

Insulin detemir for the treatment of obese patients with type 2 diabetes

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Abstract: The risk for developing type 2 diabetes (T2DM) is greater among obese individuals. Following onset of the disease, patients with T2DM become more likely to be afflicted with diabetic micro- and macrovascular complications. Decreasing body weight has been shown to lower glycosylated hemoglobin and improve other metabolic parameters in patients with T2DM. Medications used to lower blood glucose may increase body weight in patients with T2DM and this has been repeatedly shown to be the case for conventional, human insulin formulations. Insulin detemir is a neutral, soluble, long-acting insulin analog in which threonine-30 of the insulin B-chain is deleted, and the C-terminal lysine is acetylated with myristic acid, a C14 fatty acid chain. Insulin detemir binds to albumin, a property that enhances its pharmacokinetic/pharmacodynamic profile. Results from clinical trials have demonstrated that treatment with insulin detemir is associated with less weight gain than either insulin glargine or neutral protamine Hagedorn insulin. There are many potential reasons for the lower weight gain observed among patients treated with insulin detemir, including lower risk for hypoglycemia and therefore decreased defensive eating due to concern about this adverse event, along with other effects that may be related to the albumin binding of this insulin that may account for lower within-patient variability and consistent action. These might include faster transport across the blood-brain barrier, induction of satiety signaling in the brain, and preferential inhibition of hepatic glucose production versus peripheral glucose uptake. Experiments in diabetic rats have also indicated that insulin detemir increases adiponectin levels, which is associated with both weight loss and decreased eating.

Keywords: basal insulin, body mass index, detemir, insulin analog, satiety

Introduction

The population of overweight (body mass index [BMI] 25.0–29.9 kg/m²) and obese (BMI ≥ 30 kg/m²) individuals in the USA continues to increase, and these conditions are a major clinical problem with respect to the development and treatment of type 2 diabetes mellitus (T2DM).^{1,2} It has been estimated that 82%–87% of individuals with diabetes are either overweight or obese,³ and it is also well known that cardiovascular risk factors beyond hyperglycemia, such as overweight/obesity, elevated blood pressure, and abnormal lipid levels, are important predictors of all-cause and cardiovascular mortality in patients with diabetes.⁴ Weight gain is also an important concern as a potential side effect of treatment for patients with T2DM receiving certain oral therapies or insulin;^{5,6} it has been suggested that the increase in body weight associated with antidiabetes therapy may blunt the clinical benefit of improved glycemic control associated with such therapy.⁷ Weight gain in patients with T2DM can also contribute

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to patient frustration with treatment, may negatively impact their adherence to therapeutic regimens, and could deter their motivation to adhere to lifestyle modifications.⁸

Results from numerous clinical trials have demonstrated that weight reduction decreases cardiovascular risk factors, and it is likely that this benefit extends to patients with T2DM.^{9–12} In addition, multiple studies have shown that obesity is an important contributor to insulin resistance and thus has the potential to blunt the benefit of oral secretagogues and insulin therapy.^{13–15} Data from the weight loss arm of the Trials of Hypertension Prevention study showed that even modest weight loss (–4.4 kg at 6 months, –2.0 kg at 18 months, and –0.2 kg at 36 months) led to clinically significant long-term reductions in blood pressure (BP) (–3.7, –1.8, and –1.3 mm Hg for systolic BP; and –2.7, –1.3, and –0.9 mm Hg for diastolic BP at 6, 18, and 36 months, respectively) and reduced risk for hypertension by 42% at 6 months, 22% at 18 months, and 19% at 36 months. Subjects who lost ≥ 4.5 kg at 6 months and maintained this weight reduction for the next 30 months had the greatest reduction in BP and a 65% reduction in the risk for hypertension.¹⁶ A 2-year weight reduction study (via weight-loss diets) in moderately obese individuals showed that a diet that leads to weight loss favorably modifies metabolic parameters related to cardiovascular risk (ie, low density lipoprotein cholesterol, triglycerides, high-density lipoprotein cholesterol).¹⁷ One-year results from the Action for Health in Diabetes (Look AHEAD) trial showed that clinically significant weight loss in patients with T2DM was associated with improved glycemic control and an improved cardiovascular risk profile.¹⁸ Recently published 4-year results from the Look AHEAD trial indicated that patients receiving intensive lifestyle intervention had a significantly greater percentage of weight loss than participants who received only diabetes education (–6.15% versus –0.88%, $P < 0.001$), greater reductions in glycosylated hemoglobin (A1C) levels (–0.36% versus –0.09%, $P < 0.001$), greater decreases in systolic and diastolic BP and triglycerides, and significantly greater increases in high density lipoprotein cholesterol.⁹

