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Long-acting insulin analogues

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More than 80 years ago, the discovery of insulin in Canada was a landmark event that changed the face of diabetes treatment. Insulin gave life to people with type 1 diabetes mellitus (T1 DM) who, until then, succumbed to their disease. Presently, millions of people use insulin for the treatment of T1 and T2 DM. Over the years, insulin preparations have evolved from the initial animal insulins that were crude and contaminated with split products, impurities, and other pancreatic hormones, to the more purified animal insulins, the biosynthetic human insulins and, most recently, insulin analogues. The latter technology has resulted in the creation of rapid and long-acting analogues that provide optimal meal and basal insulins, respectively. A review of the characteristics of the long-acting insulin analogues, with a focus on glargine and detemir, is the subject of this issue of *Endocrinology Rounds*. Insulin glargine is available in Canada under the trade name, Lantus, while insulin detemir (Levemir), although released in Europe last fall, is not yet available in Canada.

Characteristics of ideal basal insulin

The ideal basal insulin should provide a sustained peakless action profile when injected once daily, have reproducible effects once steady state is achieved, and control blood glucose as effectively as an insulin pump. Until recently, such an insulin was unavailable to people with diabetes mellitus. The classical intermediate and long-acting insulins – NPH and Ultralente – lack such characteristics and their use as basal insulin not infrequently results in erratic glycaemic control and frequent hypoglycemia.

Structure and mechanism of the prolongation of action

Glargine

Insulin glargine is an insulin analogue that is produced by modifying human insulin using recombinant DNA technology. Asparagine is substituted for by glycine at position 21 of the A chain and 2 arginine molecules are added on positions B31 and B32 of the B chain of insulin (Figure 1). It is a clear solution, with a pH of 4. Because of amino acid changes, the isoelectric point of the molecule is shifted so that the insulin is soluble at a pH of 4, but precipitates in the neutral pH of subcutaneous tissue. The presence of a small amount of zinc (30 µg/ml) is needed for the formation of glargine microprecipitates in subcutaneous tissue, from which insulin is released gradually. Consequently, there is delayed and prolonged absorption from the injection site following subcutaneous (s.c.) administration. There may be inter- and intra-individual variations in its time profile activity;¹ however, there are no differences in the rates of absorption from various injection sites (eg, abdomen, leg, or arm) when injected into healthy volunteers.²

In different studies, metabolic activity was found to last up to 24 hours^{3,4} and, in one study, up to 30 hours.⁵ In most patients, glargine exerts such prolonged action when injected once daily.



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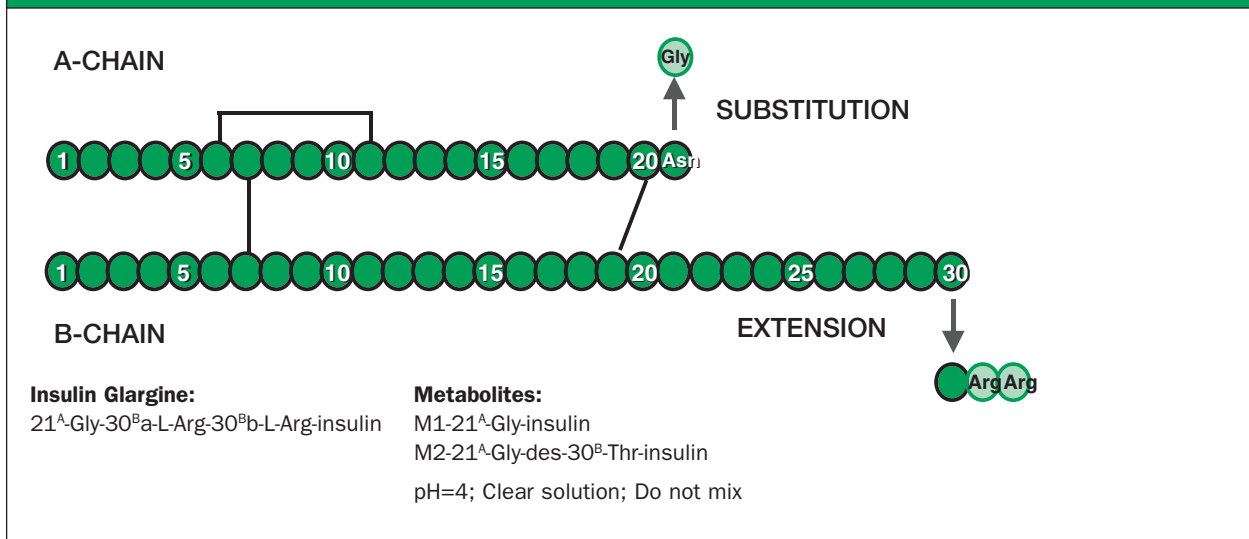
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Figure 1: Insulin glargine – structure



