Insulin detemir: evidence, efficacy and applications

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ARTICLE POINTS

1 For many people with type 1 diabetes, controlling blood glucose is considered a balancing act.

2 Insulin detemir has protracted, consistent and predictable absorption with lower within-patient variability, lower risk of hypoglycaemia and less weight gain when compared to NPH insulin or insulin glargine.

3 People likely to benefit from insulin detemir are: those with poor or erratic blood glucose control, those experiencing frequent hypoglycaemic episodes and those who fear weight gain.

4 Variability of insulins actions can be a limiting factor in achieving metabolic targets, and avoiding hypoglycaemia and weight gain.

KEY WORDS
- **Type 1 diabetes**
- **Insulin detemir**
- **Nocturnal hypoglycaemia**
- **Weight neutral**
- **Basal insulin**

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Introduction

Controlling blood glucose is considered a 'balancing act' by many people who have type 1 diabetes, and any imbalance can lead to hypoglycaemia (and possible weight gain), hyperglycaemia or erratic blood glucose levels. Absorption peaks and within-patient variability can be problematic with many basal insulins which can lead to suboptimal blood glucose control. The efficacy of the basal analogue, insulin detemir, is considered in this article and compared to others, such as NPH insulin. The suitability of insulin detemir for the treatment of people with type 1 diabetes is also discussed.

For many people with type 1 diabetes mellitus, controlling their blood glucose is considered a 'balancing act' – insulin, food and exercise. If there is any imbalance then this can have a detrimental effect on their blood glucose control. This could include hyperglycaemia, hypoglycaemia (possibly leading to weight gain) or erratic blood glucose levels.

As healthcare professionals we strive to encourage people to maintain good glycaemic control. However, people's fears of hypoglycaemia could result in them maintaining higher blood glucose levels, with increased risks of complications (Diabetes Control and Complications Trial [DCCT], 1993). In addition to this, non-compliance (with diet and insulin), weight gain (eating in order to avoid hypoglycaemic events) and the unpredictable nature of neutral protamine Hagedorn (NPH) insulin all adds to the difficulties of people achieving glycaemic targets.

Do we need an improved basal insulin?

Currently available intermediate- and long-acting human insulin preparations have significant limitations to their use as basal insulins. For example, widely-used NPH insulin, such as Insulatard, has a peak of insulin absorption, and therefore glucose-lowering action, several hours after it is injected subcutaneously. For some people this can be problematic – even if NPH insulin is injected at bedtime, this peak can occur in the middle of the night, at which time it could possibly result in nocturnal hypoglycaemia.

Another important quality for a basal insulin is a constant absorption of insulin from the subcutaneous depot into the circulation. Unexpected 'highs' or 'lows' in insulin absorption could cause episodes of hyperglycaemia in a person with diabetes, thereby compromising metabolic control, and/or putting the person at risk of hypoglycaemic events. Ideally, a basal insulin should provide optimal control of overnight and fasting plasma glucose, but without incurring nocturnal hypoglycaemia.

However, the absorption profile (and hence the glucose-lowering response) of NPH insulin can vary significantly from injection to injection (Heise et al, 2004). This variability is partly due to the formulation of NPH insulin (Kurtzhals, 2004; Chen et al, 2003). As NPH insulin is a suspension of crystals of protaminated insulin, patients need to shake the preparation thoroughly before each injection to avoid erratic dosing. Further variability in absorption can arise after injection, however, because dissolution of the insulin crystals must take place before absorption into the blood stream can occur, and this may be an unpredictable process. Moreover, blood flow to the injection site can vary. Insulin glargine is presented as a solute that does not require resuspension and this avoids part of the problem, but the formation and subsequent redissolution of a precipitate after injection might explain why variability in absorption can still occur (Heise

et al, 2004; Kurtzhals, 2004).

Insulin detemir is a basal insulin analogue that differs from other available basal insulin preparations by remaining soluble before and after injection, and in terms of its structure. Relative to human insulin, insulin detemir's structure is slightly changed with the attachment of a naturally occurring lipid. This enhances the self-associating properties of the molecule, prolonging its association as hexamers, which are slow to absorb into the blood through capillary walls (Havelund et al, 2004). Furthermore, the lipid side-chain enables insulin detemir to bind reversibly to human albumin in the subcutaneous depot, further delaying absorption (Havelund et al, 2004). Once absorbed into the blood stream, reversible albumin binding in plasma may buffer the effect of any change in absorption rate caused by variable blood flow to the injection depot (Kurtzhals, 2004) Together, these characteristics of insulin detemir leads to a protracted and consistent absorption rate from the injection site into the circulation and consistency in the blood glucose-lowering profile (Kurtzhals, 2004).

