Insulin Detemir and Its Unique Mechanism of Action

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Citation

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Abstract

Tight glycemic control with minimal risk for hypoglycemia is the goal of insulin therapy. Such control is difficult to accomplish with older insulin formulations, such as regular human insulin and neutral protamine Hagedorn (NPH) insulin because their pharmacokinetic/pharmacodynamic profiles poorly match normal physiologic insulin secretion. Insulin detemir is an analogue of human insulin engineered to have a prolonged and consistent time-action profile with no distinct peak. Glucose clamp studies demonstrate that insulin detemir results in a less variable glucose-lowering effect than either insulin glargine or NPH insulin. Clinical trial results indicate that insulin detemir in combination with either oral antidiabetic drugs or prandial insulin provides glycemic control comparable or superior to NPH insulin and similar to insulin glargine with lower within-patient variability, decreased risk for hypoglycemia, and less weight gain. Therefore, use of insulin detemir may be advantageous in a treatment regimen in patients with type 1 or 2 diabetes.

ABBREVIATIONS

BMI, body mass index; GIRs, glucose infusion rates; A1C, glycosylated hemoglobin; SD, standard deviation;

INTRODUCTION

The primary goal of insulin therapy in patients with diabetes is to achieve tight glycemic control in order to decrease the risk for macrovascular and microvascular complications associated with poorly controlled blood glucose [1,2,3,4]. Tight glycemic control should be accomplished with minimal risk for side effects of antidiabetic therapy, specifically hypoglycaemia [5,6], which is considered to be the most significant barrier to effective insulin treatment [7]. While glycemic control is well-established as the primary goal of antidiabetic therapy, it is often difficult to achieve tight glycemic control with older insulin formulations, such as regular human insulin and neutral protamine Hagedorn (NPH) insulin. The pharmacokinetic/pharmacodynamic profiles of these older insulin preparations do not match normal physiologic insulin secretion, and this limits their ability to tightly control both fasting and postprandial plasma glucose [8,9]. Conventional insulin preparations also have highly variable pharmacokinetic and pharmacodynamic profiles that result in substantial within- and between-patient variability in plasma glucose [10]. The variable actions of older insulin preparations complicate determination of appropriate daily dosing, increase the risk for hypoglycaemia between meals and at night, and make it very difficult for patients to achieve and maintain glycemic control [8,11]. Treatment with conventional insulin preparations has also been associated with weight gain in patients with diabetes [7].

Insulin detemir is a new long-acting insulin analog developed for patients who require basal insulin for the control of hyperglycemia. Insulin detemir has the potential to reduce the risk for hypoglycemia and the incidence of weight gain while in some cases providing better glycemic control with lower glucose variability than older insulin formulations. The aims of this paper are to describe the structure, mechanism of action, pharmacokinetic and pharmacodynamic profiles, and clinical efficacy and safety of insulin detemir, and to compare them with those of the other currently available long-acting insulin formulations, NPH insulin and the other basal insulin analogue, insulin glargine.

STRUCTURE OF INSULIN AND EFFECTS ON PHYSICOCHEMICAL PROPERTIES

INSULIN STRUCTURE AND APPROACHES TO PROLONGING DURATION OF ACTION

The insulin molecule consists of two polypeptide chains, an A chain of 21 amino acids and a B chain of 30 amino acids. Physiologic insulin is active as a monomer, but this protein crystallizes as layers of hexameric units with three insulin dimers aggregated around two zinc ions to form a globular, hexameric structure [12,13]. The classic approach to production

of longer acting insulin preparations has been preparation of crystalline or amorphous suspensions that form a slowly dissolving depot after subcutaneous injection [12]. These preparations (NPH, Lente, and Ultralente insulin) display variable absorption that typically results in suboptimal and erratic control over plasma glucose in patients with diabetes [12].

