Can J Diabetes 37 (2013) S56–S60

Contents lists available at SciVerse ScienceDirect

Canadian Journal of Diabetes

journal homepage: www.canadianjournalofdiabetes.com

Clinical Practice Guidelines

Pharmacotherapy in Type 1 Diabetes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Basal-bolus insulin regimens (e.g. multiple daily injections or continuous subcutaneous insulin infusion) are the insulin regimens of choice for all adults with type 1 diabetes.
- Insulin regimens should be tailored to the individual's treatment goals, lifestyle, diet, age, general health, motivation, hypoglycemia awareness status and ability for self-management.
- All individuals with type 1 diabetes should be counseled about the risk, prevention and treatment of insulin-induced hypoglycemia.

Introduction

Insulin is lifesaving pharmacological therapy for people with type 1 diabetes. Insulin preparations are primarily produced by recombinant DNA technology and are formulated either as structurally identical to human insulin or as a modification of human insulin (insulin analogues) to alter pharmacokinetics. Human insulin and insulin analogues are preferred and used by most adults with type 1 diabetes; however, preparations of animal-sourced insulin are still accessible in Canada (1).

Insulin preparations are classified according to their duration of action and are further differentiated by their time of onset and peak actions (Table 1). Premixed insulin preparations are available and are not generally suitable for intensive treatment in patients with type 1 diabetes in whom frequent adjustments of insulin are required.

There may be a role for adjunctive therapy in some people with type 1 diabetes to aid in achieving optimal glycemic targets. Pharmacotherapy for prevention of complications and treatment of risk factors will be addressed in other chapters.

Insulin Delivery Systems

Insulin can be administered by syringe, pen or pump (continuous subcutaneous insulin infusion [CSII]). Insulin pen devices facilitate the use of multiple injections of insulin. CSII therapy is a safe and effective method of intensive insulin therapy in type 1 diabetes and has shown improvements in glucose control over NPH-based regimens and, in fewer studies, over long-acting analogue regimens with less severe hypoglycemia (2,3). Advancements in basal insulins may lessen the value of CSII in type 1 diabetes. CSII may provide some advantages over other methods of intensive therapy, particularly in individuals with higher baseline glycated hemoglobin (A1C) (4–9) In patients using CSII, insulin aspart and insulin lispro have been shown to be superior to regular insulin by improving postprandial glycemic control and reducing hypoglycemia (10–13). Advances in continuous glucose monitoring systems (CGMSs) may augment CSII (14,15). For CSII and CGMS, adverse events, cost and mortality data are lacking (3).

Initiation of Insulin Therapy

Patients with type 1 diabetes will be initiated on insulin therapy immediately at diagnosis. This will involve both the selection of an insulin regimen and the start of education. Patients must receive initial and ongoing education that includes comprehensive information on how to care for and use insulin; prevention, recognition and treatment of hypoglycemia; sick-day management; adjustments for food intake (e.g. carbohydrate counting) and physical activity; and self-monitoring of blood glucose (SMBG).

Insulin Regimens

Insulin regimens should be tailored to the individual's treatment goals, lifestyle, diet, age, general health, motivation, hypoglycemia awareness status and ability for self-management. Social and financial aspects also should be considered. After insulin initiation, some patients go through a "honeymoon period," during which insulin requirements may decrease. This period is, however, transient (usually weeks to months), and insulin requirements will increase with time.

While fixed-dose regimens (conventional therapy) once were common and still may be used in some circumstances, they are not preferred. The Diabetes Control and Complications Trial (DCCT) conclusively demonstrated that intensive treatment of type 1 diabetes significantly delays the onset and slows the progression of microvascular and macrovascular complications (16,17). The most successful protocols for type 1 diabetes rely on basal-bolus (basal-prandial) regimens that are used as a component of intensive diabetes therapy. Basal insulin is provided by an intermediate-acting insulin or a long-acting insulin analogue once or twice daily. Bolus insulin is provided by a short-acting insulin or a rapid-acting insulin analogue given at each meal. Such protocols attempt to duplicate normal pancreatic insulin secretion. Prandial insulin dose must take into account the carbohydrate content and glycemic index of the carbohydrate consumed, exercise around mealtime

