Insulin detemir: a long-acting insulin analog for the treatment of Type 1 and 2 diabetes

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Many patients are apprehensive about initiating insulin. Worries about injections, hypoglycemia and weight gain as a result of insulin therapy may contribute to their concerns, and consequently pose a challenge to achieving or maintaining optimal glycemic control. Basal insulin replacement has proven to be effective and safe for initiating insulin therapy in Type 2 diabetes. With increasing β-cell dysfunction, the addition of rapid-acting prandial insulin to basal insulin therapy represents the gold standard for physiologic insulin replacement. Insulin detemir's beneficial profile in terms of offering less weight gain and a reduced risk of hypoglycemic episodes compared with neutral protamine Hagedorn insulin makes it an attractive alternative for basal insulin therapy. This review provides a comprehensive update on the pharmacology, clinical efficacy and safety of insulin detemir in Type 1 and 2 diabetes.

Challenges in diabetes management

Lifestyles are changing around the world, with many people increasing their caloric intake while being less physically active. This has resulted in a pandemic of obesity that is not only increasing the incidence of diabetes, but also reducing the typical age of onset of Type 2 diabetes. The number of children diagnosed as overweight has more than doubled in the past 30 years [1]. Statistics from the USA collected in 2003–2004 demonstrated that 17.1% of children were obese, and the comparison of 2003–2004 data with 1999–2000 data revealed a trend for increasing obesity [2]. Childhood and adolescent obesity is also becoming an issue in countries such as China owing to the major economic and social changes that are taking place [3]. Increasing obesity among our youth is likely to lead to increasing prevalence of diabetes at an earlier age. Estimates based on current US obesity rates suggest that younger-onset Type 2 diabetes, in individuals aged 44 years or under, will more than double to approximately 5.6 million by 2050 [4]. In developing countries, it is estimated that the prevalence of diabetes will increase from approximately 30 million in 2000 to approximately 55 million by 2030 [5]. Health systems worldwide will have to face the challenge of an increasing number of younger patients with diabetes, along with the potential burden of long-term complications related to the disease.

Optimizing diabetes control in order to reduce related micro- and macrovascular complications can be a difficult task. While there is clinical evidence that lowering glycemic exposure can reduce the incidence of microvascular damage, there is ongoing debate regarding the impact of strict glycemic control on macrovascular disease risk, especially given the conflicting data from preliminary reports of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and Action in Diabetes and Vascular Disease (ADVANCE) trials. Additionally, achieving strict glycemic control can be a challenge, made even more difficult by the increasing risk of hypoglycemia associated with intensified treatment [6–9]. In addition to concerns about hypoglycemia, patients with Type 2 diabetes often resist initiating insulin therapy, even when faced with poor glycemic control, because of worries about injections and weight gain with insulin treatment, as well as misconceptions regarding insulin itself [10]. Ideally, antihyperglycemic agents, and in particular insulin analog preparations, should provide predictable glycemic control with reduced risks of side effects, such as hypoglycemia or weight gain.

Insulin detemir is a long-acting insulin analog approved for once- or twice-daily subcutaneous administration for the treatment of adult and pediatric patients with Type 1 diabetes mellitus or adult patients with Type 2 diabetes mellitus. Its absorption into the circulation and action profile following injection is less variable than that of neutral protamine Hagedorn (NPH) insulin, as has also been shown with insulin glargine when compared with NPH, and, consequently, it has the potential for a more consistent blood glucose-lowering effect [11]. Additionally, insulin detemir appears to be consistently associated with less weight gain than NPH insulin in patients with

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Type 1 or 2 diabetes. This review provides a comprehensive update on the pharmacology, clinical efficacy and safety of insulin detemir in Type 1 and 2 diabetes.

When to start insulin therapy

For patients with Type 1 diabetes, the American College of Endocrinology (ACE) and the American Association of Clinical Endocrinologists (AACE) recommend intensive insulin therapy with either a basal–bolus regimen or continuous subcutaneous insulin infusion [12].

The current American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) and ACE/AACE guidelines for individuals with Type 2 diabetes are summarized in **Tables 1 & 2** [12,13]. In the proposed treatment algorithm, insulin therapy is an option for patients who are not achieving appropriate glycemic control with monotherapy or combination oral antidiabetic drug (OAD) therapy (**Table 1**), and can be added to ongoing oral medications [12,13]. The ADA/EASD recommend that patients start with basal insulin replacement with either an intermediate- or long-acting insulin, with the option of adding short-acting prandial insulin doses if daytime pre- or post-prandial targets are not being met [13]. The AACE, on the other hand, recommends initiating insulin in the form of a basal analog if fasting blood glucose (BG) is elevated, or premixed insulin analogs if post-prandial hyperglycemia is present [12].

Basal insulin therapy should be considered in subjects with Type 2 diabetes who are inadequately controlled on, or intolerant of, oral agent therapy. Basal insulin replacement is most effective when fasting hyperglycemia is associated with a glycosylated hemoglobin level (HbA_{1C}) of less than 8.5% [12]. For patients with HbA_{1C} values above 8.5%, the use of twice-daily premixed insulin therapy appears to be a more effective treatment option, although it is associated with more weight gain and hypoglycemia than a basal insulin strategy [14]. Subjects on basal insulin replacement whose fasting BG levels are close to target, but whose postprandial BG excursions and HbA_{1C} exceed the recommended range, should consider the addition of prandial therapy in the form of rapid-acting insulin at one or more meals.

Pharmacological profile of insulin detemir

Structure of insulin detemir molecule & formulation

To better approximate background physiologic insulin secretion, long-acting insulin analogs, such as insulin detemir and insulin glargine, have been developed as alternatives to NPH insulin. Insulin analogs are created by modifying specific amino acids along the β-chain of the insulin molecule, thereby affecting its absorption and distribution characteristics (pharmacokinetics [PK]), as well as its action profile (pharmacodynamics [PD]) [15,16]. The removal of the amino acid threonine at the B30 locus and the acylation of myristic acid at the lysine of the B29 locus allow reversible binding of the insulin detemir molecule to albumin, as well as increased self-association of insulin detemir molecules. Given these changes, insulin detemir has a reduced molar potency, which is approximately 25% of that of human insulin *in vivo* [17,18]. Because of this, insulin detemir is marketed at a fourfold increased molar concentration versus human insulin to ensure comparable unit doses and injection volumes to other insulin preparations. Despite a reduced molar potency, *in vitro* studies have shown that it remains a fully functional agonist of the insulin receptor [19]. At high concentrations, insulin can also cross-react with the insulin-like growth factor-1 (IGF-1) receptor, potentially causing mitogenic growth in cells expressing the receptor; however, the amino acid

Table 1. Current treatment recommendations from the ADA/EASD for patients with Type 2 diabetes.

