Note: This is a two-article spread with a shared commentary. Please scroll down for the second article.

THERAPEUTICS

Review: Insulin monotherapy and insulin combined with oral hypoglycemic agents provide similar glycemic control

Goudswaard AN, Furlong NJ, Rutten GE, Stolk RP, Valk GD. **Insulin monotherapy versus combinations of insulin with oral hypoglycaemic agents in patients with type 2 diabetes mellitus.** Cochrane Database Syst Rev. 2004;(4):CD003418.

QUESTION

In patients with type 2 diabetes mellitus and inadequate glycemic control, how do insulin monotherapy and insulin combined with oral hypoglycemic agents (OHAs) compare?

METHODS

Data sources: 5 databases.

Study selection and assessment: Randomized controlled trials (RCTs) with ≥ 2-month follow-up that compared insulin monotherapy with combinations of insulin and single or multiple OHAs in patients with type 2 diabetes and inadequate glycemic control. Study quality was assessed using the Maastricht–Amsterdam Criteria List, which considered randomization procedure, allocation concealment, blinding, withdrawals and dropouts, and intention-to-treat analysis (total score range 0 to 7).

Outcomes: Main outcomes were any diabetes-related morbidity (myocardial infarction, angina, heart failure, stroke, renal failure, amputation, vitreous hemorrhage, retinal photocoagulation, blindness in 1 eye, or cataract extraction) and glycemic control. Additional outcomes included hypoglycemia, insulin requirement, and weight gain.

MAIN RESULTS

22 articles reporting 20 RCTs (n = 1811, mean age 60 y, 54% women, mean known duration of diabetes 9.6 y) met the inclusion criteria. Study quality was generally low (mean score 2.6). No RCTs reported diabetes-related morbidity, mortality, or all-cause mortality. 13 RCTs (21 comparisons) provided sufficient data on glycemic control to be pooled. 5 comparisons of a single evening injection with evening insulin combined with sulfonylurea showed less lowering from baseline of glycated hemoglobin (HbA_{1c}) with insulin monotherapy (Table). Of 4 other comparisons that could not be included in the meta-analysis, 2 showed better outcome with combination therapy and 2 showed no difference. Twice-daily insulin monotherapy was compared with combination insulin and OHAs in 10 comparisons. Greater lowering of HbA_{1c} levels was seen with twice-daily insulin monotherapy than morning NPH insulin plus sulfonylurea or plus sulfonylurea and metformin (4 comparisons). Among RCTs comparing multiple daily insulin injections with insulin plus OHAs, no difference was seen for lowering of HbA_{1c} levels (5 comparisons). Of 14 RCTs (22 comparisons) that assessed hypoglycemia, all but 1 comparison showed no difference between monotherapy and combination therapy: 1 comparison showed more hypoglycemic events with monotherapy. Combination therapy resulted in a 46% weighted mean relative reduction in daily insulin requirement. Few RCTs showed a difference in weight gain: 1 comparison showed 3.7 kg less weight gain with bedtime NPH insulin plus metformin compared with twice-daily monotherapy, and 3 comparisons showed 1.1 kg less weight gain with combination therapy compared with multiple daily monotherapy.

CONCLUSION

In patients with type 2 diabetes, insulin monotherapy and insulin combined with oral hypoglycemic agents provide similar improvements in glycemic control.

Source of funding: Not stated.

For correspondence: Dr. A.N. Goudswaard, University Medical Center Utrecht, Houten, The Netherlands. E-mail lex@goudswaard.cx. ■

Insulin monotherapy vs insulin combination therapy with oral hypoglycemic agents for type 2 diabetes*

Outcome	Number of comparisons	Insulin monotherapy regimen	Combination therapy regimen	Weighted mean difference (95% CI)
HbA_{1c} change from baseline	5	Insulin once daily	Evening insulin NPH + sulfonylurea	0.33% (0.03 to 0.62)†
	4	Insulin twice daily	Morning insulin NPH + sulfonylurea or sulfonylurea and metformin	0.43% (0.05 to 0.82)‡

*HbA_{1c} = glycated hemoglobin. CI defined in Glossary. Study duration ranged from 3 months to 2 years. A random-effects model was used.
†Difference favors insulin combination therapy.
‡Difference favors insulin monotherapy.