1499-2671/$ – see front matter
http://dx.doi.org/10.1016/j.jcjd.2013.01.020

Table 1
Types of insulin

Insulin type (trade name)	Onset	Peak	Duration
Bolus (prandial) insulins			
Rapid-acting insulin analogues (clear)			
Insulin aspart (NovoRapid®)	10–15 min	1–1.5 h	3–5 h
Insulin glulisine (Apidra®)	10–15 min	1–1.5 h	3–5 h
Insulin lispro (Humalog®)	10–15 min	1–2 h	3.5–4.75 h
Short-acting insulins (clear)			
Humulin®-R	30 min	2–3 h	6.5 h
Novolin® ge Toronto			
Basal insulins			
Intermediate-acting (cloudy)			
Humulin®-N	1–3 h	5–8 h	Up to 18 h
Novolin® ge NPH			
Long-acting insulin analogues (clear)			
Insulin detemir (Levemir®)	90 min	Not applicable	Up to 24 h (glargine 24 h, detemir 16–24 h)
Insulin glargine (Lantus®)			
Premixed insulins			
Premixed regular insulin–NPH (cloudy)	A single vial or cartridge contains a fixed ratio of insulin (% of rapid-acting or short-acting insulin to % of intermediate-acting insulin)		
Humulin® 30/70			
Novolin® ge 30/70, 40/60, 50/50			
Premixed insulin analogues (cloudy)			
Biphasic insulin aspart (NovoMix® 30)			
Insulin lispro/lispro protamine (Humalog® Mix25 and Mix50)			

Physicians should refer to the most current edition of *Compendium of Pharmaceuticals and Specialties* (Canadian Pharmacists Association, Ottawa, Ontario, Canada) and product monographs for detailed information.

and the fact that the carbohydrate-to-insulin ratio may not be the same for each meal (breakfast, lunch and dinner). Prandial insulins also can be used for correction doses to manage hyperglycemia.

Compared with regular insulin, insulin aspart, insulin glulisine or insulin lispro, in combination with adequate basal insulin, results in improved postprandial glycemic control and A1C while minimizing the occurrence of hypoglycemia (when using insulin lispro or insulin aspart) (18–23). Regular insulin should ideally be administered 30 to 45 minutes prior to a meal. In contrast, insulin aspart, insulin glulisine and insulin lispro should be administered 0 to 15 minutes before meals. In fact, their rapid onset of action allows for these insulins to be administered up to 15 minutes after a meal. However, preprandial injections achieve better postprandial control and, possibly, better overall glycemic control (22,24,25). Insulin aspart has been associated with improved quality of life (26). Insulin glulisine has been shown to be equivalent to insulin lispro for glycemic control, with greater A1C reduction when given preprandially as opposed to postprandially (22,27).

When used as a basal insulin in patients with good glycemic control, the long-acting analogues, insulin detemir and insulin glargine (with regular insulin or rapid-acting insulin analogues for meals), result in lower fasting plasma glucose levels and less nocturnal hypoglycemia compared with once- or twice-daily NPH insulin (18,28–37). Given the potential severe consequences of nocturnal hypoglycemia (discussed below), the avoidance of this complication is of critical clinical importance. Patients report increased treatment satisfaction and quality of life with use of insulin glargine compared with use of NPH in a basal-bolus insulin regimen (38,39).

When compared with 4-times-daily NPH insulin, insulin glargine was associated with lower A1C and less hypoglycemia (32). Among people with type 1 diabetes, insulin glargine has been shown to have a longer duration of action compared with detemir (40); however, 15% to 30% of patients using insulin glargine will experience preinjection hyperglycemia, which is prevented by twice daily administration of the insulin (41). Insulin detemir has a flatter pharmacodynamic profile than NPH insulin (33). Twice-daily insulin detemir as the basal component of a basal-bolus insulin regimen has been shown to reduce nocturnal hypoglycemia compared with twice-daily NPH insulin (34,42). There has been a trend toward improved A1C with both insulin detemir and insulin glargine that has reached significance in several studies (36,38,42–46). Due to concerns that alterations in the pharmacokinetics may occur, mixing detemir or glargine with other insulins in the same syringe is not recommended by the manufacturers.

An ultra-long-acting insulin analogue, insulin degludec, has been shown to have comparable safety and tolerability to insulin glargine when used as a basal insulin in type 1 diabetes and less hypoglycemia (47).

Adjunctive therapy for glycemic control

As the incidents of obesity and overweight increase in the population, including those with type 1 diabetes, there is increasing interest in the potential use of oral medications that improve insulin sensitivity for these patients. The use of metformin in type 1 diabetes reduces insulin requirements and the total cholesterol/low-density lipoprotein ratio and may lead to modest weight loss, but it does not result in improved A1C (48). Metformin use in type 1 diabetes is off-label and potentially harmful in the setting of renal or heart failure.