The results from Look AHEAD and other trials are consistent with the suggestion that the care of individuals with T2DM may be too glucocentric and that patient management must consider a wider range of factors that may contribute to the development of micro- and macrovascular disease, including obesity, hypertension, and dyslipidemia.^{18,19} The benefit of a more multifaceted and integrated approach to the management of patients with T2DM that simultaneously addressed multiple cardiovascular

risk factors has been demonstrated by results from the Steno-2 trial.²⁰ In this study, 160 patients with T2DM and microalbuminuria received either intensive multifaceted treatment or conventional therapy. Patients in Steno-2 were followed for 13.3 years; over this period, 24 patients in the intensive therapy group died versus 40 in the conventional treatment group (hazard ratio [HR] = 0.54, $P = 0.02$). Intensive therapy was associated with a lower risk of death from cardiovascular causes (HR = 0.43, $P = 0.04$), cardiovascular events (HR = 0.41, $P < 0.001$), diabetic nephropathy (relative risk [RR] = 0.44, $P = 0.004$), and requirement for retinal photocoagulation (RR = 0.45, $P = 0.02$).²⁰

While it has been shown to improve the long-term prognosis in patients with T2DM, treatment with insulin therapy is complicated by weight gain, which may delay initiation of this treatment in patients not maintaining glycemic control on oral drugs and/or intensification of dosing to maintain control in those already receiving insulin.²¹ Because insulin detemir is associated with less weight gain than insulin glargine,^{22,23} the aim of this paper is to review the role of insulin detemir in the treatment of patients with T2DM, with a focus on efficacy in obese patients and effects on body weight.

Cost of agents is always a consideration. However, the question of cost is a complex topic requiring a thorough balance between direct and indirect costs and short term versus long-term costs. Such an analysis is beyond the scope of this paper. However, reports do suggest a cost advantage of long-acting insulin analogs over neutral protamine Hagedorn (NPH) insulin.²⁴

Insulin therapy and body weight

A very large percentage of patients with T2DM ultimately require insulin to maintain control over blood glucose, due to the progressive nature of the disease and the exhaustion of pancreatic β -cells.^{25,26} Results from 61,890 patients with T2DM indicated that after more than 20 years following diagnosis, 50% were receiving insulin.²⁷ Insulin, when properly dosed, is the most effective drug currently available to achieve optimal glycemic control and avoid long-term disease complications. Although there is no maximum dose or ceiling effect, insulin treatment is commonly associated with weight gain brought on by multiple factors. Mechanisms believed to be involved in weight gain associated with insulin therapy include reduced glycosuria and associated loss of caloric intake; stimulation of fatty acid conversion into triglycerides in adipose tissue, which favors an increase in adipose mass; and inhibition of muscle proteolysis, resulting in a positive

nitrogen balance and an increase in lean mass.²⁸ The anabolic effect of insulin (inhibition of muscle proteolysis) is reflected by the fact that patients with diabetes who are receiving insulin gain lean as well as fat mass. Nevertheless, results from one evaluation indicated that nearly two-thirds of the weight gain associated with insulin treatment was fat mass.²⁹ Defensive snacking behaviors, driven by fears of hypoglycemia, can also contribute to weight gain in patients using insulin.³⁰