Detemir

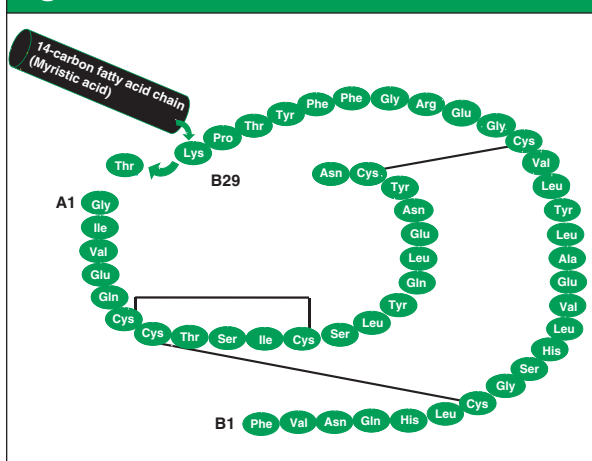
Detemir is a soluble insulin analogue given once or twice daily that is absorbed from the s.c. depot with very low variability. It has a fatty acid side-chain attached at position B29 that serves to bind to albumin (Figure 2). It is a clear solution with a neutral pH. In subcutaneous tissue, it exists predominantly in a di-hexameric form.⁶ Since these large structures are slow to penetrate the capillary wall, they present an opportunity for albumin binding. With depletion of the zinc component in the insulin, the hexamers break down into monomers. The 14-C fatty acid side-chain binds to albumin (detemir is 98% albumin-bound), contributing to the aggregation of hexamers, delaying their dissociation and absorption from the subcutaneous depot.⁷ Studies in pigs⁸ suggest that disappearance from the injection site (T-50%) was 10.2 ± 1.2 hours. The prolonged action is primarily related to albumin binding at the injection site, possibly self-

association in the s.c. depot and, to some extent, albumin binding in the circulation.

Pharmacokinetics and pharmacodynamics

Within-subject variability was compared in patients with T1 DM utilizing the euglycemic clamp. A dose of insulin detemir, glargine, or NPH (0.4 unit/Kg body weight) was injected s.c. once daily (in the morning). Each patient was studied on 4 different occasions using the same insulin as per his or her initial randomization. Detemir was associated with less within-subject variability in the glucose infusion rate (GIR) area under the curve (AUC) at 0-12 hours and 0-24 hours than both NPH and glargine (co-efficient of variation 27% detemir vs 59% NPH vs 46% glargine) $P < 0.001$. This is most probably related to the different modes of protraction. Metabolic activity was ongoing after 24 hours in 24% of detemir-injected patients, 14% of NPH-injected patients, and 39% of glargine-injected patients.⁹

