Short-acting insulin analogues vs. regular human insulin in type 2 diabetes: a meta-analysis

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Background

Short-acting insulin analogues:

- Provide a greater control of postprandial glucose than HRI
- Superiority on HbA1c is controversial
Methods

- Randomized controlled trials >4 weeks comparing insulin analogues (lispro, aspart or glulisine) with HRI in T2DM patients were retrieved. Those with a duration of >12 weeks were analyzed.

- Data on HbA1c, PP glucose, and incidence of severe hypoglycemia were extracted and meta-analyzed.
Primary outcome

- Effect of rapid-acting analogues, compared with regular human insulin, on HbA1c at the end of the trial

Secondary outcomes

- 2 h post breakfast, lunch, and dinner GB

- Severe hypoglycemia (mild hypoglycemic episodes were not considered because of the heterogeneity of diagnostic definitions across trials)
Separate analyses were performed for:

- trials with different insulin analogues (lispro, aspart and glulisine)
- trials with intensive insulin treatment
  - prandial insulin, usually combined with at least one administration of basal insulin
  - two daily mixtures of prandial (regular human insulin or analogue) and NPH insulin (usually premixed)
- trials enrolling patients already treated with human insulin, insulin naïve or both were analyzed separately with respect to HbA1c
13 retrieved trials (7 lispro, 4, aspart and 2 glulisine)

- 5 reported a significant improvement of HbA1c with analogues

- 7 studies, no difference was detected between groups with respect to HbA1c

- All studies except one were open label

- In the double-blind study, analogue and human insulin were administered immediately before the meal; in other trials, analogue and human insulin were administered immediately before and 20–30 min before the meal respectively
Results

- “Short-acting analogues reduced HbA1c by 0.4% (0.1–0.6%) (p = 0.027) in comparison with HRI”

- “Short-acting analogues produced a significant improvement [by 0.10% (0.01–0.19%), p = 0.037] of HbA1c in comparison with HRI”

- Similar results were observed [by 0.11% (0.02–0.20%), p = 0.018] when excluding the only study in which regular human insulin was administered immediately before the meal
Results

- A significant improvement was observed also in self-monitored 2 h post breakfast and dinner blood glucose.

- The overall rate of severe hypoglycemia was not significantly different with short-acting analogues and HRI.

- In different analogues analysis, a similar improvement of HbA1c was detected with aspart and lispro, while the effect of glulisine was apparently smaller.
Results

- Analogues were superior over HRI in trials in which prandial insulin was administered three times a day.

- No significant advantage was detected when analogues were used twice a day (usually as premixed formulations).

- In trials enrolling patients who were previously treated with human insulin, short-acting insulin analogues did not produce a significant reduction of HbA1c in comparison with human insulin.

- When the sample enrolled was composed by patients failing to oral hypoglycemic agents, the effect of analogues on HbA1c was apparently greater than that of regular human insulin (not statistically significant).
Results

The standardized difference in HbA1c did not show any significant correlation with:

- **Mean age** \(( r = -0.01, p = 0.96 )\)
- **Duration of diabetes** \(( r = 0.16, p = 0.62 )\)
- **BMI** \(( r = -0.01, p = 0.99 )\)
- **HbA1c** \(( r = 0.03, p = 0.92 )\) at enrolment
Results

Postprandial glucose control

3 trials---short-acting insulin analogues provided a significant improvement of BG

- after breakfast [by 0.7 mmol/l (0.4–0.9 mmol/l), p < 0.001]
- after dinner [0.6 mmol/l (0.3–0.8 mmol/l), p < 0.001]
- not after lunch (data not shown)
Results

Hypoglycemia

- Five trials reported the number of patients experiencing at least one episode of severe hypoglycemia. [MH-OR for this event with analogues vs HRI, was 0.61 (0.25–1.45)]
Conclusion

In T2DM, short-acting insulin analogues provide a better control of HbA1c and postprandial glucose than regular human insulin, without any significant reduction of the risk of severe hypoglycemia.
Discussion

- The reduction of HbA1c is probably because of their greater efficacy on postprandial hyperglycemia.

- The methods for the evaluation of postprandial glucose differ greatly across trials, preventing a reliable meta-analysis.

- Most of the trials were sponsored by manufacturers of short-acting analogues. (Poor reporting of some trials)
Discussion

- The description of trials in available papers was often inadequate

- In most instances, patients enrolled were previously treated with regular human insulin. Bias in favor to analogues

- Those new to analogues needed to acquire some experience. Bias in favor of HRI
Discussion

- A previous meta-analysis had not shown any difference in HbA1c between regular human insulin and short-acting analogues in patients with type 2 diabetes.

- The overall number of hypoglycemic events was very small, limiting the statistical power of this analysis.