Hypoglycemia

Insulin-induced hypoglycemia is a major obstacle for individuals trying to achieve glycemic targets. Hypoglycemia can be severe and result in confusion, coma or seizure, requiring the assistance of other individuals. Significant risk of hypoglycemia often necessitates less stringent glycemic goals. The negative social and emotional impact of hypoglycemia may make patients reluctant to intensify therapy. The diabetes healthcare team should review the patient's experience with hypoglycemia at each visit. This should include an estimate of cause, frequency, symptoms, recognition, severity and treatment, as well as the risk of driving mishaps with hypoglycemia.

Intensive vs. conventional insulin therapy

Hypoglycemia is the most common adverse effect of intensive insulin therapy in patients with type 1 diabetes. In the DCCT, 35% of patients in the conventional treatment group and 65% in the intensive group experienced at least 1 episode of severe hypoglycemia (49,50). In a meta-analysis of 14 trials, the median incidence of severe hypoglycemia was 4.6 and 7.9 episodes per 100 patient-years in the conventionally treated and intensively treated patients, respectively (51). Studies have suggested that with adequate self-management education, appropriate glycemic targets, SMBG and professional support, intensive therapy may result in less hypoglycemia than reported in the DCCT (52–55). CSII leads to reductions in severe hypoglycemia compared to multiple daily injections (56). CGMS used in addition to CSII or with multiple daily injections is associated with less hypoglycemia than with the use of traditional glucose testing (57,58).

Insulin analogues vs. regular and intermediate-acting insulins

Although there are no differences in the magnitude and temporal pattern of the physiological, symptomatic and counter-regulatory hormonal responses to hypoglycemia induced by

regular human insulin or rapid-acting analogues (59,60), the frequency of hypoglycemic events has been shown to be reduced with rapid-acting insulin analogues compared with regular insulin (18–21).

Long-acting insulin analogues may reduce the incidence of hypoglycemia and nocturnal hypoglycemia when compared to intermediate-acting insulin as the basal insulin (36,37,61–64).

Lifestyle factors

Deviations from recommended or appropriate self-management behaviours (e.g. eating less food, taking more insulin, engaging in more activity) account for 85% of hypoglycemic episodes (65,66). For patients managed with fixed-dose insulin regimens, care should be taken to develop an individualized meal and activity plan that the person can and will follow (67). Adding bedtime snacks may be helpful to prevent nocturnal hypoglycemia among those taking NPH as the basal insulin or in those individuals at high risk of severe hypoglycemia (regardless of insulin type), particularly when bedtime plasma glucose levels are <7.0 mmol/L (68,69).

Knowledge of the acute effects of exercise is mandatory. Low- to moderate-intensity exercise lowers blood glucose (BG) levels both during and after the activity, increasing the risk of a hypoglycemic episode. These effects on BG levels can be modified by altering diet, insulin, and the type and timing of exercise. In contrast, high-intensity exercise raises BG levels during and immediately after the event. SMBG before, during and especially for many hours after exercise is important for establishing response to exercise and guiding the appropriate management of exercise. If ketosis is present (urine ketone level >8.0 mmol/L or blood ketone level >3.0 mmol/L), exercise should not be performed as metabolic deterioration will occur (70). Exercise-induced hypoglycemia may be lessened with the use of detemir as the basal insulin (71).

Hypoglycemia unawareness and nocturnal hypoglycemia

Hypoglycemia unawareness occurs when the threshold for the development of autonomic warning symptoms is close to, or lower than, the threshold for the neuroglycopenic symptoms, such that the first sign of hypoglycemia is confusion or loss of consciousness. Severe hypoglycemia is often the primary barrier to achieving glycemic targets in people with type 1 diabetes (72) and occurs frequently during sleep or in the presence of hypoglycemia unawareness (73,74). The sympathoadrenal response to hypoglycemia is reduced during sleep (75,76). Asymptomatic nocturnal hypoglycemia is common and often lasts >4 hours (73,77–80). Severe hypoglycemia, resulting in seizures, is more likely to occur at night than during the day (81). To reduce the risk of asymptomatic nocturnal hypoglycemia, individuals using intensive insulin therapy should periodically monitor overnight BG levels at a time that corresponds with the peak action time of their overnight insulin.