Figure 2: Insulin detemir



Clinical studies in T1 and T2 DM

Glargine in T1 DM – studies regarding time and frequency of injections

In a study by Hamann et al,¹⁰ patients previously treated with other basal insulins were randomized to inject glargine once daily: before breakfast, before dinner, or at bedtime. Titration of glargine was undertaken to attain pre-breakfast glucose levels of 4.4 to 6.7 mmol/L. Baseline A1C was similar in all groups (7.5% to 7.6%). A similar reduction (0.1% to 0.2%, non-significant [NS]) in adjusted A1C occurred in all groups. There were no significant differences in 8-point blood glucose profiles between the 3 groups. In the breakfast group, there was a larger decrease in mean 24-hour glucose values from

baseline (0.6 mmol/L; $P=0.036$). Only minor changes were observed in other glucose parameters. Variability in fasting blood glucose (FBG) levels was significantly lower in the breakfast group compared to the dinner and bedtime groups ($P<0.001$). Nocturnal hypoglycemia was less in the breakfast group (59.5%) vs 71.9% for the dinner ($P=0.029$) and 77.5% for the bedtime ($P<0.0013$) group. There were no differences in efficacy regardless of whether glargine was injected at breakfast, dinner, or bedtime. However, when injected at breakfast, it was associated with less nocturnal hypoglycemia.¹⁰

A retrospective study was performed by Garg et al¹¹ in patients treated with multiple daily insulin injections, with glargine as the basal insulin for at least 6 months. The study compared the effect of treatment with glargine and the time of its injection. Patients took glargine either in the morning, evening, or as a split-dose given twice per day. Sixty-three patients took glargine in the morning, 125 at bedtime, and 104 had split-dose injections. The rapid acting insulin used in this study was either aspart or Lispro.

A1C values decreased by an average of 0.3% when all glargine-treated groups were combined, comparing A1C in those being treated with other basal insulins vs with glargine ($P<0.001$). The subjects receiving evening and split-dose glargine had similarly lower A1C compared to baseline ($P<0.01$), but not the subjects receiving glargine in the morning. Total and basal insulin doses at baseline (pre-glargine) were higher than after 1 year of glargine treatment in all groups combined ($P=0.01$ to $P<0.001$). The difference in total and basal dose was 5 and 5.4 units respectively. There were no differences in the meal-insulin doses. Severe hypoglycemic episodes were less (379 episodes at baseline versus 167 at follow-up); however, this was not observed in the group receiving glargine twice per day. Body weight increased in the evening glargine group by 1.1 Kg ($P<0.05$) and in the split-dose group by 1.5 Kg ($P<0.01$). Patients reported better quality of life with glargine treatment.

Studies comparing glargine with NPH

Porcellati et al¹² studied 121 patients whose baseline A1C was 7.1%, mean duration of diabetes 14 years, and average insulin dose 0.65 units per Kg body weight. All were being treated with intensive insulin therapy: NPH with each meal and at bedtime and Lispro before each meal. Patients were randomized either to stay on the same insulin regimen or changed to glargine once daily at dinnertime plus 4 times per day Lispro. Treatment was continued for 1 year. Insulin dose was titrated by the patients to reach the same glycemic targets in both groups: 6.4-7.2 mmol/L in the fasting state, before meals and at bedtime, and 8.0-9.2 mmol/L 2 hours after meals.

Blood glucose was lower in the fasting state and before meals. Mean daily glucose was lower with glargine (7.6 ± 0.11 vs 8.1 ± 0.22 mmol/L, $P<0.05$). However, 3 AM blood glucose was lower with NPH (7.5 ± 0.16 vs 8.4 ± 0.27 with glargine, $P<0.05$). A1C at 4 months did not change with NPH, but decreased from 7.1 ± 0.1 to 6.7 ± 0.1 with glargine and remained lower with glargine at 12 months compared to NPH (6.6 ± 0.1 , $P<0.05$). There were no severe episodes of hypoglycemia in this study. Frequency of mild hypoglycemia (glucose ≤ 4 mmol/L with or without symptoms) was lower with glargine: 7.2 ± 0.5 episodes vs 13.2 ± 0.6 episodes/patient month with NPH, $P<0.05$). This was true both during the day and night. There was no change in body weight in either group.

In a similarly designed study,¹³ 534 patients with T1 DM treated with glargine at bedtime were compared to those treated with NPH either at bedtime or twice per day. The study duration was 28 weeks. The meal insulin administered was regular human insulin. Basal insulin was titrated to attain an FBG of 4.4-6.7 mmol/L. There were no differences in the A1C or fasting plasma glucose (FPG) between the 2 groups, but there was a trend towards a reduction in capillary fasting glucose with glargine. There was a significant decrease in symptomatic hypoglycemia (39.9% vs 49.2%, $P=0.0219$) and nocturnal hypoglycemia (18.2% vs 27.1%, $P=0.0116$) in the glargine vs NPH group, respectively.