Stage of treatment	Treatment recommendation
Initial treatment	Lifestyle intervention, including weight management and metformin therapy (if no contraindications)
Step 1: additional therapy following failure to meet glycemic targets at 3 months	Add insulin, sulfonylureas, thiazolidinediones or other drugs (α-glycosidase inhibitors, exenatide, glinides or pramlintide)
Step 2: following failure to meet glycemic targets at follow-up visit	Intensify or add insulin to OAD therapy

ADA: American Diabetes Association; EASD: European Association for the Study of Diabetes; OAD: Oral antidiabetic drug.
Table adapted from [13].

Table 2. Current treatment recommendations from the ACE/AACE for patients with Type 2 diabetes.

Stage of treatment	Treatment recommendation
Naive to pharmacologic therapy	
Initial treatment	Lifestyle intervention, including weight management
Initial HbA_{1C} 6–7%	OAD monotherapy. Consider combination therapy if glycemic goals are not achieved by 2–3 months
Initial HbA_{1C} 7–8%	Combination OAD therapy
Initial HbA_{1C} >10%	Initiate insulin
Currently treated pharmacologically	
Initial treatment	Exenatide may be combined with oral therapy in patients who have not achieved glycemic goals
Initial HbA_{1C} 6.5–8.5%	Add insulin therapy if patient on maximal combination oral therapy
Initial HbA_{1C} >8.5%	Consider initiating basal–bolus insulin therapy

AACE: American Association of Clinical Endocrinologists; ACE: American College of Endocrinology; HbA_{1C}: Glycosylated hemoglobin level; OAD: Oral antidiabetic drug.
Table adapted from [12].

modifications of the insulin detemir molecule do not increase its affinity for the IGF-1 receptor relative to its affinity for the insulin receptor, as compared with human insulin preparations [18].

Mode of protraction

Absorption of insulin from the interstitial space to the circulation occurs most rapidly when insulin molecules are not bound to each other (monomers), and more slowly when they self-associate (hexamers). Insulin detemir, as with most other insulin preparations, is in a hexameric form upon injection. In addition, due to the myristic acid side chains, these insulin hexamers can bind together to form dihexamers. All forms of insulin detemir, monomeric, dimeric, hexameric and dihexameric, can bind to albumin. This albumin binding, along with the strong self-association of detemir molecules, contributes to protracted absorption of insulin detemir into the circulation from the injection depot [16,20].

Albumin binding can also buffer insulin detemir against PD variability by reducing the effect of bloodflow on the absorption from the subcutaneous insulin depot, and by reducing the effect of changing plasma insulin concentrations on target tissue insulin concentrations [15]. Insulin is absorbed from the subcutaneous tissue into the bloodstream via the capillaries, at a rate that is partly dependent on the concentration difference of free insulin between the interstitial fluid and the capillary. When bloodflow is high, the local capillary concentration of human insulin drops and absorption is increased. In contrast, if bloodflow is slow, free-insulin concentrations in the capillaries are increased and absorption is decreased [15]. This variability in absorption is reduced with insulin detemir: as it enters the capillary bed, insulin detemir immediately binds to serum albumin, which lowers the free-insulin concentration. In addition, albumin binding results in a molecular complex of increased size, limiting diffusion of insulin back across the capillary wall into the interstitial space. Based on these principles, it would appear that albumin binding reduces the effect of bloodflow on the rate of absorption of insulin detemir compared with human insulin [15]. The binding of insulin detemir can also buffer the effects of shifting plasma insulin concentrations on tissue concentrations, as only 2% of insulin detemir in the circulation is unbound and available for transcapillary transport [15]. More consistent insulin absorption and albumin binding may, based on the principles described, explain the significant reductions in within-patient PD variability observed with insulin detemir compared with other basal insulins [11,21].

Despite 98% of insulin detemir molecules being bound to albumin upon entering the circulation, insulin detemir circulates at far lower molar serum concentrations than albumin. Furthermore, there are at least eight fatty acid binding sites on each albumin molecule, which means that insulin detemir occupies only a small fraction of available albumin-binding sites [15]. Consequently, insulin detemir does not interact competitively with clinically relevant concentrations of free fatty acids, or albumin-binding drugs such as phenylbutazone, warfarin, ibuprofen, diazepam, tolbutamide, glibenclamide, aspirin or valproate [22].

Onset, duration & variability of action of insulin detemir

Basal human insulins such as NPH have three main PK/PD disadvantages:

- A pronounced peak in activity, which can increase the risk of nocturnal hypoglycemia when it is administered in the evening
- A 12–14 h duration of action, which may require twice-daily dosing in certain patients (for example, those with Type 1 diabetes and thin, insulin-sensitive patients with Type 2 diabetes)
- Within-subject variability in absorption that can cause unpredictable glucose-lowering effects [23]

Long-acting insulin analogs such as insulin detemir or insulin glargine were developed to provide more physiologic basal insulin replacement, characterized by a time–action profile that is flatter, more prolonged and more consistent. Slowing absorption makes once-daily insulin dosing feasible, while a flatter time–action profile and more consistent blood-glucose lowering effect should translate into a reduced risk of hypoglycemia.

Euglycemic clamp studies are the 'gold standard' for investigating the PD of insulin, although they do have some inherent limitations that need to be considered in their interpretation. In healthy volunteers, for example, they may lead to incorrect estimations of duration of action because of the effect of endogenous insulin secretion [23]. Additionally, the calculated duration of action of an insulin preparation may be reported differently, since it is usually based on the onset of action, which is variably defined in clamp studies. While some studies label the onset of action as the time after subcutaneous insulin dosing at which the basal intravenous insulin infusion is decreased by 50%, in other studies duration of action is measured from initial subcutaneous insulin dosing [23]. With these caveats in mind, euglycemic clamps are still the best method to determine the time–action profile of an insulin.