Thus, in contrast to NPH insulin, insulin detemir remains in solution in the subcutaneous depot, and has a more protracted and smooth time-action profile (Pieber et al, 2002; Heise et al, 2004). This has been demonstrated in a glucose clamp study in 54 patients with type 1 diabetes receiving either insulin detemir, insulin glargine or NPH insulin (Heise et al, 2004). The glucose-lowering action (*Figure 1a*) and insulin absorption of insulin detemir were less variable than those of NPH insulin or insulin glargine (*Figures 1b and c*). Variability (Coefficient of Variation, CV%) was higher with NPH insulin (68%) and insulin glargine (48%) than with insulin detemir (27%). Clinically, these figures relate to the possible hypoglycaemic risk of an insulin, i.e. a patient would experience a higher than average glucose lowering effect (potentially leading to hypoglycaemia) approximately once every two years with insulin detemir, 24 times a year with NPH insulin, and 10 times a year with insulin glargine (Heise et al, 2004).

From these data, we might expect that treatment with insulin detemir would cause fewer unexpected periods of hyper- or hypoglycaemia in comparison with treatment using NPH insulin or insulin glargine. This expectation has been supported by data (discussed below) showing reduced variability in glycaemic control and/or a reduced risk of hypoglycaemia with insulin detemir in comparison with NPH insulin (Russell-Jones et al, 2004; Home et al, 2004; Vague et al, 2003; Hermansen et al, 2004; De Leeuw et al, 2004).

Who is going to benefit from insulin detemir?

The more predictable and constant time-action profile of insulin detemir is clinically relevant if it underlies predictability in metabolic parameters, such as fasting blood glucose (FBG) control, the level of risk of experiencing hypoglycaemia, or the degree of weight change in people using insulin. Therefore, insulin detemir could be particularly suited to people with diabetes who have problems with erratic blood glucose control, who experience hypoglycaemia (especially at night), or who find it difficult to manage their weight once blood glucose control improves.

People with poor or erratic blood glucose control

Due to its predictable action, insulin detemir could be appropriate for people with diabetes who have active lifestyles and

PAGE POINTS

1 Insulin detemir's lipid side-chain enables it to bind to human albumin in the subcutaneous depot, giving it a protracted and consistent absorption from the injection site into the circulation.

2 In a glucose clamp study, glucose-lowering action and insulin absorption of detemir were less than insulin glargine or NPH insulin.

3 Insulin detemir could be particularly suited to people who have problems with their blood glucose control, who experience hypoglycaemia – particularly at night – or who find it difficult to manage their weight.

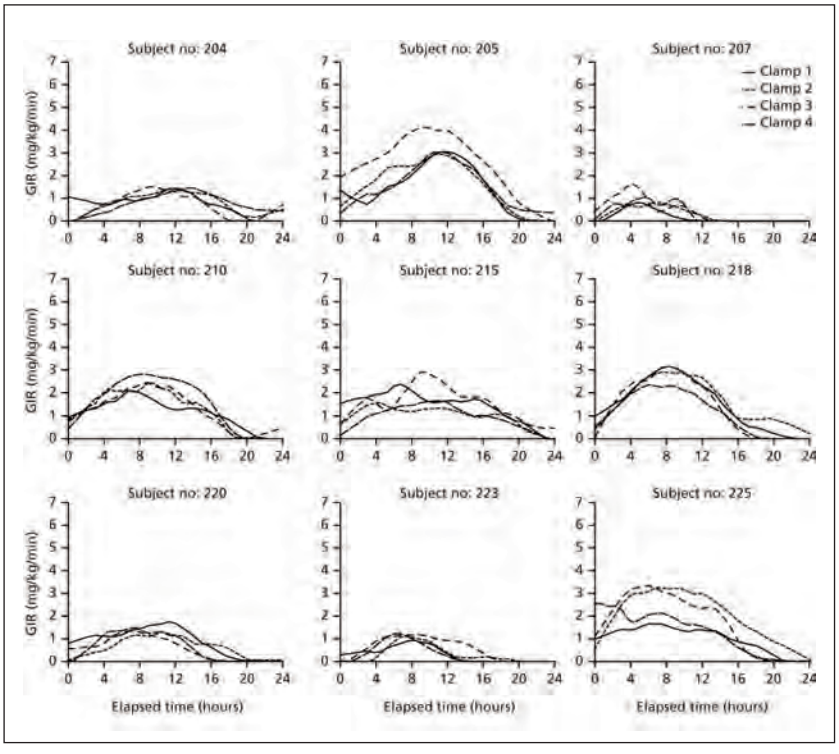


Figure 1a. Glucose infusion rate curves for insulin detemir (Adapted from Heise et al, 2004).