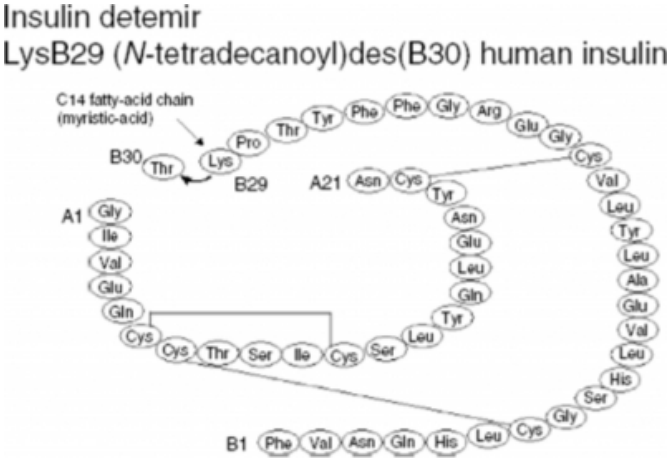
STRUCTURE OF CURRENT LONG-ACTING INSULIN PREPARATIONS

INSULIN DETEMIR

The strategy employed in the development of insulin detemir is qualitatively different from that used to manufacture older long-acting insulin preparations. Insulin detemir is a neutral, noncrystalline, clear, soluble insulin preparation in which residue B29 Lysine, which is not required for biologic activity, has been covalently bound to a 14-carbon, myristoyl fatty acid (myristic acid) (Figure 1) [14]. The fatty acid addition in insulin detemir facilitates increased self-association of insulin detemir molecules and reversible binding of insulin detemir to albumin, the principal extracellular plasma protein. Albumin has a molecular weight of about 67 kDa and binds reversibly to many endogenous molecules (eg, fatty acids) as well as pharmacologic agents.

Figure 1

Figure 1: Structure of insulin detemir. (Reprinted with permission from Garber)



Acetylation (ie, adding a fatty acid chain) of insulin can be accomplished at the N-termini α-amino groups of the A- and B-chains and the ε-amino group LysB29. Addition of a fatty acid chain at LysB29 is the only form of acetylation that permits normal hexamer formation and does not interfere with insulin action [14]. The fatty acid side chain of insulin detemir binds primarily to albumin domain III and weakly to domain I. Insulin detemir is 98% bound to albumin in plasma and 96% in the interstitial fluid [15]. The association constant for binding of insulin detemir to albumin is about 10^4–10^5/M [16]. The fatty acid chain in insulin detemir has been placed at the end of the B chain. X-ray analysis of insulin detemir showed that the position of the fatty acid makes it readily available for interaction with albumin [12]. This modification of insulin detemir and the resultant binding to albumin is unique to this insulin preparation [15,16]. It does not disrupt aggregation of insulin detemir into hexamers and it has no effect on insulin detemir's physiologic activity, which does not differ from that of human insulin [17].

Structural studies of insulin detemir have been conducted to assess the effect of the fatty acid chain on the insulin structure. The insulin detemir structure is composed of four molecules of insulin in an asymmetric unit plus four zinc ions, four chloride ions, four phenol molecules, four fatty acid side chains, and 153 water molecules. The four insulin molecules aggregate to form dimers and zinc and phenol promote formation of hexamers similar to that for physiologic human insulin. The fatty acid side chains also contribute to hexamer and dihexamer formation. This highly self-associated insulin is absorbed more slowly into the circulation than monomeric insulin and the fatty acid side chains are thought to delay hexamer dissociation and insulin absorption and thus contribute to the prolonged action of insulin detemir [12,15,18].

At doses commonly administered to patients with diabetes, insulin detemir occupies only a very small fraction of the available binding sites on albumin, and it has not demonstrated any clinically significant interactions with other drugs that are bound to this plasma protein [19,20]. Binding of fatty acids to albumin is not likely to interfere with binding of insulin detemir to this plasma protein. The molar serum concentration of insulin detemir is about 1/50,000 of that for albumin at therapeutic doses, and each albumin molecule has eight fatty acid binding sites. Thus, insulin detemir will only occupy a very small number of the total albumin binding sites [21]. It has been shown that binding of one free fatty acid molecule to albumin does not interfere with binding of insulin detemir [20], and that the capacity of albumin for binding acetylated insulin detemir is very high, exceeding 5 monomers [12].