In type 1 diabetes, hypoglycemia was reported to occur at a mean rate of approximately 2 episodes per week. Frequent hypoglycemia can decrease normal responses to hypoglycemia (82) and lead to hypoglycemia unawareness and defective glucose counterregulation. Both hypoglycemia unawareness and defective glucose counterregulation are potentially reversible. Strict avoidance of hypoglycemia for a period of 2 days to 3 months has been associated with improvement in the recognition of severe hypoglycemia, the counterregulatory hormone responses or both (52,82–88). Structured educational and psychobehavioural programs (e.g. BG awareness training) may help improve detection of hypoglycemia and reduce the frequency of severe hypoglycemia (89,90).

RECOMMENDATIONS

Insulin regimens for type 1 diabetes

1. To achieve glycemic targets in adults with type 1 diabetes, basal-bolus insulin regimens or CSII as part of an intensive diabetes management regimen should be used [Grade A, Level 1A (16)].
2. Rapid-acting bolus insulin analogues, in combination with adequate basal insulin, should be used instead of regular insulin to minimize the occurrence of hypoglycemia, improve A1C [Grade B, Level 2 (19,21,23)] and achieve postprandial glucose targets [Grade B, Level 2 (23,91)].
3. Rapid-acting insulin analogues (aspart or lispro) should be used with CSII in adults with type 1 diabetes [Grade B, Level 2 (10,11)].
4. A long-acting insulin analogue (detemir, glargine) may be used as the basal insulin [Grade B, Level 2 (28-31)] to reduce the risk of hypoglycemia [Grade B, Level 2 (63) for detemir; Grade C, Level 3 (64) for glargine], including nocturnal hypoglycemia [Grade B, Level 2 (63) for detemir; Grade D, Consensus for glargine].

Hypoglycemia

5. All individuals with type 1 diabetes should be counselled about the risk and prevention of insulin-induced hypoglycemia, and risk factors for severe hypoglycemia should be identified and addressed [Grade D, Consensus].
6. In individuals with hypoglycemia unawareness, the following strategies may be used to reduce the risk of hypoglycemia and to attempt to regain hypoglycemia awareness:
   a. Increased frequency of SMBG, including periodic assessment during sleeping hours [Grade D, Consensus]
   b. Less stringent glycemic targets with avoidance of hypoglycemia for up to 3 months [Grade C, Level 3 (87,88)]
   c. A psychobehavioural intervention program (blood glucose awareness training) [Grade B, Level 2 (90)]

Abbreviations:
CSII, continuous subcutaneous insulin infusion; *SMBG,* self-monitoring of blood glucose.

Other Relevant Guidelines

Targets for Glycemic Control, p. S31
Monitoring Glycemic Control, p. S35
Physical Activity and Diabetes, p. S40
Pharmacologic Management of Type 2 Diabetes, p. S61
Hypoglycemia, p. S69
In-hospital Management of Diabetes, p. S77
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Type 1 Diabetes in Children and Adolescents, p. S153
Type 2 Diabetes in Children and Adolescents, p. S163
Diabetes and Pregnancy, p. S168
Diabetes in the Elderly, p. S184

References

1. Health Canada website. www.hc-sc.gc.ca. Accessed February 28, 2013.
2. Hoogma RP, Hammond PJ, Gomis R, et al. Comparison of the effects of continuous subcutaneous insulin infusion (CSII) and NPH-based multiple daily insulin injections (MDI) on glycaemic control and quality of life: results of the 5-nations trial. Diabetic Medicine 2005;23:141–7.
3. Misso ML, Egberts KJ, Page M, et al. Continuous subcutaneous insulin infusion (CSII) versus multiple insulin injections for type 1 diabetes mellitus. Cochrane Database Syst Rev 2010;1:CD005103.
4. Pickup J, Mattock M, Kerry S. Glycaemic control with continuous subcutaneous insulin infusion compared with intensive insulin injections in patients with type 1 diabetes: meta-analysis of randomised controlled trials. BMJ 2002;324:705.