PAGE POINTS

1 To avoid nocturnal hypoglycaemia people may eat at bedtime or deliberately let their overnight blood glucose levels run high.

2 A study of 447 people with type 1 diabetes showed that using insulin detemir instead of NPH insulin reduced the risk of overall hypoglycaemia by 22% and nocturnal hypoglycaemia by 34%.

3 Weight gain is an undesirable consequence of insulin therapy in many people; however, insulin detemir showed lower weight gain compared with NPH insulin in type 1 and 2 diabetes.

consequently find it challenging to control effectively their blood glucose levels on a day-to-day basis. As part of a flexible basal-bolus regimen with analogue insulins or soluble human insulin as prandial components, insulin detemir has been shown to improve the glycaemic control profile compared with NPH insulin in a number of clinical studies.

Long-term treatment with insulin detemir has shown promising results. Once-daily insulin detemir resulted in lower home-monitored FBG in comparison with NPH insulin (7.5 vs 8.3 mmol/l, $p<0.001$) (Russell-Jones et al, 2004).

Furthermore, twice-daily insulin detemir resulted in lower fasting plasma glucose (FPG), lower day-to-day variation in FPG for each patient and lower HbA_{1c}, compared with NPH insulin treatment over 16 weeks (*Table 1*) (Home et al, 2004).

People experiencing frequent hypoglycaemic episodes

It is well recognised that hypoglycaemia is a common and serious side-effect of insulin therapy. The distressing effects of hypoglycaemia include confusion, mood swings, hunger, dizziness and headache, and in severe cases hypoglycaemia can result in convulsions, coma and death. Consequently, people with diabetes are concerned about hypoglycaemia occurring at any time when help from a third party, if needed, may not be readily available. To avoid nocturnal hypoglycaemia they may eat at bedtime or deliberately let their overnight blood glucose levels run high.

Despite better fasting blood glucose levels seen with insulin detemir treatment in clinical trials, the risk of hypoglycaemia is not increased. Indeed, the risk of experiencing nocturnal hypoglycaemia was significantly reduced with insulin detemir in comparison with NPH insulin (Vague et al 2003; Hermansen et al, 2004; De Leeuw et al, 2004). Home et al (2004) showed a 53% reduction in minor nocturnal hypoglycaemia with insulin detemir morning and bedtime, $p<0.001$, and Russell-Jones et al (2004) found a 26% reduction in the relative risk of nocturnal hypoglycaemia with insulin detemir treatment, $p=0.003$.

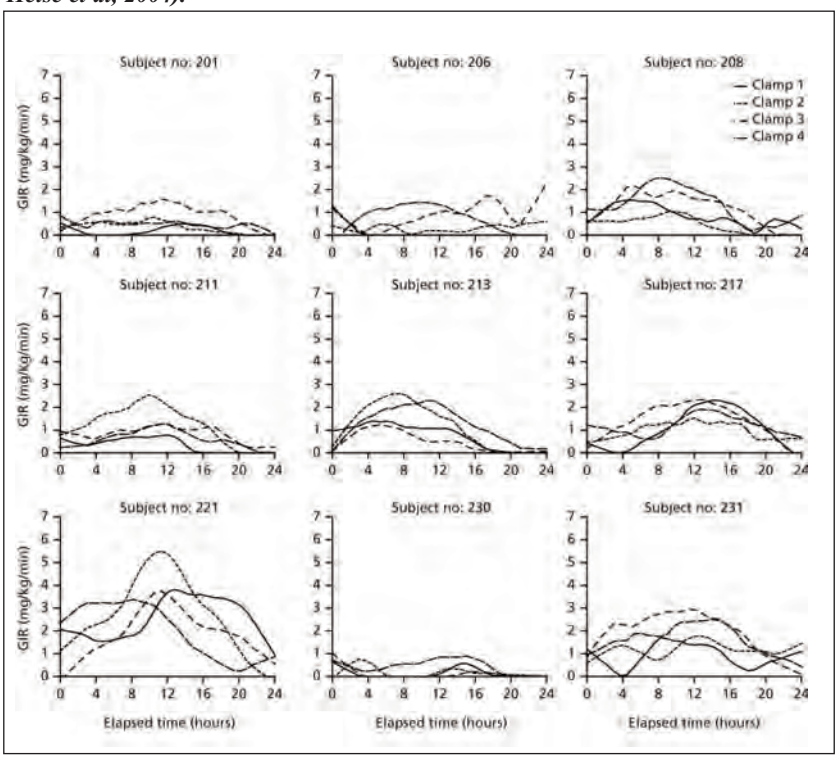
These advantages of insulin detemir were confirmed in a study comparing an all-analogue basal-bolus regimen (insulin detemir plus insulin aspart) compared with a human insulin basal-bolus regimen (NPH insulin plus soluble human insulin) (Hermansen et al, 2004). At the end of this 18-week trial, HbA_{1c} levels and risk of hypoglycaemia (particularly with overall and major nocturnal hypoglycaemia) were both significantly lower with the all-analogue regimen compared with NPH and human soluble insulin (*Figure 2*).

