CRD summary
This review concluded that continuous subcutaneous insulin infusion and multiple daily injections had similar effects on glycaemic control and hypoglycaemia. This conclusion may be unreliable as it confuses absence of evidence with evidence of no difference. The review also concluded that continuous glucose monitoring was superior to self-monitoring without increasing the risk of hypoglycaemia. This conclusion is probably reliable.

Authors' objectives
To assess the effectiveness of rapid acting, analogue-based continuous subcutaneous insulin infusion, compared with multiple daily injections, in reducing glycated haemoglobin (HbA1c) and hypoglycaemia, in adults and children with types one and two diabetes.

To assess the effectiveness of self-monitoring of blood glucose, compared with real-time continuous glucose monitoring, for the same population.

Searching
MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched, using specified search terms, without language restrictions, for articles included from inception to February 2012. Reference lists, reviews, and a public registry of trials were checked and authors were contacted to identify further items.

Study selection
The authors included studies that compared continuous infusion with multiple injections (at least three per day) or continuous monitoring with self-monitoring of blood glucose (at least three times daily) amongst patients with type one or two diabetes. They included both randomised controlled trials (RCTs) and observational studies that evaluated microvascular or macrovascular outcomes, or mortality. Other outcomes were assessed only in RCTs. The authors listed many outcomes, but the conclusions were largely based on glycated haemoglobin and hypoglycaemia.

Two reviewers independently assessed study eligibility, with discrepancies resolved through consensus or adjudication.

For infusion versus injections, the patients were mainly young (mean age 16.5 years injection group, 11.4 years infusion group). Glycaemic control was suboptimal at the time of enrolment (mean glycated haemoglobin 8.5% injection group, 8.6% infusion group). Duration of therapy ranged from 3.5 to 24 months, with six of nine studies having 12 or more months of follow-up.

For the comparison of monitoring, the patients were older (mean age 24.5 years; range 8.5 to 44.6 years). Average baseline glycated haemoglobin was 8.3% for both self-monitoring and continuous monitoring. Five studies required the continuous monitoring to be continuous, whilst three required monitoring for 70% of the time. For both comparisons, ethnicity was not reported in most studies.

Assessment of study quality
RCTs were assessed using the Cochrane Collaboration's risk of bias tool, which included sequence generation, allocation concealment, blinding, incomplete outcome data, pharmaceutical support, substantive company involvement, and loss to follow-up. Observational studies were assessed using the Downs and Black quality checklist.

Two reviewers independently assessed study quality; it was unclear how discrepancies were resolved.

Data extraction
Data were abstracted to calculate risk ratios for binary outcomes (occurrence of hypoglycaemia) and weighted mean differences for continuous outcomes (between-group difference in change from baseline glycated haemoglobin). If a study did not report the standard deviation for the change from baseline, this was calculated assuming a correlation of 0.5. For crossover trials, the results were abstracted only from the first period.
One reviewer extracted the data, and a second reviewer checked it. Further random checks were performed.

**Methods of synthesis**

Effect sizes were pooled using random-effects models (DerSimonian and Laird) for continuous variables; fixed-effect model (Mantel-Haenszel) results were reported for the risk or odds of severe hypoglycaemia. Heterogeneity was quantified using I² with a X² test of statistical significance. It was also explored in subgroup analyses and meta-regression.

**Results of the review**

**Continuous infusion versus daily injections:** For children and adolescents with type one diabetes, seven RCTs (238 patients, groups ranging from six to 34 patients) presented data on change in glycated haemoglobin, from baseline after 16 or more weeks of follow-up. There was no significant difference between infusion and injections (mean difference -0.17, 95% CI -0.47 to 0.14). There was substantial variation in the estimates from the seven trials, all of which had large confidence intervals, which counterbalanced, resulting in low statistical heterogeneity (I²=0.0). All seven studies were assessed as medium risk of bias. Five studies (168 patients) of severe hypoglycaemia had similar results.

For adults with type one diabetes, four RCTs (170 patients, groups ranging from seven to 40) at medium risk of bias, compared the change in glycated haemoglobin between infusion and injections, and found a small statistically significant effect when pooled (mean difference -0.30, 95% CI -0.58 to -0.02; I²=64.5). This result was dependent on one trial with the remaining three small trials having imprecise effect estimates. Three studies (143 patients) reporting severe hypoglycaemia found no significant difference, with similarly imprecise small trials.

For adults with type two diabetes, four small trials (338 patients, groups ranging from 20 to 66) at medium risk of bias could not distinguish differences in change in baseline glycated haemoglobin between infusion and injections (mean difference -0.18, 95% CI -0.43 to 0.08, I²=0.0). Three studies (279 patients) presented data on severe hypoglycaemia for this population (pooled RR 0.76, 95% CI 0.26 to 2.19).

**Continuous monitoring versus self-monitoring:** Ten trials (1,066 patients), assessed as low risk of bias, indicated that continuous monitoring was more effective in reducing glycated haemoglobin (mean difference -0.26, 95% CI -0.33 to -0.19). Heterogeneity was substantial (I²=69.9) and partly explained by adherence to monitoring (meta-regression coefficient -0.85, p=0.007). There was no difference in severe hypoglycaemia in nine trials (1,102 patients; OR 0.88, 95% CI 0.53 to 1.46).

Further analysis of four trials (606 patients), at medium risk of bias, indicated that sensor-augmented insulin pumps decreased glycated haemoglobin more than self-monitoring plus injections (mean difference -0.68, 95% CI -0.81 to -0.54, I² =53.7%). Only two trials (562 patients) reported on the hypoglycaemia outcome and the use of different measures precluded pooling of the four trials reporting severe hypoglycaemia.

**Authors’ conclusions**

Continuous subcutaneous insulin infusion and multiple daily injections had similar effects on glycaemic control and hypoglycaemia, except in adults with type one diabetes where infusion achieved better glycaemic control. Continuous monitoring was superior to self-monitoring and sensor-augmented insulin pumps were superior to self-monitoring with multiple daily injections, without increasing the risk of hypoglycaemia.

**CRD commentary**

This review addressed clear questions with appropriate inclusion criteria. The search strategy was comprehensive and appropriate methods were used to assess study eligibility, extract the data, and assess their quality. The meta-analytical methods were appropriate, but the reason for conducting fixed-effect or random-effects analyses was unclear.

The authors’ conclusions for the effectiveness of infusion and multiple daily injections might not fully reflect the evidence. The pooled point estimates for glycated haemoglobin suggested that there was no difference in effectiveness (or a small difference in adults with type one diabetes), but the trials were small and of low to moderate quality. This lack of evidence of an effect may have been confused with evidence of no effect.

Similarly the variety between trials reduces the certainty that continuous monitoring was superior to self-monitoring even though the authors accounted for some of this inconsistency with meta-regression. The comparison of sensor-
augmented insulin pumps to self-monitoring plus multiple daily injections only assessed glycaemic control, not hypoglycaemia as did the comparison of continuous monitoring to self-monitoring.

The authors’ conclusion that continuous subcutaneous insulin infusion and multiple daily injections had similar effects is unlikely to be reliable, but their conclusion that continuous monitoring was superior to self-monitoring is likely to be reliable.

Implications of the review for practice and research
Practice: Intensive insulin therapy could be delivered according to patient preference. The addition of continuous monitoring to insulin infusion was better than multiple daily injections plus self-monitoring, in decreasing glycated haemoglobin levels.

Research: Future research should include larger studies, of elderly and minority populations where the incidence of diabetes mellitus is increasing, and they should report clinically meaningful outcomes, adherence to treatment, and cost-effectiveness.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.