While albumin binding makes only a minor contribution to prolonging insulin detemir's duration of action, it plays a

much more important role in buffering against sudden changes in absorption and thus providing more consistent blood levels of this insulin preparation. In the circulation, insulin detemir is 98% bound to albumin and this has two potentially important buffering effects. First, the rate of absorption for insulin detemir is only slightly affected by variations in injection site blood flow. In addition, the high binding of insulin detemir to albumin means that the potential effect of abrupt rises in plasma concentration, should they occur, would have only minimal effects on the concentration of this insulin at its receptors in target tissues. This would be the case since only 2% of the circulating insulin detemir is unbound and available for transport across capillary walls. These two buffering mechanisms both contribute to the low within-subject pharmacokinetic and pharmacodynamic variability that has been demonstrated for insulin detemir [21].

NPH INSULIN

Intermediate-acting NPH insulin was developed in the 1940s by adding protamine to soluble animal insulin. This same approach has been used to extend the duration of action for recombinant human insulin [14]. The addition of protamine to human insulin results in the formation of a suspension that delays dissolution and absorption. The requirement for resuspension of NPH insulin prior to injection may contribute significantly to within- and between-patient variability in its action due to the fact that the actual amount of insulin administered may vary greatly from one injection to the next as a result of variation in mixing [22].

INSULIN GLARGINE

Insulin glargine was the first clinically available long-acting human insulin analogue. It differs from native human insulin by virtue of amino acid substitutions in both A and B chains of the protein. In the A chain, asparagine is substituted for glycine at position 21. The B chain is elongated at the C-terminus by the addition of two arginine residues. The changes in the A chain increase the stability of the molecule, while those in the B chain result in a more neutral isoelectric point. As a result of these structural changes, insulin glargine is soluble in the acidic (pH = 4.0) solution in which it is provided, but rapidly precipitates into stable hexamers after injection owing to the neutral pH in the subcutaneous tissues. This greatly slows the absorption of insulin glargine [11,14].

PROTRACTION OF THE ACTION OF INSULIN

DETEMIR AND OTHER LONG-ACTING INSULINS

The increased self-association of insulin detemir molecules and binding of insulin detemir to albumin slows absorption following subcutaneous injection, and thus increases its duration of action. Insulin detemir is soluble at a neutral pH and is injected as a hexamer, but interactions between fatty acid side chains on the insulin detemir molecule promote formation of hexamer aggregates at the injection site. This results in a hexamer-dihexamer equilibrium with the dihexamers formed by contact between fatty acid chains. These fatty acid side chain interactions slow the absorption of insulin detemir into the circulation and protract its duration of action. Because it is soluble at a neutral pH, insulin detemir remains as a liquid depot after subcutaneous injection, providing a larger surface area for absorption. This may contribute to the low within-patient pharmacokinetic and pharmacodynamic variability observed for insulin detemir versus other long-acting insulin preparations that form precipitates at a physiologic pH [11,15,21,23,24]. While the majority of protraction of action for insulin detemir results from self-aggregation and its slow absorption from the subcutaneous depot, its action is additionally prolonged via reversible binding to albumin in the plasma [18,19]. Only free dissociated insulin detemir can penetrate capillary walls (ie, the endothelial barrier) [15]. Thus, binding to albumin also slows diffusion of insulin detemir monomers into the interstitial compartment [19].

The mechanisms responsible for slowing the absorption of insulin detemir differ significantly from those used to increase the durations of action for insulin glargine and NPH insulin. The action of both of these insulins is protracted by formation of insulin suspensions at the injection site [11,14]. The lack of requirement for resuspension (needed for NPH insulin) and not forming a precipitate at the injection site (as is the case for both insulin glargine and NPH insulin) removes two potential sources of variation in the action of insulin detemir [25]. The mechanism employed to prolong the duration of action for insulin detemir provides more predictable absorption and glucose lowering than either NPH insulin or insulin glargine [26], and glycemic control that is as good or better than that achieved with these insulin preparations [24].