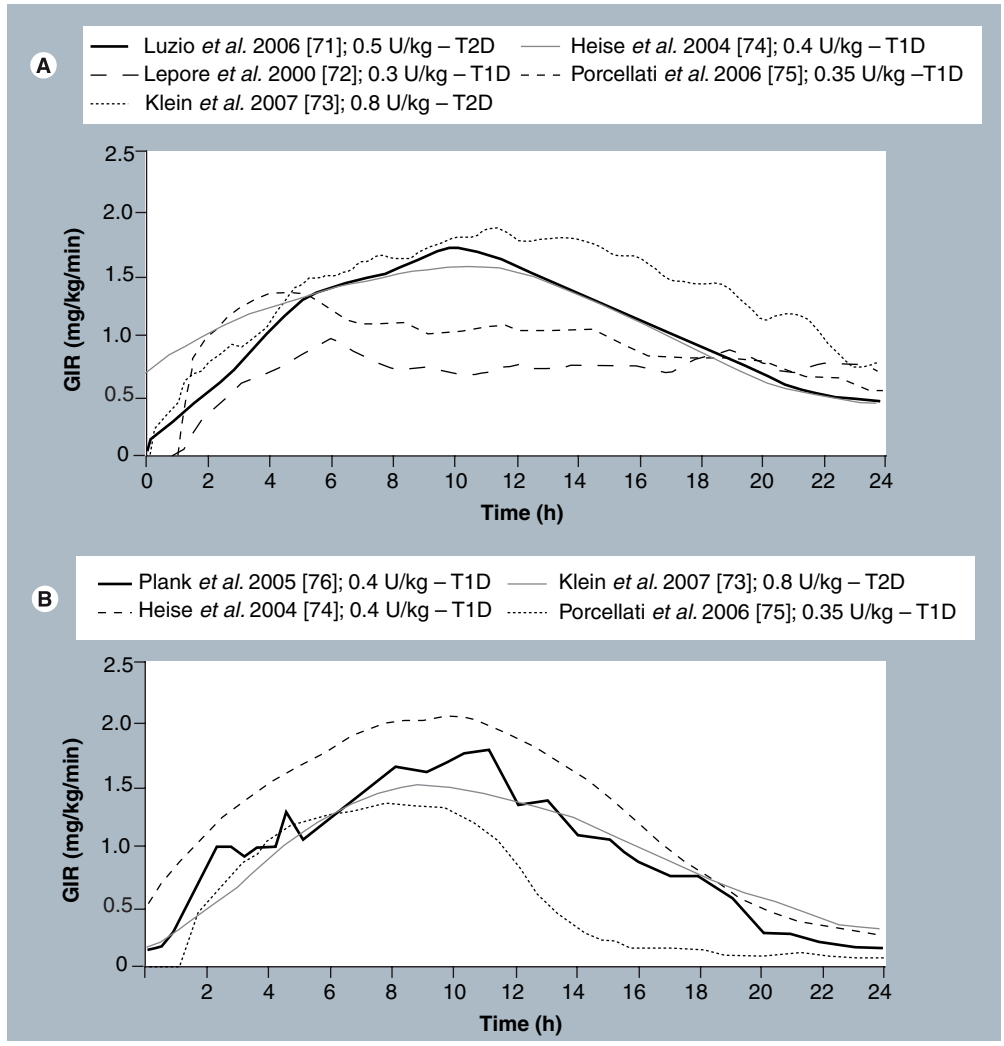
To define onset of action for insulin detemir, a euglycemic clamp study was conducted in 12 patients with Type 1 diabetes, and demonstrated a dose-dependent decrease in time to onset of action – defined as a 50% decrease in intravenous infusion of insulin from baseline – from 2 to 0.8 h for doses between 0.1 and 1.6 U/kg of insulin detemir [24]. For the most clinically relevant insulin detemir doses (0.4 and 0.8 U/kg), onset of action was calculated as 1.6 and 1.1 h, respectively [24]. In comparison, the onset of action for NPH insulin was 1.8 h for a dose of 0.3 U/kg [24]. Another study in subjects with Type 1 diabetes demonstrated an onset of action of 1.5 and 0.8 h for NPH and insulin glargine, respectively, when dosed at 0.3 U/kg [25].

A recent review on insulin duration of action from seven euglycemic clamp studies in Type 1 (five studies) and Type 2 (two studies) diabetes reported that, at clinically relevant doses, both insulin detemir and insulin glargine had a duration of action near to 24 h in Type 1 diabetes, and over 24 h in Type 2 diabetes when standard definitions are applied (**Figure 1**) [23]. However, it should be remembered that individual patients can show striking differences in duration of insulin action and, for some patients, mostly with Type 1 diabetes, a once-daily dose of insulin detemir or insulin glargine may not be sufficient to provide appropriate basal insulin replacement over a 24-h period [23].

Intra- or within-subject variability in the glucose-lowering effect of insulin can result in clinically significant effects on blood glucose levels, with an increased risk of unpredictable glycemic fluctuations, and possibly hypoglycemic episodes. In addition, within-subject variability in fasting blood glucose (FBG) has been shown, in epidemiologic analysis, to be an independent risk factor for retinopathy in patients with Type 2 diabetes [26]. Within-subject variability can be demonstrated with repeat euglycemic clamp studies. One such study in patients with Type 1 diabetes confirmed that insulin detemir showed significantly ($p < 0.001$) lower within-subject variability for PD end points (glucose-lowering effect in a euglycemic clamp test) and lower within-subject variability for PK end points (serum insulin concentrations) compared with insulin glargine and NPH insulin [11]. Significantly lower within-subject PD variability (glucose-lowering effects in a euglycemic clamp test) has also been demonstrated for insulin detemir versus insulin glargine in patients with Type 2 diabetes ($p < 0.001$) [21]. This finding of lower variability in the PK of insulin detemir compared with insulin glargine has also recently been reported in children and adolescents with Type 1 diabetes [27].

In clinical studies, these differences in variability appear to be more pronounced in subjects with Type 1 diabetes who are inherently more insulin deficient and less insulin resistant. Other than a potential reduction in hypoglycemia risk from a more consistent time–action profile, the clinical implications of these findings are yet to be determined. Consistent differences in hypoglycemia have been shown when comparing basal analogs with NPH insulin, but not when comparing analogs with each other.

Figure 1. Glucose infusion rates from euglycemic clamp studies.



Studies carried out in Type 1 and 2 diabetes for **(A)** insulin glargine and **(B)** insulin detemir [23].
GIR: Glucose infusion rate; T1D: Type 1 diabetes; T2D: Type 2 diabetes.
Data taken from [71–76].

Even with improved formulations, between-subject variability of insulin preparations remain and should alert the prescribing physician so that they can individualize both the initiation and the subsequent titration of the insulin dose to achieve glycemic goals [23].

Clearance & PK/PD aspects in special circumstances

Although reports in the literature suggest that clearance of human insulin is decreased in individuals with low kidney function, the PK of insulin detemir was similar in individuals with renal impairment and healthy volunteers [28]. On the other hand, subjects with severe hepatic dysfunction but without diabetes have lower insulin area under the curve (AUC), suggesting a reduced exposure to insulin detemir in this population compared with healthy volunteers [28]. Therefore, for patients with renal or hepatic impairment, glucose levels should be monitored carefully and dose adjustments should be implemented as needed [29].

PK/PD across age groups

The PK properties of insulin detemir appear to be minimally altered in children and elderly subjects. The PK of insulin detemir was compared in children (aged 6–12 years), adolescents (aged 13–17 years) and adults (aged 18–65 years) [30] with Type 1 diabetes, and showed no statistically significant differences in plasma AUC or C_{max}

among these groups when using a 0.5 U/kg dose [30]. In the same study, administration of 0.5 U/kg of NPH insulin increased AUC and C_{max} when administered to children compared with adults, although the differences did not achieve statistical significance [30]. In elderly patients (aged ≥68 years) on the other hand, a slightly higher insulin AUC (up to 35%) has been observed compared with younger adults (aged 25–35 years) [Data on file]. It appears that, while for children and adolescents similar titration guidelines to those of adults can be used, for elderly individuals slightly lower U/kg doses of insulin detemir might be appropriate.