Studies comparing glargine with ultralente

In a study by Kudva et al, 22 patients with a baseline A1C of $6.94\pm 0.14\%$ were randomized to either glargine or ultralente (UL) insulin at bedtime.¹⁴ Conversion from prior insulin dose was made on a unit per unit basis. Insulin aspart was the prandial insulin. Titration of the basal insulin dose targeted a fasting, premeal, and bedtime glucose of 4.4 mmol/L to 6.7 mmol/L. Once titration was accomplished, patients continued on the basal insulin for 16 weeks and then crossed over to the other basal insulin for another 16-week period.

Neither the dose of basal insulin nor the time taken to titrate to a stable dose was different between the groups. The number of changes and the amount of prandial insulin was greater with UL vs glargine. Glargine vs UL treatment was associated with a lower A1C ($6.82\pm 0.13\%$ vs $7.02\pm 0.13\%$, respectively, $P=0.03$). The order in which the basal insulin was given did not alter the A1C differences between the two groups. FPG was lower with glargine vs UL (8.6 mmol/L vs 10.6 mmol/L, respectively, $P=0.047$).

There were more hypoglycemic episodes reported by patients treated with UL than with glargine (31.1 vs 24.5 episodes, $P=0.05$). There was less nocturnal variability

Table 1: Titration algorithm¹⁶

- **Starting dose of insulin 10 IU/day at bedtime**
- **Subjects self-monitored daily using a plasma-referenced glucose-testing system**
- **Weekly forced-titration**

Mean of FPG for last two days	Insulin increase IU/day
≥ 10 mmol/L	8
7.8-10 mmol/L	6
6.7-7.8 mmol/L	4
5.5-6.7 mmol/L	2

Exceptions

If hypoglycemia <4 mmol/L (72 mg/dL) in prior week, no increase

If severe hypoglycemia or <3.1 mmol/L, decrease 2-4 IU/day

(2.7 vs 3.6 mmol/L; $P=0.04$) and less daytime hypoglycemia ($P=0.0015$). Nocturnal hypoglycemia was not significantly different in patients taking UL or glargine. There were no significant differences in the occurrence of severe hypoglycemia in patients taking glargine vs UL

Studies with glargine in T2 DM

Yki-Jarvinen, et al¹⁵ compared bedtime NPH to bedtime glargine once daily for one year. In this study, 426 patients with T2 DM treated with oral antihyperglycemic agents, aged 59 years, BMI 28.9 Kg/m², and with poor glycemic control, were randomized to either NPH or glargine. Oral agents were continued. The average glucose improved similarly with both insulins; A1C levels for glargine vs NPH were 8.3% vs 8.2%, respectively, $P<0.001$, compared to baseline. Post-dinner glucose was lower in patients receiving glargine ($P=0.0094$). Nocturnal hypoglycemia was less with glargine vs NPH (9.9% vs 24% respectively, in all patients, $P<0.02$). Insulin dose and weight gain were comparable. Post-dinner glucose levels were lower with glargine vs NPH.

The Treat to Target Trial¹⁶ was a randomized, open-label, parallel group, multicentre study of 24 weeks duration. This trial enrolled 756 overweight T2 DM patients with a baseline A1C of 8.5%-8.6% who were on 1 or 2 oral agents. Patients continued on oral agents and received bedtime glargine or NPH starting at 10 units, titrated weekly using a simple algorithm (Table 1). Target A1C was set at 7%. At the endpoint, the mean FPG was similar at 6.5 mmol/L vs 6.7 mmol/L in the glargine vs NPH patients, respectively; A1C was 6.96% vs 6.97%.