Using insulin detemir instead of NPH insulin reduced the risk of overall hypoglycaemia by 22% ($p<0.05$) in a 447-patient study in type 1 diabetes (Vague et al, 2003). The risk of nocturnal hypoglycaemia in this six-month study was reduced by 34% with insulin detemir ($p<0.005$). These findings were also in the context of similar glycaemic control between the two treatment groups (HbA_{1c} with insulin detemir: 7.60% vs NPH insulin: 7.64%, non-significant). A further six-month extension to the above study confirmed these results (De Leeuw et al, 2004): glycaemic control was maintained and a 32% risk reduction in nocturnal hypoglycaemia remained with insulin detemir compared with NPH insulin ($p=0.016$).

People who fear weight gain

Weight gain is an undesirable consequence of insulin therapy in many people with diabetes.

Figure 1b. Glucose infusion rate curves for insulin glargine (Adapted from Heise et al, 2004).



People with diabetes tend to want to have good glycaemic control. However, there can be an associated weight gain which may contribute to lower self-esteem. Reduced metabolic rate, the anabolic effects of insulin, the perceived fear of hypoglycaemia and hence defensive eating may all contribute to insulin's weight-gaining effect. This may then lead to the requirement of increases in insulin dose and subsequently increasing risks of hypoglycaemia.

An unexpected, but remarkably consistent, finding with insulin detemir is a lower weight gain compared with NPH insulin in people with type 1 or type 2 diabetes (Standl et al, 2004; Vague et al, 2003; Pieber et al, 2004; Haak et al, 2004; Hermansen et al, 2004; Raslova et al, 2004; Home et al, 2004; Russell-Jones et al, 2004; De Leeuw et al, 2004) (*Table 2*).

The predictability in action of insulin detemir may explain this finding. People may be less fearful of experiencing hypoglycaemia with insulin detemir treatment compared with NPH insulin, therefore eating less defensively, which may explain the differences in weight seen between the two treatment groups in all the above trials. A more predictable insulin resulting in reduced risks of weight gain would be welcome.

Summary

The variability of insulin action is an important, but often overlooked, issue. It is clear that variability can be a significant limitation for people with diabetes in their endeavours to achieve metabolic targets and avoid the spectre of hypoglycaemia or weight gain. Consequently, despite the best efforts of the person with diabetes or healthcare provider, achieving these treatment goals may be restricted by the insulin itself. With the advent of more predictable insulin analogues, people could expect to strive for better glycaemic control without increasing the risk of unwanted effects. One such analogue is the basal insulin, insulin detemir. This insulin, in conjunction with other insulin analogues, can form the basis of a flexible and more predictable basal bolus regimen, with potentially positive benefits and fewer problems, such as nocturnal hypoglycaemia.