5. Tsui E, Barnie A, Ross S, et al. Intensive insulin therapy with insulin lispro: a randomized trial of continuous subcutaneous insulin infusion versus multiple daily insulin injection. Diabetes Care 2001;24:1722–7.
6. DeVries JH, Snoek FJ, Kostense PJ, et al, Dutch Insulin Pump Study Group. A randomized trial of continuous subcutaneous insulin infusion and intensive injection therapy in type 1 diabetes for patients with long-standing poor glycemic control. Diabetes Care 2002;25:2074–80.
7. Hirsch IB, Bode BW, Garg S, et al, Insulin Aspart CSII/MDI Comparison Study Group. Continuous subcutaneous insulin infusion (CSII) of insulin aspart versus multiple daily injection of insulin aspart/insulin glargine in type 1 diabetic patients previously treated with CSII. Diabetes Care 2005;28:533–8.
8. Retnakaran R, Hochman J, DeVries JH, et al. Continuous subcutaneous insulin infusion versus multiple daily injections: the impact of baseline A1c. Diabetes Care 2004;27:2590–6.
9. Monami M, Lamanna C, Marchionni N, Mannucci E. Continuous subcutaneous insulin infusion versus multiple daily insulin injections in type 1 diabetes: a meta-analysis. Acta Diabetologica 2010;47(suppl 1):S77–81.
10. Zinman B, Tildesley H, Chiasson JL, et al. Insulin lispro in CSII: results of a double-blind crossover study. Diabetes 1997;46:440–3.
11. Bode B, Weinstein R, Bell D, et al. Comparison of insulin aspart with buffered regular insulin and insulin lispro in continuous subcutaneous insulin infusion: a randomized study in type 1 diabetes. Diabetes Care 2002;25:439–44.
12. Radermecker RP, Scheen AJ. Continuous subcutaneous insulin infusion with short-acting insulin analogues or human regular insulin: efficacy, safety, quality of life, and cost-effectiveness. Diabetes Metab Res Rev 2004;20: 178–88.
13. Siebenhofer A, Plank J, Berghold A, et al. Meta-analysis of short-acting insulin analogues in adult patients with type 1 diabetes: continuous subcutaneous insulin infusion versus injection therapy. Diabetologia 2004;47:1895–905.
14. O'Connell MA, Donath S, O'Neal DN, et al. Glycaemic impact of patient-led use of sensor-guided pump therapy in type 1 diabetes: a randomised controlled trial. Diabetologia 2009;52:1250–7.
15. Bergenstal RM, Tamborlane WV, Ahmann A, et al. Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes. N Engl J Med 2010;4: 311–20.
16. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–86.
17. Nathan DM, Cleary PA, Backlund JY, et al, Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005;353:2643–53.
18. DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. JAMA 2003;289:2254–64.
19. 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 2006;2:CD003287.
20. Heller SR, Colagiuri S, Vaaler S, et al. Hypoglycaemia with insulin aspart: a double-blind, randomised, crossover trial in subjects with type1 diabetes. Diabet Med 2004;21:769–75.
21. Plank J, Siebenhofer A, Berghold A, et al. Systematic review and meta-analysis of short-acting insulin analogues in patients with diabetes mellitus. Arch Intern Med 2005;165:1337–44.
22. Garg SK, Rosenstock J, Ways K. Optimized basal-bolus insulin regimens in type 1 diabetes: insulin glulisine versus regular human insulin in combination with basal insulin glargine. Endocr Pract 2005;11:11–7.
23. Gough S. A review of human and analogue insulin trials. Diabetes Res Clin Pract 2007;77:1–15.
24. Schernthaner G, Wein W, Shnawa N, et al. Preprandial vs. post-prandial insulin lispro: a comparative crossover trial in patients with type 1 diabetes. Diabet Med 2004;21:279–84.
25. Jovanovic L, Giammattei J, Acquistapace M, et al. Efficacy comparison between preprandial and postprandial insulin aspart administration with dose adjustment for unpredictable meal size. Clin Ther 2004;26:1492–7.
26. Bott U, Ebrahim S, Hirschberger S, et al. Effect of the rapid-acting insulin analogue insulin aspart on quality of life and treatment satisfaction in patients with type 1 diabetes. Diabet Med 2003;20:626–34.
27. Dreyer M, Prager R, Robinson A, et al. Efficacy and safety of insulin glulisine in patients with type 1 diabetes. Horm Metab Res 2005;37:702–7.
28. Warren E, Weatherley-Jones E, Chilcott J, et al. Systematic review and economic evaluation of a long-acting insulin analogue, insulin glargine. Health Technol Assess 2004;8:1–57.
29. Wang F, Carabino JM, Vergara CM. Insulin glargine: a systematic review of a long-acting insulin analogue. Clin Ther 2003;25:1541–77.
30. Dunn CJ, Plosker GL, Keating GM, et al. Insulin glargine: an updated review of its use in the management of diabetes mellitus. Drugs 2003;63:1743–78.
31. Chapman TM, Perry CM. Insulin detemir: a review of its use in the management of type 1 and 2 diabetes mellitus. Drugs 2004;64:2577–95.
32. Rossetti P, Pampanelli S, Fanelli C, et al. Intensive replacement of basal insulin in patients with type 1 diabetes given rapid-acting insulin analog at mealtime: a 3-month comparison between administration of NPH insulin four times daily and glargine insulin at dinner or bedtime. Diabetes Care 2003;26:1490–6.
33. Plank J, Bodenlenz M, Sinner F, et al. A double-blind, randomized, dose-response study investigating the pharmacodynamic and pharmacokinetic properties of the long-acting insulin analog detemir. Diabetes Care 2005;28: 1107–12.