Clinical effectiveness, hypoglycemia & weight gain

Type 1 diabetes

Overall

Insulin detemir is an effective basal insulin in patients with Type 1 diabetes, with predictable glycemic control and a lower risk of hypoglycemia and less weight gain in comparison with NPH insulin. The important clinical outcomes from randomized, controlled trials (RCTs) in Type 1 diabetes are summarized in **Table 3**.

Phase III studies (RCTs for regulatory submissions)

Most trials have reported similar effectiveness of insulin detemir and NPH insulin in reducing HbA_{1C} when used as the basal component of a basal–bolus regimen [31–38]. Given that in most of these trials the insulin doses were titrated to similar glycemic targets, the finding is not surprising [31–38]. There are, however, a few exceptions. In one study that compared an analog combination with a human insulin combination in a basal–bolus regimen, insulin detemir plus insulin aspart treatment for 18 weeks resulted in slightly better glycemic control versus NPH insulin plus regular human insulin (7.88 vs 8.11%; $p < 0.001$) [39]. The improvement in glycemic control was associated with statistically and clinically significant lower plasma glucose variability, less hypoglycemia (especially nocturnal hypoglycemia) and less weight gain for the insulin detemir/aspart combination. In another study, insulin detemir administered twice daily in two different combinations (pre-breakfast and at bedtime or at 12-h intervals) was compared with NPH insulin administered pre-breakfast and at bedtime, each in combination with prandial doses of insulin aspart. Although the HbA_{1C} for each individual insulin detemir group was comparable with the NPH insulin group, when data from both insulin detemir groups were pooled, slightly better glycemic control was demonstrated for insulin detemir versus NPH insulin (difference -0.18%; $p < 0.027$) [37]. As was seen in the previous study, the insulin detemir group experienced significantly less overall and nocturnal hypoglycemia, as well as less weight gain than the group using NPH insulin as basal replacement. Consistent with these findings, in the majority of insulin detemir Phase III trials, the relative risk of nocturnal hypoglycemia is significantly reduced by 26–55% compared with NPH insulin ($p < 0.05$) [31,32,34,36–39], while weight gain is consistently less ($p < 0.05$ versus NPH insulin) [33–39]. Although most studies with insulin detemir used NPH insulin as a comparator, there are a few trials evaluating this new analog against insulin glargine. A recently published 26-week, multicenter, open-label, parallel-group trial of 320 patients with Type 1 diabetes showed that, compared with insulin glargine, insulin detemir achieved comparable glycemic control with significantly lower rates of severe and nocturnal hypoglycemia ($p < 0.05$) [40]. Body weight gain did not differ significantly between patients in the insulin detemir and insulin glargine groups (0.52 and 0.96 kg, respectively; $p = 0.193$) [40].

While differences in efficacy between analog and non-analog insulin preparations have been difficult to demonstrate, a recent 2-year, multinational, open-label, parallel-group trial of 497 patients with Type 1 diabetes comparing insulin detemir with NPH insulin as basal replacement in patients using insulin aspart as the bolus component demonstrated statistically significant reductions in HbA_{1C}, nocturnal hypoglycemia and weight gain in favor of insulin detemir [41].

As supported by the findings from euglycemic clamp studies, Phase III studies in Type 1 diabetes have demonstrated that insulin detemir is associated with significantly reduced variability in pre-breakfast FBG compared with NPH insulin [31–33,35–39].

Observational or 'real-world' studies

Observational trials are an important addition to randomized clinical studies that can provide additional information on the efficacy and safety of drugs in large populations in a more 'real-life' scenario [42]. The ongoing Predictable Results and Experience in Diabetes through Intensification and Control to Target: an International

Table 3. Glycemic control, nocturnal hypoglycemia and weight loss/gain associated with insulin detemir in Type 1 diabetes.

Trial	Patients (n)	Comparator	HbA_{1C} (%)	Reduction in relative risk of nocturnal hypoglycemic episodes (%)*	Mean body weight change (kg)	Ref.
Robertson *et al.* (2007)	347	NPH insulin	-0.80 DET -0.80 NPH	-26 (p = 0.041)	Mean BMI Z-score was lower with DET versus NPH (p < 0.001)	[31]
Pieber et al. (2007)	320	Insulin glargine	-0.60 DET -0.50 GLA	-32 (p < 0.050)	+0.52 DET +0.96 GLA	[40]
Kølendorf et al. (2006)	130	NPH insulin	-0.30 DET -0.30 NPH	-50 (p < 0.001)	Inconclusive due to cross-over trial design	[32]
de Leeuw et al. (2005)	308	NPH insulin	-0.64 DET -0.56 NPH	-32 (p < 0.020)	-0.10 DET +1.20 NPH (p < 0.001)	[34]
Russell-Jones et al. (2004)	749	NPH insulin	-0.06 DET +0.06 NPH	-26 (p = 0.003)	-0.23 DET +0.31 NPH (p = 0.024)	[36]
Home et al. (2004)‡	408	NPH insulin	-0.82 DET -0.65 NPH	-53§ (p < 0.001)	-0.60 DET versus NPH (p < 0.040)	[37]
Hermansen et al. (2004)	595	NPH insulin	-0.50 DET -0.28 NPH (p < 0.001)	-55 (p < 0.001)	-0.95 DET +0.07 NPH (p < 0.001)	[39]
Standl et al. (2004)	252	NPH insulin	Similar in both groups	-29 (p < 0.067)	-0.30 DET +1.40 NPH (p = 0.002)	[35]
Vague et al. (2003)	448	NPH insulin	-0.55 DET -0.55 NPH	-34 (p < 0.005)	-0.60 +0.60 (p = 0.001)	[38]

**Percentage relative risk reduction of nocturnal hypoglycemia with insulin detemir versus comparator insulin.*

‡DET morning and bedtime.

§Minor nocturnal hypoglycemia.

DET: Insulin detemir; GLA: Insulin glargine; NPH: Neutral protamine Hagedorn.

Variability Evaluation (PREDICTIVE™) study is a large, multinational, observational study assessing the safety and efficacy of insulin detemir [43–45]. In PREDICTIVE, data from 20,531 patients (7420 with Type 1 diabetes) in 11 European countries demonstrated that 14 weeks of insulin detemir treatment in individuals with Type 1 diabetes significantly improved mean HbA_{1C} by -0.5%, mean fasting glucose by -31 mg/dl (-1.7 mmol/l), and mean within-patient fasting glucose variability by -13 mg/dl (-0.7 mmol/l) (p < 0.0001) [45]. In addition, insulin detemir treatment significantly reduced the number of total reported hypoglycemic episodes by 25.2/patient-year, major hypoglycemic episodes by 2.2/patient-year and nocturnal hypoglycemic episodes by 10/patient-year (p < 0.0001 for all). Individuals with Type 1 diabetes also experienced a mean 0.1 kg weight loss following 14 weeks of insulin detemir treatment (p < 0.01) [45].