The type of insulin used for treatment also influences weight gain. For example, results from multiple clinical trials have demonstrated that patients with T2DM treated with NPH insulin gained between 0.3 and 2.8 kg.^{31–33} The development of insulin analogs has the potential to significantly ameliorate the weight gain associated with basal insulin therapy; this has been shown most clearly and consistently for insulin detemir. In fact, although improvements in A1C were not significantly different between patients treated with insulin glargine ($-1.46\% \pm 1.09\%$) or insulin detemir ($-1.54\% \pm 1.11\%$, between group $P=0.149$), those treated with insulin detemir had significantly less weight gain (difference: 0.77 kg, $P < 0.001$).²³ Similar differences in weight gain were found in earlier studies as well;²² however, no studies have yet been designed to assess whether such lower amounts of weight gain can translate into improvements in long-term outcomes, such as morbidity and mortality. The evidence that exists from both the Diabetes Control and Complications Trial and the UK Prospective Diabetes Study supports the concept that better glucose control does relate to less morbidity and mortality,³⁴ although there is no established link between improved morbidity and mortality and insulin detemir.

Insulin detemir

Insulin detemir is a neutral, soluble, long-acting insulin analog in which threonine is deleted from position B30 of the insulin

B-chain and the ϵ -amino group of lysine B29 is acetylated with a 14-carbon myristoyl fatty acid (Figure 1).^{35–37} This fatty acid modification allows insulin detemir to reversibly bind to the long-chain fatty acid binding sites of albumin, and this contributes to the extended time action profile for this analog.³⁸ Insulin detemir is soluble at neutral pH, which enables it to remain in a liquid form following subcutaneous injection. This property contrasts with NPH insulin, which is a preformed crystalline precipitate suspension, and insulin glargine, which is an acidic solution that precipitates in the subcutaneous tissue after administration. The solubility of insulin detemir may contribute to its low variability in pharmacokinetic and pharmacodynamic properties.^{35,36}

Pharmacokinetics/Pharmacodynamics

Once-daily insulin detemir provides 24-hour control over blood glucose equivalent to that for insulin glargine, the other long-acting insulin analog.³⁹ Insulin detemir administered twice daily reaches steady state after the second injection and shows a constant metabolic effect over time under steady-state conditions.⁴⁰ It has a duration of action of about 24 hours and concentrations in blood that increase with dose (Figure 2).^{41–43} The effects of body weight on the pharmacokinetics are not known due to the fact that published studies concerned with studying pharmacodynamics of insulin detemir have typically included nonobese subjects and because insulin detemir was dosed on the basis of body weight.^{40,44}

Multiple studies have provided clear support for a once-daily dosing regimen with insulin detemir. For example, results from the European cohort of the Predictable Results and Experience in Diabetes through Intensification and Control to Target: an International Variability Evaluation (PREDICTIVETM) study showed that switching from twice