COMMENTARY

The effective use of insulin in clinical practice remains an important clinical challenge for many practitioners. Indeed, insulin treatment is often delayed or withheld in patients with type 2 diabetes, and most practitioners appreciate that insulin-treated patients often have poorer glycemic control than those receiving oral agents. Two issues key to insulin use are examined in the reviews of Goudswaard and Siebenhofer and their colleagues: What is the potential benefit of combining OHAs with insulin in type 2 diabetes, and what is the benefit of such rapid-acting insulin analogues as lispro, aspart, and glulisine?

The review by Goudswaard and colleagues concludes that no significant clinical advantage exists with the use of combination OHA-insulin therapy compared with insulin monotherapy. However, this result is not entirely unexpected because many of the trials used combination sulfonylurea–insulin therapy. These 2 insulin-providing treatments might not be expected to have substantial advantages over insulin injection alone. Most studies of OHA combination suggest that the use of both insulin-providing and insulin-sensitizing therapy (e.g., adding metformin and/or thiazolidinedione [TZD] to sulfonylurea) specifically targets the metabolic defects that give rise to hyperglycemia and may in fact achieve superior control. Given this, an assessment of combined insulin–metformin or insulin–TZD therapy might reveal distinctly different results. Further, many of the included trials used only once- or twice-daily insulin injections, whereas optimal insulin therapy may require ≥ 3 injections in many patients.

The review by Goudswaard and colleagues simply confirms that use of either sulfonylurea or metformin with low-dose once- or twice-daily insulin is of limited benefit. The broad conclusion that insulin monotherapy and insulin combined with OHAs provide similar glycemic control should be viewed with caution. Further assessment of oral agents added to optimized multidose insulin and specific analysis of

(continued on page 63)

Review: Short-acting insulin analogues reduce glycosylated hemoglobin more than regular human insulin but only in adults with type 1 diabetes

Siebenhofer A, Plank J, Berghold A, et al. **Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus.** Cochrane Database Syst Rev. 2004;(4):CD003287.

QUESTION

In patients with diabetes, is a short-acting insulin analogue more effective than regular human insulin?

METHODS

Data sources: 3 databases, references of studies and reviews, abstracts of major diabetology meetings, hand-searches of diabetes journals, the International Register of Clinical Trials Registers, the register of Current Science, 3 main pharmaceutical companies producing short-acting insulin analogues (Aventis, Eli Lilly, and Novo Nordisk), experts and approval agencies, and bibliographies of standard textbooks.

Study selection and assessment: Randomized controlled trials (RCTs) ≥ 4 weeks in duration that compared short-acting insulin analogues with regular human insulin in patients with type 1, type 2, or gestational diabetes. Methodological quality was assessed using the criteria in the Cochrane Handbook and the criteria of Schulz and Jadad.

Outcomes: Glycemic control, glycemic episodes, and quality of life (QOL).

MAIN RESULTS

42 RCTs (n = 7933) met the inclusion criteria. 25 RCTs were in patients with type 1 diabetes, 5 in patients with type 2 diabetes, 5 in a combined diabetes population, 3 in children, 1 in adolescents, 1 in pregnant women with type 1 diabetes, and 2 in women with gestational diabetes. 14 RCTs had parallel-group designs, and 28 had cross-over designs. 6 studies were of moderate methodological quality, and 36 were of poor quality. Glycated hemoglobin (HbA_{1c}) was reduced more with short-acting insulin analogues than with regular human insulin in patients with type 1 diabetes; no difference was seen in patients with type 2 diabetes (Table). Hypoglycemic episodes did not differ between treatment groups in type 1 or type 2 diabetic patients (Table). In the RCT of pregnant women with type 1 diabetes, short-acting insulin analogues reduced HbA_{1c}. Hypoglycemic episodes were reduced with short-acting insulin analogues in the RCT of adolescents (P = 0.02) and increased in the RCT of pregnant women with type 1 diabetes ($P < 0.05$). For the RCTs that assessed QOL with the Diabetes Treatment Satisfaction Questionnaire (the most-used instrument), 4 RCTs showed improvement with short-acting insulin analogues, and 3 RCTs showed no difference between groups.

