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Does insulin detemir have a role in reducing risk of insulin-associated weight gain?

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Weight gain is often perceived as inevitable with insulin therapy, particularly as we strive for tight glycaemic control and are using increasingly proactive insulin titration regimes. The United Kingdom Prospective Diabetes Study documented that weight gain occurs most rapidly soon after insulin therapy is first initiated. The timing of this side effect is particularly undesirable, as weight gain may interfere with patients' adjustment to insulin therapy and may undermine appropriate diabetes self-management behaviours. Until recently, many patients had little alternative other than to accept unwanted weight gain if they were to achieve sufficient glycaemic control to reduce risk of chronic complications of diabetes. Insulin detemir is a novel basal insulin analogue that has consistently been shown in randomized, controlled trials to have a weight-sparing effect (i.e. weight loss or reduced weight gain compared with other insulins) in both type 1 and type 2 diabetes. Indeed, unlike neutral protamine Hagedorn (NPH) insulin, the weight-sparing effect of insulin detemir appears to be most prominent in people who are the most obese. The mechanisms behind the weight-sparing effect of insulin detemir are still being clarified. Reduced risk of hypoglycaemia 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, has been proposed to minimize defensive snacking by patients, and help to limit weight gain. However, even if this was proven, it would be unlikely to fully explain the weight-sparing effect of insulin detemir. Two additional theories have been put forward. One suggests that due to its novel method of prolonging action via acylation and albumin binding, insulin detemir may differentially influence hepatocytes more than peripheral tissues, thus effectively suppressing hepatic glucose output without promoting lipogenesis in the periphery. The second theory suggests that insulin detemir may be more effective than human insulin in communicating satiety signals within the central nervous system. Further clarification of these hypotheses is required.

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Introduction

The problem of weight gain induced by the exogenous administration of insulin has long been recognized as a confounding issue in diabetes therapy. Indeed, landmark trials such as the United Kingdom Prospective Diabetes Study [1] illustrated the magnitude of weight gain associated with insulin treatment for type 2 diabetes. Newly diagnosed patients with type 2 diabetes were randomized to either conventional treatment (diet alone) or intensive treatment (sulphonylurea or insulin); drugs were added to the conventional treatment group only if there were symptoms of hyperglycaemia or if fasting plasma glucose exceeded 15 mmol/l. All the groups gained weight (figure 1), but mean weight gain was greater in the groups treated with insulin or sulphonylureas.

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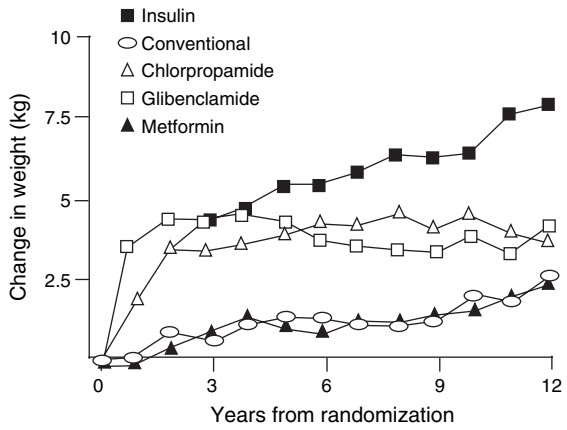

Fig. 1 Extent and rate of weight gain by treatment in intensively treated patients in the United Kingdom Prospective Diabetes Study group. Values are approximate mean changes in weight from a mean baseline of 75 kg. Reproduced with permission from UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998; **352:** 837–853 [1].

These same groups also achieved significantly better glycaemic control, compared with conventional treatment, but the results helped to reinforce the common perception that weight gain is an inevitable consequence of insulin therapy.

Common reasons for weight gain during insulin therapy include so-called 'defensive snacking' by patients, due to the perceived risk of hypoglycaemia; caloric retention from reduced urinary excretion of glucose; and lowering of metabolic rate due to decreased hepatic glucose output (HGO) [2]. The latter two explanations are a direct consequence of normalized glucose metabolism and thus, to some extent, reflect successful response to therapy. However, defensive calorie consumption is a modifiable patient behaviour that arises from the inability of current insulin regimens to continually match insulin availability with physiological need. The inherent variability of pharmacological response following repeated injections of traditional basal insulins is a major contributory factor in this problem [3].