Studies in children & adolescents

In a 26-week trial of 347 children (aged 6–11 years) and adolescents (aged 12–17 years) with Type 1 diabetes and a baseline HbA_{1C} of 8.8%, insulin detemir treatment was associated with similar decreases in HbA_{1C} compared with NPH insulin (-0.8% for both treatments; p = not significant [NS]), but with a significant 36% reduction in nocturnal hypoglycemia (p = 0.011) [31]. Within-subject variability in fasting plasma glucose (FPG) was significantly lower with insulin detemir compared with NPH insulin (standard deviation [SD] 3.3 vs 4.3, respectively; p < 0.001) and mean FPG was significantly lower

with insulin detemir versus NPH insulin (151 mg/dl [8.4 mmol/l] and 173 mg/dl [9.6 mmol/l], respectively; p = 0.022) [31].

Type 2 diabetes

Overall

Insulin detemir is an effective basal insulin in patients with Type 2 diabetes. Insulin detemir treatment offers predictable glycemic control with less risk of hypoglycemia versus NPH insulin, and comparable glycemic control and hypoglycemic risk compared with insulin glargine. In addition, insulin detemir is associated with less weight gain compared with both NPH insulin and insulin glargine in patients with Type 2 diabetes. The important clinical outcomes from RCTs in Type 2 diabetes are summarized in **Table 4**.

Phase III studies (RCTs for regulatory submissions)

Insulin detemir provides an effective and predictable basal insulin for the treatment of individuals with Type 2 diabetes. In a multinational, open-label, symmetrically randomized trial in individuals with Type 2 diabetes, 395 patients were treated with basal–bolus therapy with insulin detemir plus insulin aspart or NPH insulin plus regular human insulin [46,47]. Insulin detemir plus insulin aspart achieved similar glycemic control (7.46 vs 7.52%, respectively; p = NS) but with a 46% reduction in nocturnal hypoglycemia (p = 0.04), less weight gain (0.51 vs 1.13 kg, respectively; p = 0.038) and lower day-to-day FBG variability (22 mg/dl [1.20 mmol/l] vs 28 mg/dl [1.54 mmol/l], respectively; p < 0.001) [46,47]. In a second trial comparing insulin detemir with NPH insulin in subjects using prandial insulin aspart, patients in the insulin detemir arm experienced similar glycemic control with regards to study end HbA_{1C} and FPG, but experienced slightly lower within-subject variability in FBG (23 mg/dl [1.3 mmol/l] vs 25 mg/dl [1.4 mmol/l]; p = 0.021) and less weight gain (1.0 vs 1.8 kg; p = 0.017) [48]. The frequencies of hypoglycemia or adverse events were not different between the two groups.

Treat-to-target trials

Achieving strict glycemic control increases the risk of patients experiencing hypoglycemic episodes or weight gain. Since insulin analogs have more predictable PK/PD compared with regular human insulins, this may, in theory, allow patients to achieve similar control of their disease, but without increasing their risk of adverse events. Treat-to-target trials, when appropriately implemented, involve an intensive titration of insulin doses to achieve specific glycemic goals. The most successful trial carried out with insulin detemir was a 24-week study involving 476 patients with Type 2 diabetes inadequately controlled on oral agent therapy. Subjects with a mean baseline HbA_{1C} of 8.6% were randomized to receive twice-daily insulin detemir or NPH insulin, in addition to current OAD therapy [49]. Insulin treatment was periodically adjusted (at least weekly for the first 3 months) aiming for a pre-breakfast and pre-dinner plasma glucose target of 108 mg/dl or less (≤6.0 mmol/l). By the end of the study, subjects had experienced a significant decrease in HbA_{1C} values (1.8 vs 1.9% for insulin detemir and NPH, respectively; p = NS between-group difference), with 70% of individuals in either group achieving a HbA_{1C} of 7.0% or less. The proportion of subjects achieving this goal without any hypoglycemia during the last 12 weeks of treatment was 34% in the insulin detemir group and 25% in the NPH insulin group (p = 0.052) [49]. The relative risk for all hypoglycemia and nocturnal hypoglycemia was reduced by 47 and 55%, respectively, with insulin detemir compared with NPH insulin (p < 0.001), and by the end of the study the insulin detemir group experienced significantly less weight gain than subjects using NPH (1.2 vs 2.8 kg; p < 0.001) [49]. In a second treat-to-target study of 504 patients with Type 2 diabetes who were inadequately controlled with OADs, the addition of insulin detemir in the morning or evening resulted in statistically similar reductions in HbA_{1C} as evening NPH insulin (-1.58 and -1.48% vs -1.74%, respectively; p = NS), but with improved hypoglycemic end points [50]. Evening insulin detemir reduced 24-h and nocturnal hypoglycemia by 53% (p = 0.019) and 65% (p = 0.031), respectively, while morning insulin detemir reduced nocturnal hypoglycemia by 87% compared with evening NPH insulin (p < 0.001) [50]. Weight gain by the end of the trial was 1.2, 0.7 and 1.6 kg for morning detemir, evening detemir, and NPH, respectively, with the difference between evening detemir and evening NPH being statistically significant (0.9 kg; p = 0.005) In a third treat-to-target trial, insulin detemir administered once or twice daily compared with insulin glargine was equally effective in terms of optimizing HbA_{1C} control, and demonstrated similar hypoglycemic risk when added to OAD therapy in insulin-naive individuals with Type 2 diabetes; however, insulin detemir was

Table 4. Glycemic control, nocturnal hypoglycemia and weight loss/gain associated with insulin detemir in Type 2 diabetes.

Trial	Patients (n)	Comparator	HbA_{1C} (%)	Reduction in relative risk of nocturnal hypoglycemic episodes (%)*	Weight (kg)	Ref.
Philis-Tsimikas *et al.* (2006)	504	NPH insulin	-1.58 DET morning -1.48 DET evening -1.74 NPH	-53 DET morning (p = 0.019) -65 DET evening (p = 0.031)	+1.20 DET morning +0.70 DET evening (p = 0.005) +1.6 NPH	[50]
Rosenstock *et al.* (2008)	582	Insulin GLA	-1.40 DET -1.50 GLA	Relative risk DET/GLA 1.05	+3.00 DET +3.90 GLA (p = 0.012)	[51]
Hermansen *et al.* (2006)	476	NPH insulin	-1.80 DET -1.90 NPH	-55 (p < 0.001)	+1.20 DET +2.80 NPH (p < 0.001)	[49]
Rašlová *et al.* (2004)	395	NPH insulin	-0.65 DET -0.58 NPH	-46 (p < 0.04)	+0.51 DET +1.13 NPH (p = 0.038)	[46,47]
Haak *et al.* (2005)	505	NPH insulin	-0.20 DET -0.40 NPH	No difference	+1.00 DET +1.80 NPH (p = 0.017)	[48]

**Percentage relative risk reduction of nocturnal hypoglycemia with insulin detemir versus comparator insulin.*
DET: Insulin detemir; GLA: Insulin glargine; NPH: Neutral protamine Hagedorn.

associated with less weight gain in patients completing the trial (3.0 vs 3.9 kg, respectively; p = 0.012) [51].