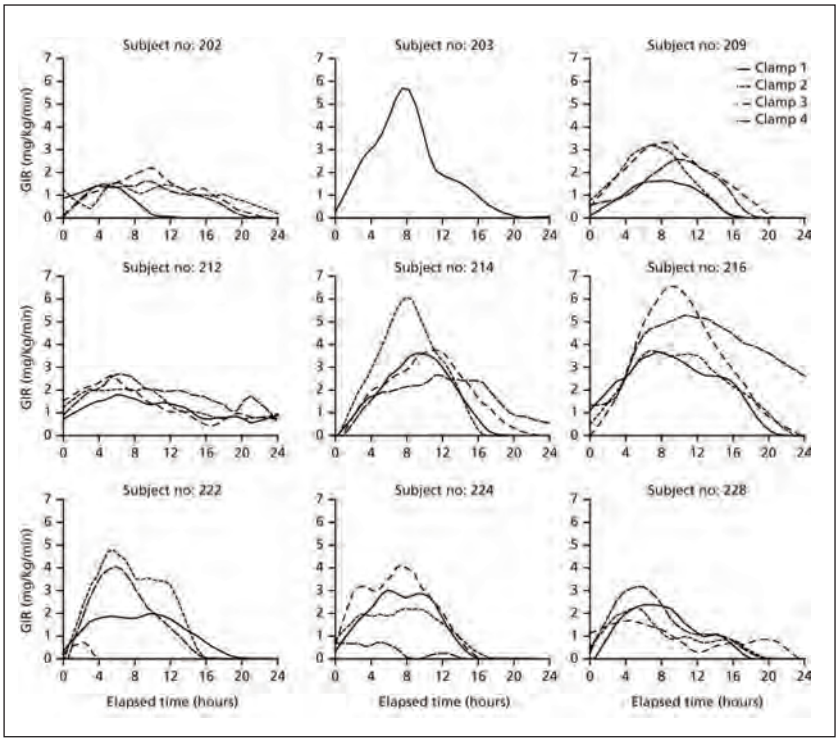


Figure 1c. Glucose infusion rate curves for NPH insulin (Adapted from Heise et al, 2004).

Table 1. Insulin detemir is less variable and achieves better metabolic control than NPH insulin. All values are mean (SE). Data taken from Home et al (2004).

	Insulin detemir$_{12h}$	Insulin detemir$_{morn+bed}$	NPH insulin	*P* value
Clinic FPG (mmol/l)	9.75 (0.37)	8.94 (0.37)	11.24 (0.38)	<0.001
Self-monitored pre-breakfast PG (mmol/l)				
Mean	8.28 (0.20)	8.26 (0.20)	9.05 (0.21)	0.005
Within patient variation (standard deviation)	2.95	2.91	3.49	<0.001
HbA_{1c} (%)	7.75 (0.07)	7.78 (0.07)	7.94 (0.07)	0.082
HbA_{1c} (%) pairwise comparison	$IDet_{combined}$ - NPH insulin	Mean difference (95% CI): -0.2 [-0.34, -0.02]		0.027

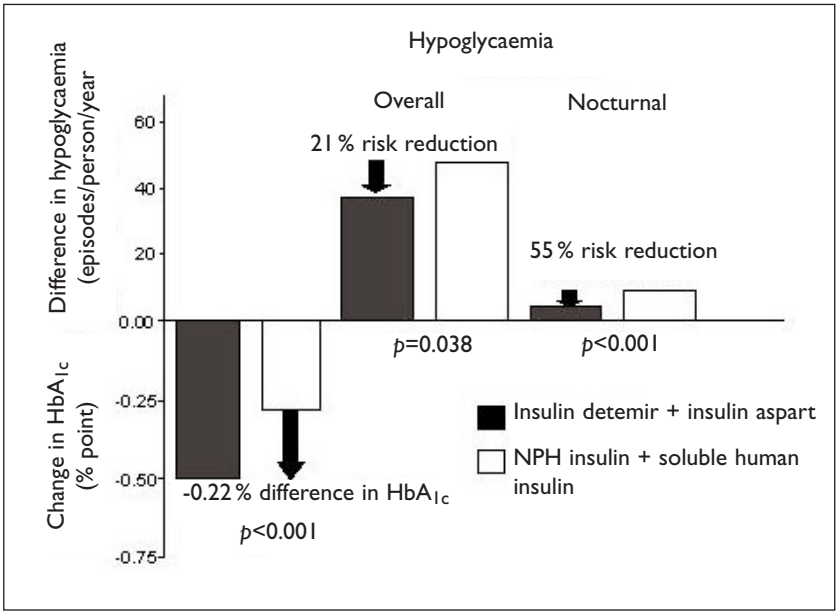


Figure 2. Treatment with insulin detemir and insulin aspart resulted in better metabolic control and a lower risk of hypoglycaemia compared with a human insulin basal-bolus regimen (adapted from Hermansen et al, 2004).