Interestingly, there is also evidence that patients with type 2 diabetes, even with good glycaemic control, feel hypoglycaemic at blood glucose levels within the normal range [4,5]. This suggests an elevation of the central nervous set point of glucose in these subjects with type 2 diabetes[4], and that blood glucose concentrations within the hyper- to normoglycaemic range represent important signals for food intake in type 2 diabetes, whereas in type 1 diabetes, the glycaemic thresholds for symptomatic perceptions of hypoglycaemia is shifted towards lower levels [6]. However, it remains to be clarified whether blood glucose levels, by modulating eating behaviour, could play an important role in the weight gain during insulin therapy.

Consequences of Weight Gain in Diabetes

Insulin-associated weight gain is often especially unwelcome in type 2 diabetes, a condition in which up to 80–90% of patients are already overweight [7]. As continued weight gain requires as little as 10–30 kcal/day excess caloric intake [8], any extra contribution from insulin therapy can potentially facilitate progression from overweight to frank obesity. A common scenario with traditional insulin treatment in type 2 diabetes involves a vicious cycle of progressive increases in body fat, secondary worsening of insulin resistance, and subsequently raised insulin requirements to maintain glycaemic control [9].

In type 1 diabetes, weight gain is often perceived as less problematic as many patients are underweight at diagnosis. However, the prospect of weight gain can discourage compliance with prescribed therapy [10,11]. Several examples are relevant here. One study of 341 women with type 1 diabetes showed that about 31% reported, at least occasionally, omitting insulin, with at least half citing concerns about weight gain [10]. In a longitudinal study of 65 teenagers with diabetes, 10 women, including 5 who already had microvascular complications, admitted under-using insulin to control weight [11].

Although an increase in body mass is the earliest and most obvious adverse effect visible in patients, weight gain also produces undesirable physiological effects, such as worsening of blood pressure and lipid profiles [12]. For example, in the Diabetes Control and Complications Trial in patients with type 1 diabetes, for any level of haemoglobin A_{1c} (HbA_{1c}), adverse changes in lipid profile were worse as weight gain increased [12]. Weight gain was also associated with poorer glycaemic control. In a follow up of 100 participants in the Finnish Multicenter Insulin Therapy Study, baseline body mass index (BMI) was the most significant predictor of deterioration in glycaemic control; in the obese patients, deterioration occurred sooner and to a greater extent than in nonobese patients [13].

These consequences of insulin-associated weight gain are also highly dependent on the nature of the weight gain (e.g. as fat or as fat-free mass) and the location (e.g. subcutaneous or visceral sites) where the increased body mass is located. Compared with fat that is deposited subcutaneously, central or visceral adiposity is associated with increased risk of cardiovascular disease [14]. Potentially, such a development could reduce the advantages

of improved glycaemic control to a lower level. However, until recently, data have been conflicting on the extent to which insulin-associated weight gain is distributed between fat or fat-free mass. Packianathan *et al.*, using a four-compartment model, studied the distribution of weight gain in 19 patients aged 35–75 years with type 2 diabetes [15]. After 6 months of insulin therapy, at least half of the weight gain was associated with central fat deposition [15]. Furthermore, the weight gain attributable to fat-free mass was entirely due to increases in body water and not lean body mass [15].

The Paradox of Insulin-associated Weight Gain

It is particularly unfortunate that the patients most at risk for insulin-associated weight gain are often those whose need for insulin is the greatest [(i.e. those who are in poor control on oral antidiabetic drugs (OADs)], who are willing to pursue the most intensive treatment regimen, and who respond most favourably to treatment. Indeed, several studies have shown that the main predictors of weight gain are high initial glycaemia and degree of improvement in glycaemic control [16,17]. Other predictors are markers of intensified therapy, such as the number of insulin injections [16] and mean daily insulin dose [1].

The time of onset of insulin-associated weight gain can be an additional barrier to the success of therapy. As shown by the slope of the curves in figure 1, the rate of weight gain tends to be greatest when insulin therapy is first initiated, presumably when glycaemic control was at its worst [1]. This is the same period when patients are becoming accustomed to using insulin and when diabetes self-management behaviours are being developed. Thus, the undesirable side effect of weight gain tends to be most pronounced when patients are likely to be sensitive to problems arising from a new treatment regimen. These findings emphasize the need for solutions to help patients achieve the glycaemic control they desire and are capable of, without the detrimental effect of insulin-associated weight gain.

Common Strategies to Address Insulin-associated Weight Gain are Often Insufficient

There are ways to minimize insulin-associated weight gain. A well-established strategy is to use insulin in conjunction with insulin-sparing OADs [16,18]. Metformin, for example, can decrease insulin requirements by as much as 32% [16]. Nevertheless, it is important to keep in mind that although combination therapy can be effective and is widely used, it is not a panacea. Many patients still gain weight despite the use of combination therapy, albeit less than what might be gained on insulin therapy alone. For example, in a large population-based study of 183 patients starting insulin therapy according to local practice standards, the average weight gain after 12 months was 6.1 kg when metformin was added, vs. 7.1 kg when insulin was used alone [19]. These values represent clinically significant weight increases. The recruitment phase of that study also served to highlight that, for many people, even this imperfect solution is not an option, as metformin was contraindicated in at least 25% (271/1150) of patients [19].