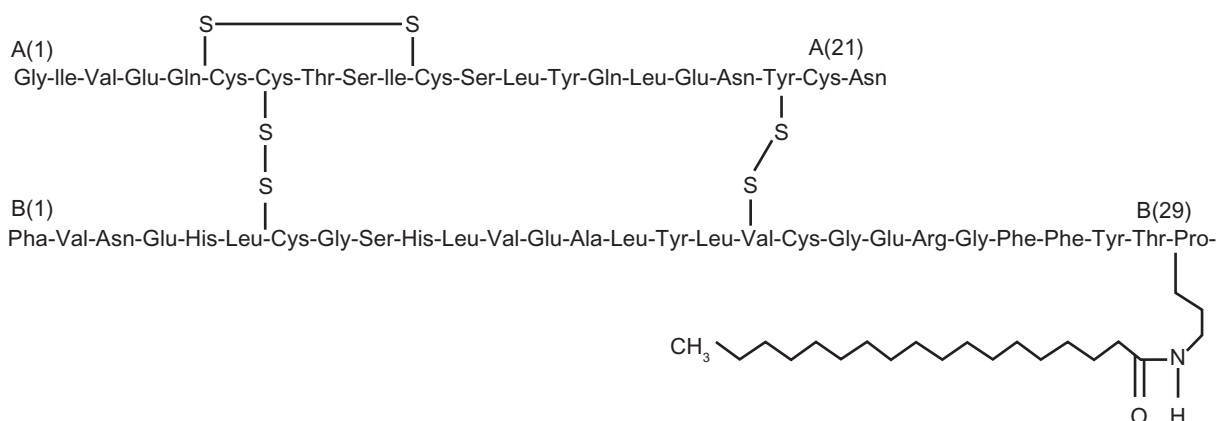


Figure 1 Structure of insulin detemir.³⁷

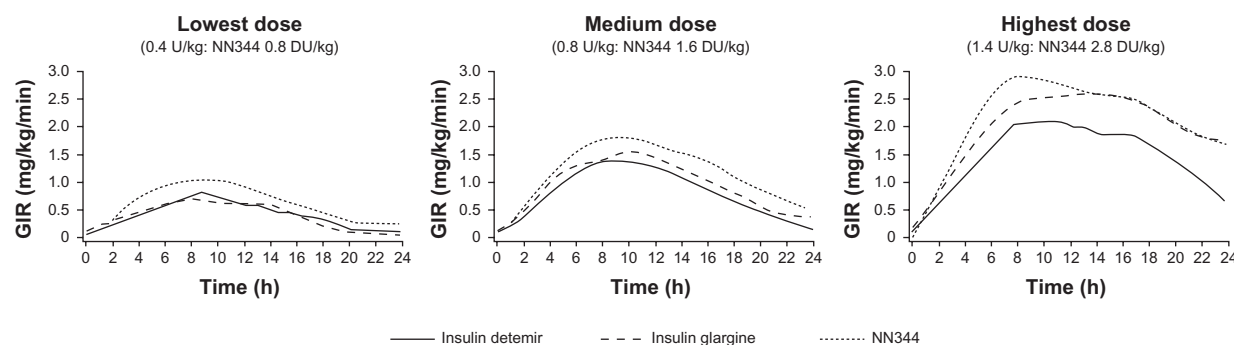


Figure 2 Pharmacodynamic profile for insulin detemir (glucose infusion rate in euglycemic glucose clamp experiments).⁴²

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Abbreviation: GIR, glucose infusion rate.

daily NPH insulin to once daily insulin detemir resulted in significant 12-week reductions in A1C ($P < 0.001$).⁴⁵ A 52-week trial included patients with T2DM who were receiving oral antidiabetes drugs and insulin detemir once or twice daily as needed or once daily insulin glargine, reported that A1C decreased from 8.6% to 7.1% with insulin detemir among patients who completed the study, whether or not they received one or two doses per day, and from 8.6% to 7.1% for all patients who received insulin glargine.²²

Clinical experience with basal insulin analogs: focus on weight gain

Results from multiple controlled clinical trials of patients with T2DM have shown that insulin detemir results in less weight gain than NPH insulin when used as monotherapy, when added to oral antidiabetes drugs, and when employed as part of basal bolus therapy.^{46–48} Additional controlled clinical studies have also demonstrated that insulin detemir is associated with less weight gain than insulin glargine when used as part of basal bolus treatment^{49,50} and when added to oral antidiabetes drugs.²² Results from a 20-week comparison of insulin detemir versus NPH insulin added to oral agents indicated that weight gain was 1.2, 0.7, and 1.6 kg with morning detemir, evening detemir, and NPH insulin, respectively ($P = 0.005$ for evening detemir versus NPH insulin).⁴⁸ Another comparison of insulin detemir versus NPH insulin, each combined with mealtime insulin aspart for 26 weeks in overweight patients (mean BMI = 31.8 kg/m²), indicated that weight gain was 0.4 kg for insulin detemir and 1.9 kg for NPH insulin ($P \leq 0.0001$).⁴⁶ A comparison of insulins detemir and glargine as part of basal bolus therapy in patients with T2DM indicated that weight gain was 1.2 kg for insulin detemir versus 2.7 kg for insulin glargine at the end of 26 weeks of treatment ($P = 0.001$).⁵⁰ Results from a 52-week, multinational, open-label, parallel-group,