CLINICAL ADVANTAGES OF THE METABOLIC PROFILE OF INSULIN DETEMIR

Clinical studies with insulin detemir have shown that its use results in lower variability in plasma glucose versus both

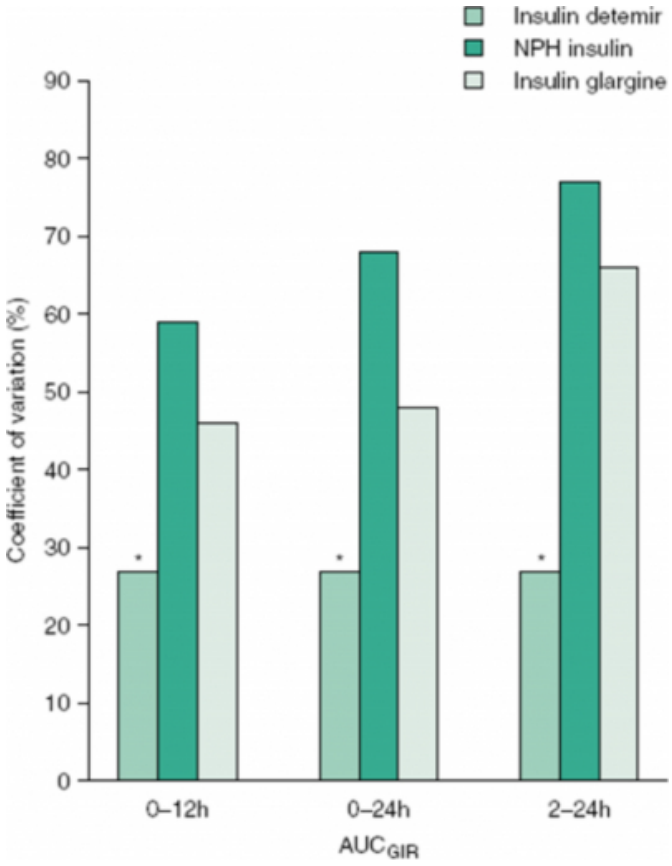
older and more recently developed long-acting insulin preparations, decreased risk for hypoglycemia, and less weight gain.

VARIABILITY IN PLASMA GLUCOSE

Insulin detemir has a similar time-action profile compared to insulin glargine [27] but has demonstrated a more consistent pharmacodynamic effect than either NPH insulin or insulin glargine [26,27] . Heise and colleagues showed that treatment with insulin detemir is associated with lower variability in plasma glucose than either NPH insulin or insulin glargine. These investigators carried out a randomized, double-blind trial that included 54 subjects with type 1 diabetes who were studied under euglycemic glucose clamp conditions (target blood glucose concentration = 5.5 mmol/L) on 4 different study days that were each one week apart. Patients were given single subcutaneous doses of 0.4 U/kg of insulin detemir, insulin glargine, or NPH insulin. Study results showed that insulin detemir was associated with less within-subject variability in glucose disposal than either NPH insulin or insulin glargine, as assessed by the coefficient of variation for glucose infusion rates (GIRs) (Figure 2). For example, the coefficients of variation were 27% for insulin detemir versus 68% and 48%, respectively, for NPH insulin and insulin glargine over 0–24 hours ($p < 0.001$ for all comparisons between insulin detemir versus insulin glargine or NPH insulin). The results from Heise and colleagues are similar to those from a 26-week comparison of insulin detemir and NPH insulin in 505 patients with type 2 diabetes. Patients in this trial received insulin detemir or NPH insulin once or twice daily along with rapid-acting insulin aspart at mealtimes. Assessment of standard deviations (SDs) for day-to-day variation in self-monitored blood glucose indicated lower variability with insulin detemir (SD = 1.3 mmol/L) than for NPH insulin (SD = 1.4 mmol/L) ($p = 0.021$) [28] .