CONCLUSIONS

In adults with type 1 diabetes, short-acting insulin analogue reduces glycosylated hemoglobin more than regular human insulin. No difference is seen for hypoglycemic episodes. In adults with type 2 diabetes, children, and women with gestational diabetes, insulin analogues and regular human insulin do not differ in effect.

Source of funding: Not stated.

For correspondence: Dr. A. Siebenhofer, Leopold Auenbrugger Medical University of Graz, Graz, Austria. E-mail andrea.siebenhofer@medunigraz-at.

Short-acting insulin analogue vs regular human insulin*

Outcomes	Diabetes patient group	Number of comparisons	Weighted mean difference (95% CI)
HbA_{1c} change from baseline	Type 1	21	–0.1% (–0.2 to –0.1)†
	Type 2	4	–0.02% (–0.1 to 0.1)
Hypoglycemic episodes (mean episodes per patient-mo)	Type 1	11	–0.2 (–1.2 to 0.9)
	Type 2	5	–0.2 (–0.5 to 0.1)

*HbA_{1c} = glycated hemoglobin. CI defined in Glossary. Mean follow-up was 3.6 months. A random-effects model was used.
†Difference favors short-acting insulin analogues.

COMMENTARY *(continued from page 62)*

combination insulin-sensitizer therapy may show distinctly different results and could lead to other advantages, such as lower rates of hypoglycemia, a need for fewer injections, or the use of a lower insulin dose. Further, metformin may limit the weight gain often seen with insulin use. Independent of the results reported, the primary goal for patients and practitioners is to achieve the best and safest control possible. The review certainly does not exclude the possibility of a benefit from combinations of OHAs and insulin, and further assessment of such an approach must be done.

Rapid-acting insulin analogues are widely used in both type 1 and type 2 diabetes. However, even after nearly a decade of experience, optimal use of such insulins is not well understood. Are they most useful in multidose regimens? Are they equally effective for type 1 and type 2 diabetes? Do they offer a safety advantage? Do they improve either glycemic control or QOL?

Clinical experience and several smaller studies suggest that mealtime administration of rapid-acting insulin may improve postmeal blood glucose control and is associated with a lower risk for hypoglycemia, particularly at night. Further, meal-time dosing of rapid-acting insulin is convenient for many patients. The review by Siebenhofer and colleagues suggests that only modest improvements in glycemic control are achieved with rapid-acting insulin. However, even these small benefits may underestimate the potential clinical advantage of such insulin. Rapid-acting insulin offers greater convenience, can allow patients to alter meal plans more readily, and may be associated with less weight gain. However, these benefits would not be expected to improve glucose control. For many, hypoglycemia risk limits the ability to intensify insulin. Is it possible that use of insulin analogues in a real-life setting would result in greater improvements in HbA_{1c} levels? This unanswered question underscores the need for well-designed clinical trials that include careful individualization of treatment regimens and carefully measure outcomes, including safety, satisfaction, flexibility, and convenience. In lieu of such trials, these reviews provide useful guidance for clinical decisions on insulin use, as always to be tempered by individual patient needs and wishes.

David M. Kendall, MD
International Diabetes Center
Minneapolis, Minnesota, USA

Reference

1. **Chase HP, Lockspeiser T, Peery B, et al.** Diabetes Care. 2001;24:430-4.