noninferiority, treat-to-target trial comparing both once and twice daily insulin detemir with once daily insulin glargine in a basal plus regimen with oral antidiabetes drugs in patients with T2DM indicated that mean weight gain at 52 weeks was significantly lower among those who received insulin detemir than insulin glargine (3.0 versus 3.9 kg, $P < 0.001$), and further analysis revealed there was even less weight gain among those who received insulin detemir once a day (2.3 kg).²² Therefore, once daily dosing with insulin detemir may be advantageous in obese or overweight patients with T2DM to minimize weight gain.

The effects of insulin detemir on weight gain have been studied across a wide range of patients, including those who are overweight or obese. Meta-analysis of five parallel group randomized controlled trials of at least 20 weeks' duration that compared once daily evening insulin glargine or insulin detemir with a common comparator, NPH insulin (evening administration), showed that patients with T2DM ($n = 2092$) who received evening insulin detemir gained significantly less weight (−1.22 kg) than those treated with insulin glargine (−0.29 kg, $P = 0.010$).⁵¹ Importantly, this analysis focused on insulin naïve, T2DM patients poorly controlled with oral antidiabetes drugs, which are the patients most likely to be switched to insulin therapy in clinical practice. The beneficial effects of insulin detemir on weight change appear greatest in patients with high body weight or BMI at the initiation of treatment.^{33,52} Results from the Treat to target with once-daily Insulin Therapy: Reduce A1C by Titrating Effectively (TITRATE™) study, in which insulin detemir was added to oral antidiabetes drugs, indicated that body weight changes from baseline after insulin detemir treatment were related to baseline BMI. Patients with baseline BMI ≤ 25 kg/m² experienced weight increases from 1.35 to 1.38 kg and those with baseline BMI > 40 kg/m² at baseline experienced weight decreases from −0.14 to −0.33 kg.⁵³

Pooled analyses have also investigated whether weight changes with insulin detemir were linked to baseline BMI in patients with diabetes. Data were collected from three randomized, parallel group trials of 22–26 weeks duration that included 1416 patients aged ≥ 65 years and 880 patients aged 18–64 years, all of whom were treated with insulin.⁵⁴ At the end of the study, A1C control and fasting plasma glucose were similar for both age groups, regardless of whether they received insulin detemir or NPH insulin. However, both older patients (mean weight at baseline: insulin detemir = 81 kg, NPH insulin = 79 kg) and younger patients (mean weight at baseline: insulin detemir = 85 kg, NPH insulin = 85 kg) gained statistically significantly less body weight with insulin detemir than NPH insulin (0.69 versus 1.62 kg for older persons, $P < 0.001$; 0.80 versus 1.93 kg for younger persons, $P < 0.001$).⁵⁴ A report of data pooled from two randomized, parallel group trials of 22 and 24 weeks' duration that included 900 insulin treated patients with T2DM who had their treatment intensified to basal bolus therapy.⁴⁷ Patients received once or twice daily insulin detemir or NPH insulin in conjunction with insulin aspart or human soluble insulin at mealtimes. Although there was no between group difference in A1C, indicating comparable glycemic control, patients treated with insulin detemir had minimal weight gain (mean < 1 kg), regardless of their BMI at entry (estimated slope -0.032); whereas, in patients treated with NPH insulin, weight gain increased as baseline BMI rose (estimated slope 0.075 , $P = 0.025$). Patients receiving NPH insulin with BMI > 35 kg/m² gained the most weight (mean of ~ 2.4 kg) while insulin detemir-treated patients with the same BMI range lost weight (~ 0.5 kg).⁴⁷

Can reduced risk for hypoglycemia explain decreased weight gain with insulin detemir?