Observational or real-world studies

The ongoing PREDICTIVE study is a large, multinational, observational study assessing the safety and efficacy of insulin detemir in individuals with Type 1 and 2 diabetes [43–45]. Patients were either started on insulin detemir if they were insulin naive, or switched to insulin detemir (from prior NPH or insulin glargine) if they were already on basal insulin replacement. Reporting on 20,531 patients (12,981 with Type 2 diabetes) from 11 European countries, PREDICTIVE demonstrated that 14 weeks of insulin detemir significantly reduced mean HbA_{1C} by 0.9%, mean fasting glucose by -47 mg/dl (-2.6 mmol/l) and mean within-patient fasting glucose variability by 9 mg/dl (0.5 mmol/l) in individuals with Type 2 diabetes (p < 0.0001). Insulin detemir treatment also significantly reduced the total number of reported hypoglycemic episodes by 6/patient-year, major hypoglycemic episodes by 0.7/patient-year and nocturnal hypoglycemic episodes by 2.7/patient-year (p < 0.0001). In addition, treatment with insulin detemir resulted in a mean 0.4 kg weight loss by study end (p < 0.0001) [45]. A subgroup analysis of the German cohort of PREDICTIVE was carried out in patients with Type 2 diabetes who were either insulin naive, or on basal insulin with or without OADs [44]. Over the course of the 14-week study mean duration, the insulin-naive cohort experienced statistically significant reductions in HbA_{1C} (-1.29%) and weight (-0.9 kg). Subjects switched from prior NPH or glargine insulin to detemir insulin also experienced statistically significant reductions in HbA_{1C} (-0.6%) and weight (-0.9 kg). Reported overall and nocturnal hypoglycemic episodes during the last 4 weeks of the study were reduced by 84 and 90%, respectively, when compared with baseline, with the greatest reductions reported in patients switched from NPH or glargine to insulin detemir [44].

The PREDICTIVE 303 trial was a prospective trial of insulin detemir carried out in North America comparing a simplified patient-adjusted dosing algorithm (303 Algorithm) versus standard-of-care physician-driven adjustment in individuals with Type 2 diabetes who were switched to, or started on, once-daily insulin detemir as their basal insulin replacement [52]. At baseline, patients enrolled in the study were treated with a variety of strategies that spanned the spectrum from diet to basal–bolus insulin therapy. The 303 Algorithm instructed patients to measure FBG

values every 3 days and adjust the insulin dose based on the following mean target blood glucose values: patients reduced their insulin dose by 3 units if FBG was less than 80 mg/dl (<4.4 mmol/l), they made no change to their current insulin dose if FBG was between 80 and 110 mg/dl (4.4–6.1 mmol/l), and they increased their insulin dose by 3 units if FBG was greater than 110 mg/dl (>6.1 mmol/l) [52]. Insulin adjustments for patients in the standard-of-care group were made directly by their treating physician. In the overall patient study population, the 303 Algorithm group experienced a slightly greater reduction in HbA_{1C} (8.5% at baseline to 7.8% at 26 weeks) than the physician-adjusted group (8.5% at baseline to 8.0% at 26 weeks; $p = 0.0106$), with no significant weight gain in either group [52]. Overall hypoglycemia was reduced by 2.61 events/patient-year and 4.58 events/patient-year in the 303 Algorithm and patient-adjusted group, respectively ($p < 0.01$). Of note is that patients treated with insulin detemir experienced modest weight loss versus baseline when they switched from insulin glargine (-0.6 kg; $p < 0.0001$) or NPH insulin (-1.6 kg; $p < 0.0001$) [53]. Analysis of the subgroup of patients in the PREDICTIVE 303 trial who were insulin naive at baseline demonstrated significant reductions in HbA_{1C} in both patient- and physician-driven groups (-1.1 and -1.0%, respectively), with no increased risk for overall or nocturnal hypoglycemia after starting basal insulin therapy with detemir, compared with baseline [54]. Overall, mean weight increased by 0.8 kg by study end ($p < 0.0001$). Subjects in the 303 Algorithm group achieved a larger dose of basal insulin than those in the physician-directed group (0.59 vs 0.49 U/kg/day, respectively; $p < 0.0001$ between-group difference). The conclusion of this study was that a simplified, patient-directed, insulin-dosing algorithm using once-daily insulin detemir was an effective and safe alternative to more traditional physician-directed basal dose adjustments.

Studies in elderly patients

In a 6-month follow-up of 748 elderly (aged ≥65 years) patients with Type 2 diabetes who enrolled in the PREDICTIVE trial, insulin detemir reduced mean HbA_{1C} by 0.7%, mean fasting glucose by 32 mg/dl (1.8 mmol/l) and mean within-patient fasting glucose variability by 9 mg/dl (0.5 mmol/l; $p < 0.0001$ vs baseline for all measures). Reported total, major and nocturnal hypoglycemic episodes were reduced by 9.4, 0.9 and 3.3 episodes per patient-year, respectively, versus baseline ($p < 0.0001$). Body weight remained stable (-0.3 kg; $p = 0.15$) following the switch to insulin detemir [55]. Basal replacement with insulin detemir appears to be safe and effective, with similar outcomes observed for the overall study population.

Clinical application

Insulin detemir can be prescribed once or twice daily. Once-daily dosing should be administered with the evening meal or at bedtime. For twice-daily dosing the evening dose can be administered with the evening meal, at bedtime or 12 h after the morning dose [29]. Insulin detemir has also been evaluated as a single dose in the morning in individuals with Type 2 diabetes, and has been shown to have similar efficacy and safety outcomes as evening insulin detemir dosing [50]. Practically speaking, as well as based on clinical trials, basal insulin replacement in the usual patient with Type 2 diabetes can be appropriately implemented with once-daily dosing, regardless of the basal insulin preparation. No differences in terms of effectiveness in HbA_{1C} lowering have been demonstrated when comparing once-daily dosing of NPH insulin with either insulin glargine [56] or insulin detemir [50]. The clinical advantage to using basal analog preparations is a consistently lower rate of hypoglycemia, especially overnight hypoglycemia, when compared with basal replacement with NPH insulin. Additionally, insulin detemir seems to be consistently associated with less weight gain, for the same degree of glycemic control, when compared with other basal insulin preparations.

Although studies have been carried out with once-daily dosing of insulin detemir in patients with Type 1 diabetes, depending on the amount of insulin required for basal replacement, a twice-daily dosing schedule may be more appropriate. These patients, especially when they are pre-pubertal (insulin detemir is approved for use in children over the age of 6 years), often need small amounts of basal insulin, which are more likely to cover their 24-h basal needs when split in two doses approximately 12 h apart. Twice-daily dosing of insulin glargine in Type 1 diabetes has also been shown to improve 24-h basal coverage [57].