While the evidence is currently based on clinical trials, as with any new treatment, it will be the usage of it as experienced by diabetes care professionals and the patients themselves that will define its optimum place in diabetes therapy. ■

Chen J-W, Christiansen JS, Lauritzen T (2003) Limitations to subcutaneous insulin administration in type 1 diabetes. *Diabetes, Obesity and Metabolism* **5**: 223–33

DCCT Research Group (1993) The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *New England Journal of Medicine* **329**(14): 977–86

De Leeuw I, Vague P, Selam J-L et al (2004) *Diabetes Obesity and Metabolism* (In press)

Haak T, Tiengo A, Draeger E, Suntum M, Waldhäusl W (2004) *Diabetes Obesity and Metabolism* (In press).

Havelund S, Plum A, Ribel U, Jonassen I, Volund A, Markussen J, Kurtzhals P (2004) The mechanism of protraction of insulin detemir, a long-acting, acylated analog of human insulin. *Pharmaceutical Research* **21**(8): 1498–504

Heise T, Nosek L, Ronn BB, Endahl L, Heinemann L, Kapitza C, Draeger E (2004) Lower within-subject variability of insulin detemir in comparison to NPH insulin and insulin glargine in people with type 1 diabetes. *Diabetes* **53**(6): 1614–20

Hermansen K, Fontaine P, Kukolja K, Peterkova V, Leth G, Gall M-A (2004) Insulin analogues (insulin detemir and insulin aspart) versus traditional human insulins (NPH insulin and regular human insulin) in basal-bolus therapy for patients with type 1 diabetes. *Diabetologia* **47**: 622–29

Home P, Bartley P, Russell-Jones D et al (2004) Insulin detemir offers improved glycemic control compared with NPH insulin in people with type 1 diabetes: a randomized clinical trial. *Diabetes Care* **27**(5): 1081–87

Kurtzhals P (2004) Engineering predictability and protraction in a basal insulin analogue: the pharmacology of insulin detemir. *International Journal of Obesity* **28**(Suppl 2): S23–S28

Pieber T, Grill V, Kristensen A, Draeger E (2004) *Diabetic Medicine* (In press)

Pieber T, Plank J, Goerzer E et al (2002) Duration of action, pharmacodynamic profile and between-subject variability of insulin detemir in subjects with type 1 diabetes. *Diabetes* **51**(Suppl. 2): A53

Raslova K, Bogoev M, Raz I, Leth G, Gall M-A, Hancu M (2004) *Diabetes Research and Clinical Practice* (In press)

Russell-Jones D, Simpson R, Hylleberg B, Draeger E, Bolinder J (2004) Effects of once-daily insulin detemir or neutral protamine Hagedorn insulin on blood glucose control in patients with type 1 diabetes mellitus using a basal-bolus regimen. *Clinical Therapy* **26**: 724–36

Standl E, Roberts A, Lang H (2004) *Diabetes Technology and Therapeutics* (In press)

Vague P, Selam J-L, Skeie S et al (2003) Insulin detemir is associated with more predictable glycaemic control and reduced risk of hypoglycaemia than NPH insulin in patients with type 1 diabetes on a basal-bolus regimen with premeal insulin aspart. *Diabetes Care* **26**: 590–96

Table 2. At the end of all clinical studies, weight change with insulin detemir was significantly lower than with NPH insulin.

Study	Insulin detemir (kg)		NPH insulin (kg)	Mean difference (kg)	*P* value
Vague et al, 2003	-0.3		+0.7	-1.0	<0.001
Standl et al, 2004	-0.3		+1.4	-1.7	0.002
De Leeuw et al, 2004	-0.1		+1.2	-1.3	<0.001
Russell-Jones et al, 2003	-0.2		+0.4	-0.5 (baseline adjusted)	0.003
Hermansen et al, 2004	-0.95		+0.07	-1.01	<0.001
Pieber et al, 2004	A.M. + bedtime	A.M. + pre-dinner	+0.7		<0.001
	+0.1	-0.6			
Home et al, 2004	12h	A.M. + bedtime	+0.86		=0.018
	+0.02	+0.24			
Haak et al, 2004 (type 2)	+1.0		+1.8	-0.8	=0.02
Raslova et al, 2004 (type 2)	+0.51		+1.13	-0.06	=0.038