Although insulin glargine can also provide less of a risk for hypoglycemia than NPH insulin,⁵⁵ insulin detemir has even less of an impact on weight gain than other basal or intermediate-acting insulin formulations, and therefore it is important to discuss mechanisms that allow this to be manifested. Several potential mechanisms that have been proposed are addressed below.

Reduced risk of hypoglycemia with insulin detemir, coupled with a more consistent and reliable delivery of the desired dose than is available with traditional basal insulin, such as NPH insulin, has been proposed as a possible mechanism that could decrease defensive snacking by patients and help to limit weight gain.⁵⁶ Insulin detemir has

been repeatedly shown to have lower risk for hypoglycemia than NPH insulin when administered either once⁴⁸ or twice³³ daily. A recent meta-analysis has shown that insulin detemir is associated with significantly lower overall risk for severe hypoglycemia versus NPH insulin (RR = 0.74, 95% confidence interval [CI] = 0.58–0.96, $P < 0.05$). Insulin detemir is also associated with significantly lower risk for nocturnal hypoglycemia versus NPH insulin (RR = 0.92, 95% CI = 0.85–0.98, $P < 0.05$).⁵⁷ Results from another meta-analysis of studies comparing insulin detemir with NPH insulin that focused on patient age indicated that the RR for all hypoglycemic episodes (insulin detemir/NPH insulin) was 0.59 (95% CI = 0.42–0.83) for older persons and 0.75 (95% CI = 0.59–0.96) for younger patients.⁵⁴ Results from the TITRATE study, which had aggressive glucose targets, indicated that overall rates of hypoglycemia episodes were low and were comparable between insulin detemir treatment groups (7.73 and 5.27 events/subject/year for the 70–90 mg/dL and 80–110 mg/dL fasting plasma target groups, respectively). A single event of major hypoglycemia was reported in the 70–90 mg/dL target group.⁵³ Results from the PREDICTIVE BMI study showed that the incidence of hypoglycemia was lower with insulin detemir versus NPH insulin (RR = 0.62 for all events and 0.43 for nocturnal events, $P < 0.0001$ for both comparisons).⁴⁶

Although the earlier described studies and meta-analysis show that the risk for hypoglycemia is significantly decreased with insulin detemir versus NPH insulin, and it is reasonable to expect that this may result in less defensive eating, decreased weight gain with insulin detemir is not completely explained by decreased risk for hypoglycemia. A 26-week, randomized, multicenter, open label, parallel group trial compared glycemic control, hypoglycemia, and weight change between insulin detemir and NPH insulin (administered in the morning and evening) in a total of 476 insulin naïve patients with T2DM who were also being treated with one or two oral antidiabetes drugs.⁵⁸ Weight gain data from this study were analyzed as a function of hypoglycemia frequency. Weight gain with insulin detemir was 1.2 kg versus 2.8 kg with NPH insulin ($P < 0.001$), and the overall risk of hypoglycemia was 47% lower with insulin detemir ($P < 0.001$). No significant relationship between hypoglycemia and weight gain was seen with insulin detemir ($P = 0.2$), but such a relationship was demonstrated for NPH insulin ($P = 0.003$). These results are consistent with observations from healthy volunteers showing that insulin detemir treatment results in increased awareness during hypoglycemia.⁵⁹ Thus, results from these two studies, when

considered together, suggest that decreased awareness of hypoglycemia and less defensive eating cannot fully explain less weight gain with insulin detemir.

Alternative explanations for decreased weight gain with insulin detemir

There are several potential reasons for decreased weight gain with insulin detemir beyond a potential reduction in defensive eating secondary to decreased risk for hypoglycemia.

Hepatic influences

Due to its novel method of prolonging action via albumin binding, insulin detemir may influence hepatic glucose metabolism to a greater extent than peripheral tissues. The association of insulin detemir with nonesterified fatty acid binding sites on albumin may limit its transfer from the circulation into the extravascular extracellular space in adipose tissue and muscle, due to the capillary endothelial cell barrier. In the liver, the open sinusoids may expose hepatocytes to insulin detemir, enabling it to have a greater effect in the liver than in peripheral tissues. Results from a study in humans indicated that at and below plasma glucose concentrations of 54 mg/dL, suppression of endogenous glucose production was greater with insulin detemir than with NPH insulin, whereas stimulation of peripheral glucose uptake was greater with NPH insulin than with insulin detemir.⁶⁰ These authors suggested that decreased peripheral glucose uptake may contribute to lower weight gain with insulin detemir versus NPH insulin.