Patients with Type 1 or 2 diabetes transitioning to or from insulin detemir from or to another basal insulin should have a unit-to-unit transition, and then adjust doses to achieve

glycemic targets [29]. During transitions to other insulins, close follow-up glucose monitoring is recommended. The dose and timing of concomitant antidiabetic medications (short-acting insulins or OADs) may need to be adjusted [29]. For insulin-naive patients with Type 2 diabetes who are not receiving adequate control with OADs, insulin detemir should be started at 0.1–0.2 U/kg once daily in the evening or 10 units once or twice daily. The dose should then be adjusted periodically to meet pre-established glycemic targets. It is important to recognize that most patients with Type 2 diabetes will require between 0.3 and 0.6 U/kg/day of basal insulin replacement, so it becomes essential to appropriately increase initial basal insulin doses until glycemic targets are achieved.

Trials have demonstrated that basal doses of insulin detemir are comparable to those of NPH insulin in Type 1 diabetes in adults [32,34,36,37,39] and children [31]. In a trial of insulin detemir versus insulin glargine in individuals with Type 1 diabetes, the mean daily dose of insulin detemir at 26 weeks was 0.47 versus 0.35 U/kg daily for insulin glargine (bolus insulin aspart dosing was 0.36 and 0.39 U/kg, respectively) [40]. However, the trial compared twice-daily insulin detemir with once-daily insulin glargine, and insulin detemir was titrated to both fasting and pre-dinner glycemic targets while insulin glargine was only titrated to fasting glucose [40]. This makes dosage comparisons difficult, as similar increases in total dose associated with twice-daily dosing have also been observed with insulin glargine. For example, in one study there was a 70% increase in the daily insulin dose in the 24.2% of patients who transitioned from once- to twice-daily glargine in order to achieve acceptable glycemic control (26 vs 44 U, respectively) [58].

In patients with Type 2 diabetes, insulin detemir can replace another basal insulin on a unit-to-unit basis, with the appropriate titration to achieve glycemic targets [29]. In some patients more insulin detemir may be required than NPH insulin [29]. Of four trials of insulin detemir versus NPH insulin in Type 2 diabetes, two have demonstrated similar basal dosing [48,50], and two demonstrated higher basal dosing with insulin detemir than with NPH insulin [46,49]. The Philis-Tsimikas trial is interesting because it compared the addition of once-daily dosing of insulin detemir and NPH insulin to OAD therapy in patients with poorly controlled Type 2 diabetes [50]. Similar doses of once-daily insulin detemir and NPH insulin provided improved glycemic control, and insulin detemir was associated with reduced incidence of overall ($p = 0.019$) and nocturnal hypoglycemia ($p = 0.031$) [50]. A trial of insulin detemir versus insulin glargine in insulin-naive subjects with Type 2 diabetes demonstrated an increased mean daily dosing for insulin detemir (0.78 U/kg) versus insulin glargine (0.44 IU/kg) [51]. In this trial, the protocol for the patients receiving insulin detemir directed investigators to add a morning injection of insulin detemir to ongoing evening basal insulin in subjects with elevated pre-dinner blood glucose levels, but on-target fasting glucose levels. The insulin glargine group, on the other hand, continued on once-daily administration for the duration of the study. At study end, subjects on once-daily insulin detemir were using an average of 0.52 IU/kg of insulin compared with a mean of 1.00 IU/kg in those switched to twice-daily insulin detemir. The additional insulin dose for insulin detemir did not result in a substantial difference in glycemic control at the end of the trial (both once- and twice-daily groups achieved an HbA_{1C} of 7.1%), but did contribute to the significantly greater amount of detemir compared with insulin glargine at 52 weeks. From this and other trials using a strategy of twice-daily basal insulin replacement in Type 2 diabetes, it appears that trying to lower pre-dinner glycemia with morning basal insulin is not an effective strategy. Rather, consideration should be given to introducing a prandial insulin component (rapid-acting insulin) to minimize post-prandial glycemic excursions during the day. Observational data from the PREDICTIVE study, which provides a more representative view of how patients with diabetes are treated in daily clinical practice, did demonstrate that transferring patients from NPH insulin and insulin glargine to insulin detemir only resulted in relatively small increases in daily insulin dose, which were correlated to improvements in HbA_{1C} [44].

Storage & shelf life

Insulin detemir should be stored between 2 and 8°C [29]. Once opened, vials can be stored in a refrigerator or at room temperature (below 30°C) for up to 42 days, while cartridges and pre-filled syringes should not be refrigerated. Insulin should be kept as cool as possible and away from direct heat or sunlight [29].

Delivery tools

Insulin detemir, as is the case for other basal insulin preparations, is available in a vial or a prefilled syringe (FlexPen®) [29]. Prefilled, disposable pen

devices for insulin injections are preferred by patients, are more discrete and user-friendly, and have the potential of reducing dosing mistakes and improving patient adherence [59–62].

Safety & tolerability

Hypoglycemia & weight change

Hypoglycemia and weight gain are often limiting factors that impact the level of glycemic control that patients are able or willing to achieve. Insulin detemir demonstrates equivalent glycemic control with fewer hypoglycemic episodes (usually nocturnal hypoglycemia) when compared with NPH insulin. This observation is most probably due to the flatter and more consistent action profile of basal insulin analogs, when compared with NPH. In addition, insulin detemir appears to have benefits in terms of weight gain versus NPH insulin in Type 1 diabetes and NPH insulin and insulin glargine in Type 2 diabetes.

Weight gain with insulin therapy may reflect both increased caloric retention from reduced urinary excretion of glucose and the anabolic properties of the hormone. There is also evidence that patients may indulge in 'defensive snacking' in an attempt to avoid the perceived risk of hypoglycemia [63]. Weight gain is particularly bothersome in patients with Type 2 diabetes, who are often overweight before starting insulin therapy [63]. As discussed previously, insulin detemir is associated with consistently less weight gain versus NPH insulin in Type 1 and 2 diabetes [34–39,46,48–50], and versus insulin glargine in Type 2 diabetes [51]. Although the weight differences are modest, the consistency of this finding across studies comparing insulin detemir and NPH insulin is impressive. In support of this finding, patients with Type 2 diabetes in the German cohort of the PREDICTIVE study or in the US PREDICTIVE 303 study transitioning from insulin glargine or NPH insulin to insulin detemir experienced a small but statistically significant decrease in weight of 0.6–0.8 kg at the end of the study compared with baseline ($p < 0.0001$) [44,53]. Interestingly, two studies have suggested that the relative weight-sparing effect of insulin detemir treatment is most marked in individuals with a higher baseline BMI [49,64].