34. De Leeuw I, Vague P, Selam JL, et al. Insulin detemir used in basal-bolus therapy in people with type 1 diabetes is associated with a lower risk of nocturnal hypoglycaemia and less weight gain over 12 months in comparison to NPH insulin. Diabetes Obes Metab 2005;7:73–82.
35. Garg S, Moser E, Dain M-P, Rodionova A. Clinical experience with insulin glargine in type 1 diabetes. Diabetes Technol Ther 2010;12:835–46.
36. Monami M, Marchionni N, Mannucci E. Long-acting insulin analogues vs. NPH human insulin in type 1 diabetes. A meta-analysis. Diabetes Obes Metab 2009; 11:372–8.
37. Szypowska A, Golicki D, Groele L, Pankowska E. Long-acting insulin analogue detemir compared with NPH insulin in type 1 diabetes. Pol Arch Med Wewn 2011;121:237–45.
38. Chatterjee S, Jarvis-Kay J, Rengarajan T, et al. Glargine versus NPH insulin: efficacy in comparison with insulin aspart in a basal bolus regimen in type 1 diabetes: the Glargine and Aspart Study (GLASS): a randomized cross-over study. Diabetes Res Clin Pract 2007;77:215–22.
39. Ashwell SG, Bradley C, Stephens JW, et al. Treatment satisfaction and quality of life with insulin glargine plus insulin lispro compared with NPH insulin plus unmodified human insulin in individuals with type 1 diabetes. Diabetes Care 2008;31:1112–7.
40. Porcellati F, Rossetti P, Busciantella NR, et al. Comparison of pharmacokinetics and dynamics of the long-acting insulin analogs glargine and detemir at steady state in type 1 diabetes: a double-blind, randomized, crossover study. Diabetes Care 2007;30:2447–52.
41. Ashwell SG, Gebbie J, Home PD. Twice-daily compared with once-daily insulin glargine in people with Type 1 diabetes using meal-time insulin aspart. Diabet Med 2006;23:879–86.
42. Home P, Bartley P, Russell-Jones D, et al, Study to Evaluate the Administration of Detemir Insulin Efficacy, Safety and Suitability (STEADINESS) Study Group. Insulin detemir offers improved glycemic control compared with NPH insulin in people with type 1 diabetes: a randomized clinical trial. Diabetes Care 2004; 27:1081–7.
43. Hermansen K, Fontaine P, Kukolja KK, et al. Insulin analogues (insulin detemir and insulin aspart) versus traditional human insulins (NPH insulin and regular human insulin) in basal-bolus therapy for patients with type 1 diabetes. Diabetologia 2004;47:622–9.
44. Kudva YC, Basu A, Jenkins GD, et al. Randomized controlled clinical trial of glargine versus ultralente insulin in the treatment of type 1 diabetes. Diabetes Care 2005;28:10–4.
45. Ashwell SG, Amiel SA, Bilous RW, et al. Improved glycaemic control with insulin glargine plus insulin lispro: a multicentre, randomized, cross-over trial in people with type 1 diabetes. Diabet Med 2006;23:285–92.
46. Bartley PC, Bogoev M, Larsen J, Philotheou A. Long-term efficacy and safety of insulin detemir compared to Neutral Protamine Hagedorn insulin in patients with Type 1 diabetes using a treat-to-treat basal-bolus regimen with insulin aspart at meals: a 2-year, randomized, controlled trial. Diabet Med 2008;25: 442–9.
47. Birkeland KI, Home PD, Wendisch U, et al. Insulin degludec in type 1 diabetes. A randomized controlled trial of a new-generation ultra-long-acting insulin compared with insulin glargine. Diabetes Care 2011;34:661–5.
48. Vella S, Buetow L, Royle P, et al. The use of metformin in type 1 diabetes: a systematic review of efficacy. Diabetologia 2010;53:809–20.
49. The Diabetes Control and Complications Trial Research Group. Adverse events and their association with treatment regimens in the Diabetes Control and Complications Trial. Diabetes Care 1995;18:1415–27.
50. The Diabetes Control and Complications Trial Research Group. Hypoglycemia in the Diabetes Control and Complications Trial. Diabetes 1997;46: 271–86.
51. Egger M, Davey Smith G, Stettler C, et al. Risk of adverse effects of intensified treatment in insulin-dependent diabetes mellitus: a meta-analysis. Diabet Med 1997;14:919–28.
52. Fanelli CG, Epifano L, Rambotti AM, et al. Meticulous prevention of hypoglycemia normalizes the glycemic thresholds and magnitude of most of neuroendocrine responses to, symptoms of, and cognitive function during hypoglycemia in intensively treated patients with short-term IDDM. Diabetes 1993;42:1683–9.
53. Bott S, Bott U, Berger M, et al. Intensified insulin therapy and the risk of severe hypoglycaemia. Diabetologia 1997;40:926–32.
54. Ahern J, Tamborlane WV. Steps to reduce the risks of severe hypoglycemia. Diabetes Spectrum 1997;10:39–41.
55. Bolli GB. How to ameliorate the problem of hypoglycemia in intensive as well as nonintensive treatment of type 1 diabetes. Diabetes Care 1999;22(suppl 2): B43–52.
56. Pickup JC, Sutton AJ. Severe hypoglycaemia and glycaemic control in Type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion. Diabet Med 2008;25: 765–74.
57. Battelino T, Phillip M, Bratina N, et al. Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes. Diabetes Care 2011;34:795–800.
58. Pickup JC, Freeman SC, Sutton AJ. Glycaemic control in type 1 diabetes during real time continuous glucose monitoring compared with self monitoring of blood glucose: meta-analysis of randomised controlled trials using individual patient data. BMJ 2011;343:d3805.