Figure 2

Figure 2: Coefficients of variation for AUC in subjects who received insulin detemir, NPH insulin, or insulin glargine in a glucose clamp study (*$p < .001$ versus comparators). (Reprinted with permission from Chapman and Perry ,)

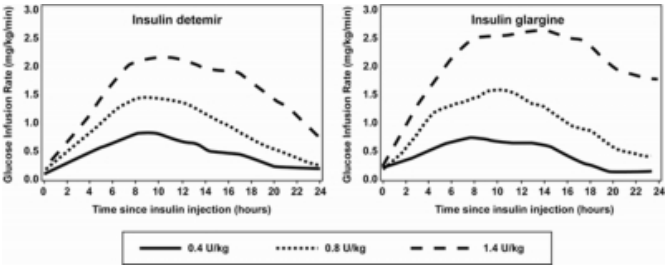


Klein and colleagues have carried out a head-to-head comparison of insulin detemir and insulin glargine in 27 subjects with type 2 diabetes. In this randomized, double-blind parallel trial, subjects received 0.4, 0.8, and 1.4 U/kg of insulin detemir or insulin glargine under glucose clamp conditions with a target blood glucose of 90 mg/dL. Study results showed that mean GIR profiles for insulin detemir and insulin glargine were similar in shape and flatness (Figure 3) and that the dose-response relationships were also similar for the two insulin preparations. However, the within-subject variability was lower for insulin detemir than for insulin glargine ($p < 0.001$). The duration of action (time from dosing to GIR <0.5 mg/kg per minute) increased with rising doses for both insulin detemir and for insulin glargine and there was no substantial difference between the two preparations at clinically relevant doses (0.4 and 0.8 U/kg). The durations of action for insulin detemir and insulin glargine when dosed at 1.4 U/kg were 1,328 and 1,440 minutes, respectively [27] . The relatively longer and flatter time-action profiles of insulin detemir and insulin glargine

more closely mimic normal physiologic insulin secretion and provide improved control over fasting plasma glucose compared to that achieved with NPH insulin. These insulin preparations are also associated with lower risks for interprandial hyperglycemia and hypoglycemia, particularly nocturnal, compared with NPH insulin [15,24,29].

Figure 3

Figure 3: Mean GIR profiles (smoothed with a local regression technique) for 0.4, 0.8, and 1.4 U/kg insulin detemir and insulin glargine. (Reprinted with permission from Klein et al. Copyright© 2006 American Diabetes Association.)



GLYCEMIC CONTROL AND HYPOGLYCEMIA

Variability in the pharmacokinetic/pharmacodynamic profiles for insulin preparations and the resulting variable effects on plasma glucose are believed to be important risk factors for the development of hypoglycemia in patients being treated for diabetes [10,25]. In addition, basal insulin with an unpredictable peak effect further increases the risk of nocturnal hypoglycemia since these preparations are often dosed in the evening [21]. The unique physicochemical structure of insulin detemir has resulted in both a relatively flat pharmacokinetic/pharmacodynamic profile and low within-patient variability and thus might be expected to substantially decrease the risks for hypoglycemia, particularly nocturnal hypoglycaemia, versus older basal insulin preparations. Heise and colleagues have attempted to directly relate within-patient variability for insulin pharmacodynamic profiles determined in glucose clamp studies (see above) with the risk for hypoglycemia. They presented within-subject coefficients of variation as prediction intervals that displayed 95% of the predicted blood glucose values. This analysis made the following predictions for patients being treated with insulin detemir, NPH insulin, or insulin glargine: a patient is likely to experience an unusually pronounced maximum effect that might result in hypoglycemia once every 2 years during treatment with once-daily insulin detemir, 24 times per year with NPH insulin, and 10 times a year with insulin glargine [26]. While such an analysis must be viewed with caution, it does provide predictions about the relative risks for hypoglycemia with these three basal insulin preparations that have been supported by clinical trial data [30,31].