About 60% of patients achieved an A1C $\leq 7\%$ and 25% more patients attained this A1C without documented hypoglycemia (glucose <4 mmol/L) with glargine (33.2% vs 26.7%, $P<0.05$). Rates of other events of symptomatic hypoglycemia were 21%-48% lower with glargine.

In another study by Fritsche et al, AM glargine was compared to bedtime NPH or bedtime glargine in patients with T2 DM who were not well-controlled on mono- or combination therapy with oral antihyperglycemic agents.¹⁷ Oral agents were stopped 4 weeks prior to randomization and were replaced by fixed dose (3 mg) glimeperide, which was continued during the 24-week follow-up period. The study randomized 695 European patients with a mean A1C of 9.1% at baseline to 3 insulin treatment arms. A1C levels decreased by 1.24% in the AM glargine group, 0.96% in the bedtime glargine group, and 0.84% in the NPH group. A1C reduction was more pronounced with AM glargine vs NPH ($P<0.001$) or bedtime glargine ($P=0.008$). FBG improved similarly in the 3 groups. Nocturnal hypoglycemia was less frequent with AM glargine (17%) and bedtime glargine (23%) than with NPH (38%), $P<0.001$.

The European Glargine Study Group¹⁸ reached similar conclusions suggesting that glargine is as safe and effective as NPH, but has the added benefit of causing fewer episodes of nocturnal hypoglycemia (19.1% of NPH patients vs 7.3% of glargine patients, $P=0.0123$). Other studies^{19,20} have confirmed the significant decrease in hypoglycemia with glargine compared to NPH.

Insulin detemir**Studies with insulin detemir in T1 DM**

Home et al²¹ studied 408 T1 DM patients from 52 sites in different countries. Patients were randomized in an open, 16-week, parallel group fashion to insulin detemir every 12 hours ($n=137$), detemir morning and bedtime ($n=139$), or NPH morning and bedtime ($n=132$). Insulin aspart was used as the meal insulin in all groups. Clinic fasting glucose was lower in the detemir groups by 1.5-2.3 mmol/L, $P<0.001$. Self-measured fasting glucose levels were lower with the insulin detemir regimens (8.26 and 8.28 mmol/L with detemir, $P<0.005$) versus NPH (9.05 mmol/L). Injecting insulin detemir twice daily, either in the morning and at bedtime or every 12 hours, resulted in better glycemic control as compared to NPH. A1C levels decreased by 0.82% and 0.85% in the detemir groups and by 0.65% in the

NPH group ($P=0.082$). The decrease in A1C level in the detemir groups combined was significantly less than in the NPH group ($P=0.027$). Minor hypoglycemia was lower in both detemir groups (25% and 32%, $P=0.046$ and $P=0.002$), which was attributed mainly to a 53% reduction in nocturnal hypoglycemia in the morning and bedtime group ($P<0.001$). Body weight increased in the NPH group, but was unchanged in the detemir groups ($P=0.018$).

In another study in patients with T1 DM, De Leeuw et al²² compared NPH to detemir as basal insulin and concluded that detemir reduced nocturnal hypoglycemia by 32% ($P=0.016$) and was associated with less weight gain ($P<0.001$).

A 6-month study with a 6-month extension in patients with T1 DM compared insulin detemir to NPH insulin using mealtime human soluble insulin in a basal-bolus regimen.²³ There was similar glycaemic control, but a trend towards a lower risk of nocturnal hypoglycemia (29% relative risk reduction), less fear of nocturnal hypoglycemia, and significant favourable weight change ($P=0.002$) with glargine.

A study by Vague et al randomized 447 T1 DM patients in an open, multinational trial to insulin detemir or NPH (in a 2:1 ratio) given twice daily.²⁴ Aspart was used as the meal insulin. Baseline A1C levels were 8.1% and 8.2%, respectively. Comparable A1C results were found after 6 months of treatment. There was a tendency towards lower fasting glucose with detemir. Within-subject variability in self-monitored glucose values was lower with detemir: SD 3.37 mmol/L vs 3.78 mmol/L, $P<0.001$. Risk of hypoglycemia and nocturnal hypoglycemia was 22% lower ($P<0.05$) and 34% lower ($P<0.005$), respectively, with detemir. Weight loss was observed with detemir compared to weight gain with NPH, a difference of 0.9 Kg, $P<0.001$.