59. Torlone E, Fanelli C, Rambotti AM, et al. Pharmacokinetics, pharmacodynamics and glucose counterregulation following subcutaneous injection of the monomeric insulin analogue [Lys(B28), Pro(B29)] in IDDM. Diabetologia 1994; 37:713–20.
60. McCrimmon RJ, Frier BM. Symptomatic and physiological responses to hypoglycaemia induced by human soluble insulin and the analogue lispro human insulin. Diabet Med 1997;14:929–36.
61. Garg SK, Gottlieb PA, Hisatomi ME, et al. Improved glycemic control without an increase in severe hypoglycemic episodes in intensively treated patients with type 1 diabetes receiving morning, evening, or split dose insulin glargine. Diabetes Res Clin Pract 2004;66:49–56.
62. Garg SK, Paul JM, Karsten JI, et al. Reduced severe hypoglycemia with insulin glargine in intensively treated adults with type 1 diabetes. Diabetes Technol Ther 2004;6:589–95.
63. Goldman-Levine JD, Lee KW. Insulin detemir: a new basal insulin analog. Ann Pharmacother 2005;39:502–7.
64. Mullins P, Sharplin P, Yki-Jarvinen H, et al. Negative binomial meta-regression analysis of combined glycosylated hemoglobin and hypoglycemia outcomes across eleven phase III and IV studies of insulin glargine compared with neutral protamine Hagedorn insulin in type 1 and type 2 diabetes mellitus. Clin Ther 2007;29:1607–19.
65. Clarke WL, Cox DJ, Gonder-Frederick LA, et al. The relationship between nonroutine use of insulin, food, and exercise and the occurrence of hypoglycemia in adults with IDDM and varying degrees of hypoglycemic awareness and metabolic control. Diabetes Educ 1997;23:55–8.
66. Fritsche A, Stumvoll M, Renn W, et al. Diabetes teaching program improves glycemic control and preserves perception of hypoglycemia. Diabetes Res Clin Pract 1998;40:129–35.
67. Cryer PE, Fisher JN, Shamoon H. Hypoglycemia. Diabetes Care 1994;17:734–55.
68. Kaufman FR, Halvorson M, Kaufman ND. A randomized, blinded trial of uncooked cornstarch to diminish nocturnal hypoglycemia at diabetes camp. Diabetes Res Clin Pract 1995;30:205–9.
69. Kalergis M, Schiffrin A, Gougeon R, et al. Impact of bedtime snack composition on prevention of nocturnal hypoglycemia in adults with type 1 diabetes undergoing intensive insulin management using lispro insulin before meals: a randomized, placebo-controlled, crossover trial. Diabetes Care 2003;26: 9–15.
70. Berger M, Berchtold P, Cüppers HJ, et al. Metabolic and hormonal effects of muscular exercise in juvenile type diabetics. Diabetologia 1977;13: 355–65.
71. Arutchelvam V, Heise T, Dellweg S, et al. Plasma glucose and hypoglycaemia following exercise in people with Type 1 diabetes: a comparison of three basal insulins. Diabet Med 2009;26:1027–32.
72. Cryer PE. Banting Lecture. Hypoglycemia: the limiting factor in the management of IDDM. Diabetes 1994;43:1378–89.
73. The DCCT Research Group. Epidemiology of severe hypoglycemia in the Diabetes Control and Complications Trial. Am J Med 1991;90:450–9.
74. Daneman D, Frank M, Perlman K, et al. Severe hypoglycemia in children with insulin-dependent diabetes mellitus: frequency and predisposing factors. J Pediatr 1989;115:681–5.