Treatment with insulin detemir has been repeatedly shown to have lower risk for the development of hypoglycemia than NPH insulin. Results from a 16-week, randomized, open-label, parallel-group study of 408 patients with type 1 diabetes who received either insulin detemir (before breakfast and at bedtime or every 12 hours) or NPH insulin (before breakfast and at bedtime), each with mealtime insulin aspart, indicated lower fasting plasma glucose for both insulin detemir regimens than for NPH insulin ($p < 0.01$) and a decreased risk of minor hypoglycemia (25% and 32% reductions for the every-12-hour and breakfast and bedtime insulin detemir regimens, respectively, versus NPH insulin, $p = .046$ and $p = .002$, respectively). There was also a 53% decrease in the incidence of nighttime minor hypoglycemia with the breakfast and bedtime insulin detemir regimen versus NPH insulin ($p < 0.01$) [32]. A similar 18-week, randomized, open-label comparison of insulin detemir administered in the morning and at bedtime along with mealtime insulin aspart versus morning and bedtime NPH insulin plus mealtime regular human insulin in 595 patients with type 1 diabetes indicated that the insulin detemir-based treatment was also more effective than NPH insulin in decreasing glycosylated hemoglobin (A1C) ($p < 0.01$) [33]. Also, self-measured 8-point plasma glucose levels including postprandial glucose were significantly lower in the detemir group ($p < 0.01$).The risks for all and nocturnal hypoglycemia were reduced by 21% and 55%, respectively, with the insulin detemir-based regimen ($p = 0.036$ and $p < 0.001$, respectively) [33]. Major nocturnal hypoglycemia (a total of four events) occurred in only three patients who received insulin detemir in this study versus 12 patients (24 total events) for those treated with NPH insulin ($p = 0.08$) [33].

A longer duration, 6-month, open-label comparison of insulin detemir and NPH insulin, each administered in the morning and at bedtime along with a rapid-acting mealtime insulin, in 747 patients with type 1 diabetes also demonstrated superiority of insulin detemir over NPH insulin in reducing fasting plasma glucose ($p = 0.01$) with comparable A1C reduction between the two groups. Treatment with insulin detemir in this trial produced a 26% reduction in the risk for nocturnal hypoglycemia versus NPH insulin ($p = 0.003$). There was no difference between treatments for all hypoglycemic episodes ($p = 0.54$) [34].

A 32-week crossover comparison of insulin detemir and NPH insulin, each administered for 16 weeks along with premeal insulin aspart, in 130 patients with type 1 diabetes indicated lower prebreakfast plasma glucose ($p < 0.01$), comparable effects on A1C (p = NS), and 50% and 18% lower risks for nocturnal and overall hypoglycemia respectively (both $p \leq 0.01$) with insulin detemir than with NPH insulin. In addition, a total of 19 severe hypoglycemic episodes occurred during treatment with insulin detemir versus 33 for NPH insulin (p = NS) [30].

Insulin detemir has also been shown to be associated with lower risk for hypoglycemia than NPH insulin when each agent was added to oral antidiabetic agents (with insulin doses titrated to achieve a prebreakfast and predinner plasma glucose target of ≤108 mg/dL) in 476 patients with type 2 diabetes who were followed for 24 weeks. At the study endpoint, A1C had decreased by 1.8% and 1.9% in the insulin detemir and NPH insulin groups, respectively (p = NS). Compared with NPH insulin, the risk for all hypoglycemia with insulin detemir was reduced by 47% ($p < 0.01$) and that for nocturnal hypoglycemia was decreased by 55% ($p < 0.01$) [35].

Insulin detemir has also demonstrated similar A1C reduction (p = NS) with a lower risk of hypoglycemia compared to insulin glargine in individuals with type 1 diabetes. A 26-week study of 322 men and women with type 1 diabetes who received either insulin detemir in the morning and at bedtime or insulin glargine at bedtime, each along with mealtime insulin aspart, indicated that the risks of major and nocturnal hypoglycemia were reduced by 72% and 32%, respectively, by treatment with insulin detemir (both $p < 0.05$) [36].