CNS influences

Another possibility that might explain less weight gain with insulin detemir versus other insulins is that it facilitates the actions of central nervous system mechanisms associated with satiety. Insulin detemir may be more effective than regular human insulin in communicating satiety signals within the central nervous system due to increased ability to cross the blood–brain barrier resulting from albumin binding. Results from a study in which insulin was administered intranasally to healthy subjects indicated that this treatment, which increases insulin levels in the cerebrospinal fluid, produced significant elevations in serum leptins and weight loss in men.⁶¹ This suggests that insulin may provide a negative feedback signal that regulates adiposity. Results from studies in human patients who received insulin injections indicated that this treatment can rapidly alter electroencephalographic activity.⁶² This effect suggests that insulin can influence

hypothalamic circuits involved in satiety and feeding.⁶¹ A study in 15 healthy volunteers showed that a bolus injection of insulin detemir during hyperinsulinemic-euglycemic clamp produced a change in the electroencephalogram not observed after injection of regular human insulin.⁶² Results from this study also showed that insulin detemir significantly decreased subsequent food intake by about 300 kcal versus regular human insulin ($P < 0.04$). However, it is important to note that other recent studies have suggested that insulin detemir is not transported across the blood–brain barrier,⁶³ and that acute intracerebroventricularly injected human insulin does not significantly inhibit food intake in rats.⁶⁴

Results from studies in experimental animals also support the suggestion that actions other than decreasing the risk of hypoglycemia may be involved in the effects of insulin detemir on body weight in patients with T2DM. It has been shown that administration of insulin detemir to Zucker diabetic fatty rats (an animal model for diabetes) results in smaller increases in fat mass than either insulin glargine or NPH insulin.⁶⁵ This result prompted the authors of this study to speculate that the reduced weight gain in patients treated with insulin detemir versus other intermediate or long-acting insulins to be due to decreased adiposity. A second study in the same strain of diabetic rats showed further that insulin detemir increases adiponectin levels to a greater extent than NPH insulin.⁶⁶ It is well known that adiponectin is decreased in obesity, and that higher adiponectin concentrations are associated with both weight loss and anorexia.⁶⁷ Both adiponectin and leptin are derived from adipose tissue and they influence food intake, insulin resistance, and lipolysis.^{68,69} Comparison of the effects of insulin detemir and human insulin on 3T3-L1 preadipocytes indicated that human insulin, but not insulin detemir, was associated with clonal expansion and that insulin detemir had reduced adipogenic effects versus human insulin.⁷⁰ Thus, while the mechanisms underlying lower weight gain with insulin detemir versus other insulins are not clear, it is reasonable to speculate that they may involve albumin binding, preferential activity in brain and liver, and favorable effects on adipocytes.⁷¹ Further studies are needed to determine which, of these or other mechanisms, underlie the positive effects of insulin detemir versus other insulin formulations.

Conclusion

Most patients with T2DM progress to treatment with insulin. The benefit of better glucose control offered by insulin can be offset by the higher weight gain and the hypoglycemia that occurs most commonly with human insulins than some analog formulations. This may lead to poor adherence to treatment by

some patients. Results from multiple clinical trials with insulin detemir have shown that its use results in less weight gain than older types of insulin, including NPH insulin. In addition, insulin detemir causes less weight gain among patients with high baseline weight or BMI. This trend for less weight gain may have a clinical impact on an individual basis. Multiple mechanisms may contribute to less weight gain with insulin detemir versus other insulins, and they all may be linked to the unique structure of the molecule, which includes a C14 fatty acid chain that enables binding to albumin.

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