years in conventionally treated patients. The combined OR (1.74, p=0.0003) indicated an increased risk of ketoacidosis with intensified treatments. In the multivariate logistic regression, there was a significant (p=0.004) interaction with the type of intensified treatment used: the OR was 7.20 (95% CI: 2.95, 17.58) for insulin pumps, 1.13 (95% CI 0.15, 8.35) for multiple daily injections, and 1.28 (95% CI: 0.90, 1.83, p=0.004) for choice between pumps and multiple injections.

Mortality rates: these ranged from 0 to 6.3 (median: 0) episodes per 100 person-years in intensively treated patients, and from 0 to 5.5 (median: 0) episodes per 100 person-years in conventionally treated patients. Fifteen deaths from all causes occurred with intensified treatment and 11 with conventional treatment (OR 1.40, 95% CI: 0.65, 3.01, p=0.83). Of the 7 deaths (5 ketoacidosis, 2 sudden death) definitely or probably associated with acute complications of insulin therapy, all were in the intensively treated patients (OR not stated, p=0.007).

Authors' conclusions
There is a substantial risk of severe adverse effects associated with intensified insulin treatment. Mortality from acute metabolic causes is increased; however, this is largely counterbalanced by a reduction in cardiovascular mortality. The excess of severe hypoglycaemia in the Diabetes Control and Complications Trial is not exceptional. Multiple daily injection schemes may be safer than treatment with insulin pumps.

CRD commentary
This was a thorough and clearly presented review. Detailed accounts were provided of the criteria used for selecting and quality assessing the studies, and the statistical methods used to combine these studies. The authors, however, have omitted to provide details of the years searched on MEDLINE and the search terms used. This makes it difficult to comment on the validity of the search and for other researchers to duplicate the search strategy. The report also lacked details of how decisions were made on the relevancy and quality of the studies. There would also appear to be a discrepancy between the numbers of participants reported in table 1 (n=2,069) and those described in the results (n=2,067). The authors' final concluding statements would appear to be valid considering the thorough reporting and analysis of the included data.

Implications of the review for practice and research
The authors state 'uncritical promotion of intensified treatment as the uniform standard of therapy for all patients with insulin-dependent diabetes mellitus should be avoided'.

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Other publications of related interest

These additional published commentaries may also be of interest. Zinman B. Review: intensive insulin therapy for type

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Blood Glucose /metabolism; Diabetes Mellitus, Type 1 /blood /drug therapy /mortality; Diabetic Ketoacidosis /etiology; Hemoglobin A, Glycosylated /metabolism; Humans; Hypoglycemia /chemically induced; Injections; Insulin /administration & dosage /adverse effects /therapeutic use; Insulin Infusion Systems; Logistic Models; MEDLINE; Odds Ratio; Randomized Controlled Trials as Topic; Risk Factors; United States

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