A 6-month study by Russell-Jones et al compared the effect of once-daily insulin detemir versus NPH basal insulin; human regular insulin was used as the meal insulin.²⁵ The parameters studied included glycaemic control, hypoglycemia, weight change, and overall safety. Of the 747 patients who were randomized 2:1 detemir to NPH, 700 completed the study. Fasting plasma glucose was lower with detemir (-1.16 mmol/L difference, $P<0.001$). Self-monitored glucose values were lower before breakfast ($P<0.001$). A1C values were not significantly different. Day-to-day variability in self-monitored glucose values was lower with detemir vs

NPH (2.82 mmol/L vs 3.6 mmol/L, respectively, $P<0.001$). Nocturnal hypoglycemia was 26% less in the detemir group ($P=0.003$). Body weight gain was significantly less with detemir (-0.54 Kg difference), $P=0.024$.

Studies with insulin detemir in T2 DM

In a study by Raslova et al, 395 people with T2 DM were treated with basal-bolus therapy using either insulin detemir in combination with mealtime insulin aspart or NPH insulin in combination with mealtime regular human insulin.²⁶ This was a 22-week, multinational, open-label, symmetrically-randomized, parallel group trial. At 22 weeks, HbA_{1c} was comparable between treatment groups with decreases from baseline of 0.65% and 0.58%, respectively. There was less within-subject variability in glycemia (standard deviation 1.2 mmol/L vs 1.54 mmol/L for detemir vs NPH, respectively, $P<0.001$). There was a 0.62 Kg less weight gain with detemir ($P=0.038$). There were no differences in the hypoglycaemic parameters.

Conclusions

- Long-acting insulin analogues provide new opportunities for T1 and T2 DM patients.
- Long-acting insulin analogues are associated with similar or better glycaemic control and different degrees of reduction in hypoglycemia.
- Using insulin glargine in T2 DM showed a suggestion of less weight gain compared to NPH. Studies with insulin detemir in T2 DM found less weight gain compared to NPH, and studies in T1 DM demonstrated either weight reduction or less weight gain than with NPH ($P<0.05$).
- Insulin glargine can be given in conjunction with oral antihyperglycaemic agents.
- Less inter-subject glucose variability has been observed with detemir > glargine > NPH.
- Differences in glycaemic control between NPH and glargine/detemir are generally modest, but in some studies, they are significant.
- Time of injection and frequency – once or twice per day – should be individualized.
- Forced titration of glargine, as recommended in the Treat To Target study, helps reach glycaemic target levels.
- Compared to human insulin, insulin glargine is more expensive than NPH or UL insulin in Canada.

References:

1. 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(16):1743-1778.
2. Owens DR, Coates PA, Luzio, SD, et al. *Diabetes Care* 2000;23(6):813-819.
3. Lepore M, Pampanelli S, Fanelli C, et al. Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin glargine, NPH insulin, and Ultralente human insulin and subcutaneous infusion of insulin. *Diabetes* 2000;49:2142-2148.
4. McKeage K, Goa KL. Insulin glargine: a review of its therapeutic use as a long-acting agent for the management of type 1 and type 2 diabetes. *Drugs* 2001; 61(11):1599-1624.
5. Heinemann L, Linkeschova, T, Rave K, et al. Time-action profile of long-acting insulin analog insulin glargine (HOE901) in comparison with those of NPH insulin and placebo. *Diabetes Care* 2000;23(5): 644-649.
6. Olsen HB, Kaarsholm NC. Structural effects of protein lipidation as revealed by LysB29-myristoyl, des(B30) insulin. *Biochemistry* 2000; 39:11893-11900.
7. Whittingham JL, Havelund S, Jonassen, I. Crystal structure of prolonged-acting insulin with albumin-binding properties. *Biochemistry* 1997;36: 2826-2831.
8. Havelund S, Plum A, Ribbel U, et al. The mechanism of protraction of insulin detemir, a long-acting acylated analog of human insulin. *Pharmaceutical Research* 2004;21:1498-1504.
9. Heise T, Nosek L, Builman Ronn B, et al. Lower within-subject variability of insulin Detemir in Comparison to NPH insulin and insulin Glargine in people with type 1 diabetes. *Diabetes* 2004;53:1614-1620.
10. Hamann A, Matthaai S, Rosak, C, et al. A randomized clinical trial comparing breakfast, dinner, or bedtime administration of insulin glargine in patients with type 1 diabetes. *Diabetes Care* 2003;26(6):1738-1744.
11. 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.
12. Porcellati F, Rossetti P, Pampanelli S, et al. Better long-term glycemic control with basal insulin glargine as compared with NPH in patients with type 1 diabetes mellitus given meal-time lispro insulin. *Diabet Med* 2004; 21:1213-1220.
13. Ratner RE, Hirsch IB, Neifing JL, et al. Less hypoglycemia with insulin glargine in intensive insulin therapy for type 1 diabetes. *Diabetes Care* 2000;23(5):639-643.
14. 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;28:10-14.
15. Yki-Jarvinen H, Dressler A, Ziemien M, et al. Less nocturnal hypoglycemia and better post-dinner glucose control with bedtime insulin glargine compared with bedtime NPH insulin during insulin combination therapy in type 2 diabetes. *Diabetes Care* 2000;23(8):1130-6.
16. Riddle M, Rosenstock J, Gerich J, et al. The Treat-to-Target Trial. Randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care* 2003;26(11):3080-3086.
17. Fritsche A, Schweitzer MA, Häring H-U, et al. Glimeperide combined with morning insulin glargine, bedtime neutral protamine Hagedorn, or bedtime insulin glargine in patients with type 2 diabetes; a randomized, controlled trial. *Ann Intern Med* 2003;138(12) 952-59.
18. The European Glargine study group. *Diabet Med* 2003; 20(7):545-5.
19. Rosenstock, J, Schwartz SL, Clark CM Jr, et al. Basal insulin therapy in type 2 diabetes: 28-week comparison of insulin glargine (HOE 901) and NPH insulin. *Diabetes Care* 2001;24(4):631-6.
20. Massi Benedetti M, Humburg E, Dressler A, Ziemien M. A one-year, randomised, multicentre trial comparing insulin glargine with NPH insulin in combination with oral agents in patients with type 2 diabetes. *Horm Metab Res* 2003;35(3):189-96.
21. Home P, Bartley P, Russell-Jones D, et al. Insulin Detemir offers improved glycemic control compared with NPH insulin in people with type 1 diabetes. *Diabetes Care* 2004; 27(5):1081-1087.
22. De Leeuw I, Vague P, Selam J-L, et al. Insulin Detemir used in basal-bolus therapy in people with type 1 diabetes is associated with a lower risk of nocturnal hypoglycemia and less weight gain over 12-months in comparison to NPH insulin. *Diabetes Obes Metab* 2005;7(1):73-82.
23. Standl E, Lang H, Roberts A. The 12-month efficacy and safety of insulin detemir and NPH insulin in basal-bolus therapy for the treatment of type 1 diabetes. *Diabetes Technol Ther* 2004; 6(5):579-88.
24. Vague P, Selam J-L, Skeie S, et al. Insulin Detemir is associated with more predictable glycemic control and reduced risk of hypoglycemia than NPH insulin in patients with type 1 diabetes on a basal-bolus regimen with pre-meal insulin aspart. *Diabetes Care* 2003;26(3):590-596.
25. Russell-Jones D, Simpson R, Hylleberg B, et al. Effects of QD insulin detemir or neutral protamine Hagedorn on blood glucose control in patients with type 1 diabetes mellitus using a basal-bolus regimen. *Clin Ther* 2004; 26(5):724-736.
26. Raslova K, Bogoev M, Raz I, et al. Insulin detemir and insulin aspart: a promising basal-bolus regimen for type 2 diabetes. *Diabetes Res Clin Pract* 2004;66(2):193-201.

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