Lifestyle/behavioural interventions such as diet and exercise are important strategies for achieving weight loss and/or preventing weight gain in diabetes. They lack the potential side effects that can occur with pharmacological interventions. However, they require major and sustained behaviour changes, which are often difficult for most individuals to achieve without significant support. Therefore, effectiveness of lifestyle/behavioural interventions is generally modest, with a mean loss of about 8% of initial weight over the first 12 months, even with interventions involving a high degree of patient contact and support [7]. Achieving and sustaining an initial weight loss may be even more problematic for patients who must confront the additional challenge of insulin-associated weight gain [7].

Targeted pharmacotherapy for obesity management is another option for the overweight person, but current evidence indicates that the mean effect is likely to be modest. A meta-analysis of 14 randomized, placebo-controlled trials involving adults with type 2 diabetes indicated that the magnitude of short-term weight loss with the available drugs (e.g. fluoxetine, orlistat, and sibutramine) was small (i.e. a mean of 2.6–4.5 kg, or 2–3% of initial body weight), and the long-term health benefits and safety unclear [20]. Therefore, given the difficulty of losing weight and the numerous detrimental effects of weight gain, limiting therapy-associated weight gain has an important part to play in the management of patients with diabetes.

Balancing Weight Gain against Improved Glycaemic Control

When using traditional insulins such as (neutral protamine Hagedorn) NPH, people with diabetes and health care professionals must often confront the trade-off between the disadvantages of weight gain and the benefits of improved glycaemic control. It may be difficult to convince patients that, as undesirable as weight gain may be, achieving target glucose values should be the overriding

priority of treatment to prevent the potentially serious chronic complications of diabetes.

The validated Center for Outcomes Research (CORE) Diabetes Model, which has been validated against data from 65 published studies of type 1 and type 2 diabetes, has recently been used to show, via simulation, that the long-term advantages of improved glycaemic control, with respect to lifespan and quality of life, outweigh the disadvantages posed by worsening lipid profile and increased blood pressure, which arise from weight gain [21].

More importantly, the same analysis also showed that additional benefits accrued if a hypothetical weight-neutral insulin, instead of a weight-promoting insulin, was prescribed. For example, when used in an intensive therapy regimen, a weight-neutral insulin was projected to increase life expectancy and quality-adjusted life expectancy by at least 4 years, and to reduce the cost of complications, compared with scenarios involving either intensive therapy with improved control but weight gain (scenario D) or traditional therapy with weight loss, but with poorer glycaemic control (scenario A) (figure 2) [21].

Insulin Detemir's Consistent Weight-sparing Effect in Clinical Trials

Until recently, it would not have been possible to realize the full impact of the encouraging results predicted by the CORE Diabetes model, because a weight-sparing basal insulin (i.e. producing weight loss or reduced weight gain, compared with other insulins) was not available. Insulin detemir is a novel, basal insulin analogue, approved in the European Union in 2004 and in the United States in 2005 that has consistently been shown to have a weight-sparing effect [22]. This weight-sparing effect has been convincingly shown in 10 multicentre, randomized, parallel-group, controlled trials, in which insulin detemir was compared with NPH. These are summarized in table 1. In seven trials of patients with type 1 diabetes (16–52 weeks' duration), there was either a mean weight loss [23–28] or a mean weight gain of <0.25 kg [27,29]. In three trials involving patients with type 2 diabetes (22–26 weeks' duration), mean weight gain was ≤ 1.2 kg [30–32].

These results have been expanded on in two recent studies involving patients with type 2 diabetes, which indicated that the weight-sparing effect of insulin detemir was not only maintained but was also even more marked for people who were obese. In one study, data were pooled from two randomized, parallel-group trials of 22 and 24 weeks' duration, in which 900 previously insulin-treated patients had their treatment intensified to basal-bolus therapy [33]. Patients received once- or twice-daily insulin detemir or NPH, in conjunction with either insulin aspart or human soluble insulin at mealtimes. Results indicated that patients treated with insulin detemir had minimal (<1 kg) mean weight gain regardless of BMI, whereas for patients treated with NPH, those with the largest BMI (>35 kg/m^2) had the largest mean weight gain (approximately 2.4 kg). By contrast, patients with a BMI > 35 who were using insulin detemir actually lost weight (mean of approximately -0.5 kg). This weight-sparing effect was accompanied by similar levels of glycaemic control and no increase in the risk of major or minor hypoglycaemic events.

