Review: Intensive insulin therapy for type 1 diabetes mellitus increases risk for severe hypoglycemia, and pump therapy increases ketoacidosis


Objective
To determine, using meta-analysis, the risks of intensified insulin treatment in patients with type 1 diabetes mellitus.

Data sources
Studies were identified by using MEDLINE, reviewing the bibliographies of research and review articles, and hand-searching 4 specialty diabetes journals.

Study selection
Studies were selected if they were parallel-group or crossover randomized controlled trials that compared intensive insulin therapy, including multiple daily injections or insulin pump therapy and frequent monitoring, with conventional therapy in patients with type 1 diabetes; had ≥ 6-month follow-up; included repeated measurements of glycosylated hemoglobin; and reported ≥ 1 outcome event. Studies of patients who were pregnant or had end-stage diabetic complications or renal transplants were excluded.

Data extraction
Data were extracted using a standardized form. Principal investigators were contacted to supply missing information. Main outcomes were episodes of severe hypoglycemia, ketoacidosis, and death. Each study was rated for methodologic quality with particular attention given to selection bias, randomization method, and use of an intention-to-treat analysis (maximum 6 points).

Main results
14 studies (2067 patients) were included with a mean quality score of 4 (range 2 to 6). The risk for having ≥ 1 episode of severe hypoglycemia was increased in intensively treated patients compared with conventionally treated patients (𝑃 < 0.001) and determined by the degree of reduction in glycosylated hemoglobin (Table). The median number of episodes was 7.9 and 4.6 per 100 person-years for intensively and conventionally treated patients, respectively. The risk for ketoacidosis was also increased in patients who received intensified insulin therapy (𝑃 < 0.001) (Table). Exclusive insulin pump therapy and not multiple daily injections or a combination of pump therapy and multiple injections accounted for the greater risk for ketoacidosis. Mortality rates did not differ between intensively treated and conventionally treated patients (15% vs 11 deaths, 𝑃 = 0.39) (Table).

Conclusions
Substantial risk for hypoglycemia and ketoacidosis exists with intensive insulin therapy for type 1 diabetes and dependent on the degree of glucose lowering and method of insulin therapy. Mortality risk is not increased.

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For article reprint: Dr. M. Egger, Department of Social Medicine, Conway Hall, Whitley Road, Bristol BS8 2PR, England, UK. E: 44-117-928-7325.


Risk for adverse outcomes from intensive insulin therapy

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Combined odds ratio</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>Hypoglycemia</td>
<td>2.99</td>
<td>2.45 to 3.64</td>
</tr>
<tr>
<td>Ketoacidosis</td>
<td>1.74</td>
<td>1.27 to 2.38</td>
</tr>
<tr>
<td>Death from all causes</td>
<td>1.40</td>
<td>0.65 to 3.01*</td>
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</tbody>
</table>

*Not significant.

Commentary
The benefits of intensified treatment of type 1 diabetes are well established and have been confirmed by several randomized controlled trials. An analysis of the Diabetes Control and Complications Trial experience showed that a 10% reduction in glycosylated hemoglobin was associated with a risk reduction of approximately 45% for the progression of diabetic retinopathy (1). Unfortunately, the same reduction in glycosylated hemoglobin was also associated with an 18% increased risk for severe hypoglycemia. The meta-analysis by Egger and colleagues also shows an increased risk for diabetic ketoacidosis with insulin pump therapy, which was unchanged from 1983 to 1992. This finding underscores the important clinical principle that patients using insulin pumps for intensive therapy must be appropriately educated in the prevention of this adverse effect. This is particularly true if short-acting insulin analogues, such as lispro insulin, are used in the pump because insulin deficiency will develop more quickly with infusion interruption.

It is hoped that the development of insulin preparations with superior pharmacokinetics will allow the benefits of intensified therapy to be realized without increasing adverse events. In a recent randomized trial of pump therapy, lispro improved glycosylated hemoglobin levels and lowered the rate of hypoglycemia (2) when compared with human insulin.

For most patients with type 1 diabetes, implementation of intensified diabetes treatment regimens will dramatically improve the long-term outcome, but individualized glycemic targets may have to be modified to avoid excessive hypoglycemia.

Bernard Zinman, MD
University of Toronto, Ontario, Canada

References

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*Evid Based Med* 1998 3: 50
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