75. Berlin I, Sachon CI, Grimaldi A. Identification of factors associated with impaired hypoglycaemia awareness in patients with type 1 and type 2 diabetes mellitus. Diabetes Metab 2005;31:246–51.
76. Schultes B, Jauch-Chara K, Gais S, et al. Defective awakening response to nocturnal hypoglycemia in patients with type 1 diabetes mellitus. PLOS Med 2007;4:0361–9.
77. Porter PA, Byrne G, Stick S, et al. Nocturnal hypoglycaemia and sleep disturbances in young teenagers with insulin dependent diabetes mellitus. Arch Dis Child 1996;75:120–3.
78. Gale EA, Tattersall RB. Unrecognised nocturnal hypoglycaemia in insulin-treated diabetics. Lancet 1979;1:1049–52.
79. Beregszàszi M, Tubiana-Rufi N, Benali K, et al. Nocturnal hypoglycemia in children and adolescents with insulin-dependent diabetes mellitus: prevalence and risk factors. J Pediatr 1997;131:27–33.
80. Vervoort G, Goldschmidt HM, van Doorn LG. Nocturnal blood glucose profiles in patients with type 1 diabetes mellitus on multiple ($>$ or $=$ 4) daily insulin injection regimens. Diabet Med 1996;13:794–9.
81. Davis EA, Keating B, Byrne GC, et al. Hypoglycemia: incidence and clinical predictors in a large population-based sample of children and adolescents with IDDM. Diabetes Care 1997;20:22–5.
82. Ovalle F, Fanelli CG, Paramore DS, et al. Brief twice-weekly episodes of hypoglycemia reduce detection of clinical hypoglycemia in type 1 diabetes mellitus. Diabetes 1998;47:1472–9.
83. Dagogo-Jack S, Rattarasarn C, Cryer PE. Reversal of hypoglycemia unawareness, but not defective glucose counterregulation, in IDDM. Diabetes 1994;43:1426–34.
84. Fanelli C, Pampanelli S, Epifano L, et al. Long-term recovery from unawareness, deficient counterregulation and lack of cognitive dysfunction during hypoglycaemia, following institution of rational, intensive insulin therapy in IDDM. Diabetologia 1994;37:1265–76.
85. Dagogo-Jack S, Fanelli CG, Cryer PE. Durable reversal of hypoglycemia unawareness in type 1 diabetes. Diabetes Care 1999;22:866–7.
86. Davis M, Mellman M, Friedman S, et al. Recovery of epinephrine response but not hypoglycemic symptom threshold after intensive therapy in type 1 diabetes. Am J Med 1994;97:535–42.
87. Liu D, McManus RM, Ryan EA. Improved counter-regulatory hormonal and symptomatic responses to hypoglycemia in patients with insulin-dependent diabetes mellitus after 3 months of less strict glycemic control. Clin Invest Med 1996;19:71–82.
88. Lingenfelser T, Buettner U, Martin J, et al. Improvement of impaired counter-regulatory hormone response and symptom perception by short-term avoidance of hypoglycemia in IDDM. Diabetes Care 1995;18:321–5.
89. Kinsley BT, Weinger K, Bajaj M, et al. Blood glucose awareness training and epinephrine responses to hypoglycemia during intensive treatment in type 1 diabetes. Diabetes Care 1999;22:1022–8.
90. Schachinger H, Hegar K, Hermanns N, et al. Randomized controlled clinical trial of Blood Glucose Awareness Training (BGAT III) in Switzerland and Germany. J Behav Med 2005;28:587–94.
91. DeVries JH, Lindholm A, Jacobsen JL, et al, Tri-Continental Insulin Aspart Study Group. A randomized trial of insulin aspart with intensified basal NPH insulin supplementation in people with type 1 diabetes. Diabet Med 2003;20:312–8.