Injection-site issues

As with other insulin therapy, lipodystrophy may occur at the injection site and delay insulin absorption [29]. Mild injection-site reactions have been reported in one study more frequently with insulin detemir than with NPH insulin [29] and insulin glargine [51], although serious adverse drug reactions reported in the PREDICTIVE observational study of 20,531 individuals with Type 1 or 2 diabetes were uncommon [45]. Other injection-site reactions with insulin therapy may include redness, pain, itching, hives, swelling and inflammation. Injection site reactions may require discontinuation of insulin detemir in rare cases. Clinicians should be aware that in some cases these reactions may be related to factors other than insulin, such as irritants in a skin-cleansing agent or poor injection technique.

Patient satisfaction & acceptability

The Diabetes Attitudes, Wishes and Needs (DAWN) study surveyed the attitudes towards starting insulin therapy among insulin-naive individuals with Type 2 diabetes [65]. The study demonstrated that there is resistance to starting insulin therapy among both healthcare providers and patients. Patients expressed doubts about the clinical benefits of insulin therapy and viewed having to start insulin as a personal failure in controlling their diabetes by other means. However, a survey of 586 individuals with diabetes, the majority of whom controlled their diabetes using insulin ($n = 414$), showed that people felt more confident regarding their blood-sugar control and avoiding symptoms of hypoglycemia, and expressed more satisfaction with their treatment in the first and second months following transfer to treatment with insulin detemir [66].

Cost–effectiveness

The cost–effectiveness of insulin detemir has been demonstrated using a validated model in the USA and UK versus insulin glargine and NPH insulin either alone or in combination with OADs [28,67–69]. Cost estimates in the USA were based on outcome data from the PREDICTIVE study [44] and patient characteristics from an ongoing prospective observational trial and a validated computer simulation model of diabetes, which were used to project the clinical and cost outcomes associated with conversion to insulin detemir treatment over a 35-year period [67]. Projected incremental cost–effectiveness ratios (ICER: the ratio of the change in costs when comparing two therapeutic interventions with the change in effect of the intervention) for transfer to insulin detemir with or without OAD were well within the range considered to represent good value in the USA: US$7412 per quality-adjusted life-year (QALY) versus OAD alone, US$6269 versus NPH insulin with or without OAD and US$3951 versus insulin glargine

Executive summary

Introduction

- Diabetes is an escalating problem, and younger age groups are developing Type 2 diabetes. Insulin therapy is a requirement in Type 1 diabetes and should be initiated in Type 2 diabetes as soon as oral antidiabetic drugs fail to provide adequate glycemic control.

Pharmacological profile of insulin detemir

- Insulin detemir and the other basal insulin analogs have flatter, more consistent time–action profiles than neutral protamine Hagedorn (NPH) insulin, and a duration of action of approximately 24 h in Type 1 and 2 diabetes.

Clinical effectiveness, hypoglycemia & weight gain

Type 1 diabetes

- Insulin detemir is an effective basal insulin in patients with Type 1 diabetes, with predictable glycemic control and a lower risk of hypoglycemia and less weight gain in comparison with NPH insulin.

Type 2 diabetes

- Insulin detemir treatment offers predictable glycemic control with less risk of hypoglycemia versus NPH insulin, and comparable glycemic control and hypoglycemic risk compared with insulin glargine. Insulin detemir is associated with less weight gain than NPH insulin and insulin glargine.

Clinical application

- Insulin detemir can be prescribed once or twice daily. Transitioning to insulin detemir can be done on a unit-to-unit basis with close glucose monitoring during the transition and follow-up periods.

Delivery tools

- Prefilled, disposable pens for insulin administration provide more accurate and consistent doses and allow less scope for dosing mistakes than treatment with vial and syringe. Pen devices may improve patient adherence.

Safety & tolerability

- Insulin detemir is associated with benefits in terms of hypoglycemic events and weight gain compared with NPH insulin. Insulin detemir is associated with slightly more mild injection-site reactions than treatment with other basal insulins.

Conclusion

- Insulin analogs, such as insulin detemir, provide improved pharmacokinetics/pharmacodynamics compared with NPH insulin, which makes it easier for patients to achieve glycemic control with a reduced risk of hypoglycemic episodes. Insulin detemir treatment is associated with less weight gain than NPH insulin in Type 1 diabetes, and with other basal insulins in Type 2 diabetes, so it is likely to be an attractive option for individuals initiating insulin.

with or without OAD [67]. These results need to be interpreted with caution given the short duration of the trials used in this analysis and the assumption that the clinical improvements at trial end would persist over time.

Comparing basal–bolus therapy with insulin detemir and NPH insulin over the lifetime of a patient using short-term studies in subjects with Type 1 diabetes, a similar computerized model (the CORE Diabetes Model) predicted an increase in quality-adjusted life expectancy of 0.09 years for subjects treated with detemir, translating to an ICER of GB£19,285 per QALY gained, which falls well within the acceptable cost–effectiveness ratio in the UK (<£35,000 per QALY gained) [70]. When analog basal–bolus therapy (insulin detemir plus insulin aspart) was compared with non-analog basal–bolus therapy (NPH insulin plus human soluble insulin), also in patients with Type 1 diabetes, using differences in HbA_{1C}, hypoglycemia frequency and weight at the end of the 18-week study, the quality-adjusted life expectancy was 0.66 QALY higher in the analog group, producing an ICER per QALY gained of GB£2500, reflecting a direct lifetime cost difference of GB£1654 for the analog approach [68]. Both of these ICER values are well within the range considered to be good value in the UK [68].

Conclusion

Insulin initiation in Type 2 diabetes is often delayed, with consequent exposure to hyperglycemia and related complications. The reasons for this delay are many, and involve patients, health providers, health systems or a combination thereof. Insulin therapy is viewed as an option of last resort by many patients and providers alike, and is therefore often delayed until no other option exists. Furthermore, patients who need to start insulin therapy are often concerned that starting insulin means their disease

process is advanced and irreversible. Additional concerns relating to the side effects of insulin therapy, such as weight gain, hypoglycemia, discomfort of injections, and the need for more complex therapy and more frequent blood glucose testing, further challenge the implementation of insulin therapy. The additional resources, time and effort needed to properly transition patients to insulin also represents a significant 'disincentive' for the busy and overwhelmed healthcare provider. Insulin analogs and the newer delivery technologies may provide an opportunity for more 'physiologic' insulin replacement in a more user-friendly, less threatening device. The potential for less weight gain and hypoglycemia and greater adherence may provide the background for patients to achieve better glycemic control. The introduction of insulin detemir represents an additional tool in our armamentarium for the management of insulin-deficient diabetes, and provides us with a physiologic alternative associated with a modest, although consistent, weight advantage for basal insulin replacement. The use of insulin detemir has been shown to be effective and safe for basal or basal–bolus insulin replacement in patients with Type 1 or 2 diabetes, and thus should be actively considered in the management of insulin-requiring and insulin-dependent patients with diabetes.

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