WEIGHT GAIN

Insulin therapy is often associated with weight gain [37]. While the mechanism underlying insulin-associated weight gain is not fully understood, it may result from higher peripheral versus hepatic insulin levels in patients receiving exogenous insulin, more efficient insulin-stimulated lipogenesis, and decreased glycosuria [37]. Body weight is also modulated by the action of insulin at receptors in the brain that, when activated, decrease appetite and food consumption [37]. It may be that the lower weight gains observed in patients treated with insulin detemir versus NPH insulin are related to its avid binding to albumin. Albumin passes freely into the liver via hepatic sinusoids and this may result in increased hepatic and decreased peripheral action for insulin detemir, leading to less weight gain [37]. Binding of insulin detemir to albumin may also enhance its penetration through the blood-brain barrier and action at insulin receptors in the brain [37,38]. The weight-neutral effect of insulin detemir is clinically important because weight gain in patients with either type 1 or type 2 diabetes may be one of the barriers to adherence to therapy, particularly treatment intensification that may be needed to achieve tight glycemic control [37]. In addition, weight gain and resulting obesity also contribute to risk for long-term macrovascular complications and worsening insulin resistance in patients with diabetes [39,40].

Results from a large number of studies of patients with either type 1 or 2 diabetes have indicated that insulin detemir is associated with less weight gain than NPH insulin. The 16-week study of 408 patients with type 1 diabetes referred to earlier that compared insulin detemir (with dosing before breakfast and bedtime or every 12 hours) and NPH insulin, each with mealtime insulin aspart, also showed that patients in the NPH insulin group gained weight while those managed with the insulin detemir regimen did not [32]. The differences between the changes in body weight for the patients who received insulin detemir every 12 hours or before breakfast and at bedtime versus NPH insulin were –0.8 and –0.6 kg (–1.8 and –1.3 lbs), respectively (p = 0.06 and p = 0.040, respectively) [32]. An 18-week comparison of insulin detemir plus insulin aspart versus NPH and regular insulin in 595 patients with type 1 diabetes also showed that, after adjustment for baseline weight and change from baseline in A1C, weight gain was 1.0 kg (2.2 lbs) lower for the insulin detemir-based regimen than for NPH insulin ($p < 0.01$) [33]. Similar results were reported in a 22-week comparison of basal-bolus therapy with insulin detemir and insulin aspart versus NPH and regular human insulin in 395 patients with type 2 diabetes. In this trial, the weight gain over 22 weeks with insulins detemir and aspart was 0.51 kg (1.1 lbs) and that for NPH and regular human insulin was 1.13 kg (2.49 lbs) (p = 0.038). There was no between-treatment difference for effects on A1C [41].

A 16-week, open-label, parallel-group study of 400 patients with type 1 diabetes compared insulin detemir (in the morning and at bedtime or dinner) versus NPH insulin (in the morning and at bedtime), each with mealtime insulin aspart. At baseline, the mean body weights in the two insulin detemir treatment groups were 75.6 and 77.0 kg (167 lbs and 170 lbs) and that for the patients who receive NPH insulin was 74.8 kg (165 lbs). By the end of treatment, both the morning and bedtime and morning and dinner insulin

detemir regimens resulted in lower mean body weights than NPH insulin (–0.6 kg and -1.3 kg (–1.3 lbs and –2.9 lbs), respectively; $p = 0.050$ and $p < 0.01$) [42] .

The differential effects of insulin detemir versus NPH insulin are maintained over longer term treatment. Results from a 6-month open-label comparison of insulin detemir and NPH insulin in 747 patients with type 1 diabetes indicated that those who received insulin detemir lost –0.23 kg (0.51 lb) over the course of the trial versus a 0.31 kg (0.68 lb) weight gain for the patients treated with NPH insulin ($p = 0.024$) [34] . These results are consistent with findings from a 26-week comparison of insulin detemir and NPH insulin, each administered with mealtime insulin aspart, in 505 patients with type 2 diabetes. Patients who received insulin detemir in this study gained 1.0 kg (2.2 lbs) over 26 weeks versus 1.8 kg (4.0 lbs) for NPH insulin ($p = 0.017$) [28] .

More recent results from several large-scale comparisons of insulin detemir with NPH insulin have been presented. These data support a reduced tendency for weight gain with insulin detemir versus the older insulin preparation. A 26-week study of 476 patients with type 2 diabetes who were receiving oral antidiabetic agents and twice-daily insulin detemir or NPH insulin added to treatment indicated smaller increases in body weight with insulin detemir (1.2 versus 2.8 kg (2.6 versus 6.2 lbs) for NPH insulin, $p < 0.01$) [35] . Among patients treated with insulin detemir, but not NPH insulin, weight gain declined with increasing body mass index (BMI) across the range from ≤25 to >31 kg/m ^{2} ($p = 0.01$ for the between-group difference) [35,43] . Results from 900 patients with type 2 diabetes receiving basal-bolus therapy including either insulin detemir or NPH insulin showed a similar trend. Patients with the highest BMI (>35 kg/m ^{2}) lost an average of –0.5 kg (–1.1 lbs) with insulin detemir and gained an average of 2.4 kg (5.3 lbs)with NPH insulin ($p = 0.025$) [44] .

The addition of nighttime insulin detemir (with the option of adding a morning dose) to oral antidiabetic therapy has also been shown to have more favorable effects on body weight than insulin glargine (dosed in the evening) in a cohort of 582 patients with type 2 diabetes who were followed for 52 weeks. Intent-to-treat analysis indicated average weight gains of 2.7 kg (6.0 lbs) for insulin detemir versus 3.5 kg (7.7 lbs) for insulin glargine ($p = 0.03$). The respective values for a completer analysis were 3.0 and 3.9 kg (6.6 and 8.6 lbs) ($p = 0.012$) [45] .

A meta-analysis of results from six Phase 3 trials of insulin detemir versus NPH insulin for basal therapy in 2,150 patients with type 1 diabetes and 899 patients with type 2 diabetes indicated a mean difference in body weight change of –0.74 kg (–1.6 lbs) favoring insulin detemir ($p < 0.01$) [46] .

SUMMARY AND CONCLUSIONS

The uniquely designed structure of insulin detemir resulted in physicochemical properties that include neutral pH, high solubility, self-association to hexamers and dihexamers, and high affinity for human serum albumin. These characteristics provide prolonged maintenance of steady-state plasma concentrations and predictable glycemic control within patients. Clinical trial results in large numbers of patients with type 1 or 2 diabetes have shown that insulin detemir provides glycemic control at least comparable to that achieved with NPH insulin or insulin glargine, but with lower within-patient variability in plasma glucose, decreased risk for overall and nocturnal hypoglycemia, and less weight gain. While there is no perfect insulin for basal therapy in all patients, the properties documented for insulin detemir support the conclusion that it has the potential to facilitate an aggressive treat-to-target approach to therapy for type 1 or 2 diabetes, particularly in obese patients. Such treatment has the potential to improve glycemic control and decrease the risk for long-term diabetes complications.

SEARCH STRATEGY

We searched MEDLINE from 1995–2006 to identify relevant studies to this topic. Search terms used combinations of the following key words: insulin analogues, variability, insulin detemir, NN304, and albumin binding.

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DECLARATION OF COMPETING INTEREST

Louis B. Chaykin, MD, has been reimbursed for being a speaker by Amylin Pharmaceuticals, Eli Lilly and Company, Novo Nordisk, Inc., Novartis Pharmaceuticals, and Sanofi-Aventis. He has been reimbursed for speaker training from Amylin Pharmaceuticals, Eli Lilly and Company, GlaxoSmithKline, Novartis Pharmaceuticals, Novo Nordisk, Inc., and Sanofi-Aventis. Dr. Chaykin has been involved in clinical research for Amylin Pharmaceuticals, Eli Lilly Company, Merck, Novartis Pharmaceuticals, Novo Nordisk, Inc., and Sanofi-Aventis. Dr. Chaykin has shares in Amylin

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