Similar findings were reported in a treat-to-target trial comparing insulin detemir with NPH [32]. In that parallel-group, multicentre trial, 476 people with inadequate blood glucose control (HbA_{1c} 7.5–10.0%) were

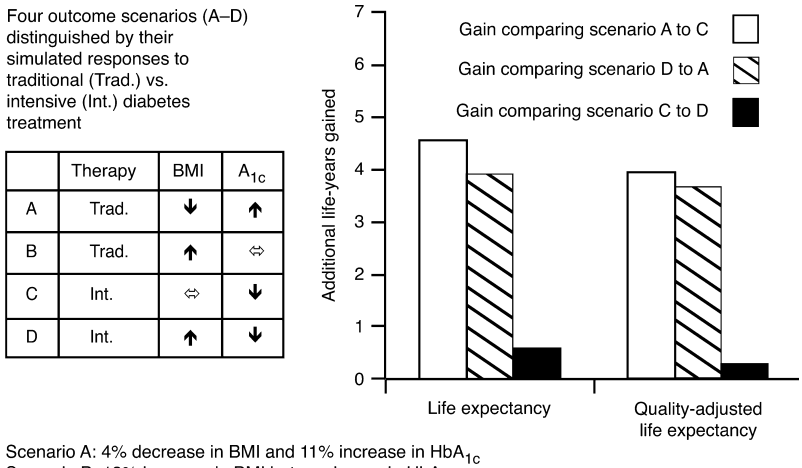

Fig. 2 Additional increased projected life expectancy and quality-adjusted life expectancy when patients with type 1 diabetes use a weight-neutral insulin in an intensive therapy regimen (outcome scenario C) compared with other treatment regimens, simulated using the CORE Diabetes Model. Data from Palmer AJ *et al.* [21].

Table 1 Change in body weight with insulin detemir and NPH insulin in randomized, controlled, clinical trials for which weight change was reported*

			Body weight change			
Reference	Patients	Duration (weeks)	Detemir (kg)	NPH (kg)	Weight difference (kg)	p
Vague *et al.* [23]	448 type 1	24	−0.2	+0.7	−0.9	<0.001
de Leeuw *et al.* [24]	316 type 1	52	−0.1	+1.2	−1.3	<0.001
Standl *et al.* [25]	288 type 1	24	−0.3	+1.4	−1.7	0.002
Russell-Jones *et al.* [26]	747 type 1	24	−0.23	+0.31	−0.5	0.024
Home *et al.*† [29]	408 type 1	16	+0.02 (morning + dinner)	+0.86	−0.8	0.006
			+0.24 (morning + bed)		−0.6	0.04
Pieber *et al.*† [27]	400 type 1	16	−0.6 (morning + dinner)	+0.7	−1.3	<0.001
			+0.1 (morning + bed)		−0.6	0.05
Hermansen *et al.*‡ [28]	595 type 1	18	−0.95	+0.07	−1.02	<0.001
Haak *et al.* [30]	505 type 2	26	+1.0	+1.8	−0.8	0.017
Raslova *et al.*‡ [31]	395 type 2	22	+0.5	+1.13	−0.63	<0.038
Hermansen *et al.*§ [32]	475 type 2	24	+1.2	+2.8	−1.6	<0.001

*Al trials were multinational, open-label, parallel-group designs.
†Two detemir groups in the study.
‡Mealtime insulin included: insulin aspart used with detemir, unmodified human insulin given with NPH insulin.
§In addition to oral antidiabetic drugs (other studies, mealtime + basal regimens).

randomized to twice-daily insulin detemir or twice-daily NPH insulin, added to OADs. Over 24 weeks, insulin doses were actively titrated towards pre-breakfast and predinner plasma glucose targets of ≤6.0 mmol/l (≤108 mg/dl). At 24 weeks, mean weight gain with insulin detemir was +1.2 kg, compared with +2.8 kg with NPH insulin ($p < 0.05$). As shown in figure 3, the weight-sparing advantage of insulin detemir appeared early in the trial. Furthermore, this weight advantage was relatively greater for patients with higher BMIs, with a clear trend for greater BMI to be associated with reduced weight gain with insulin detemir (regression equation: weight gain = 5.366 − 0.146 BMI, $p = 0.01$). This latter relationship was not found in NPH insulin. Adjustment for change in HbA_{1c} did not affect this finding (treatment difference −1.58 kg, $p < 0.001$). This suggested that the between-difference in weight was not explained by a difference in glycaemic control. More importantly, the reduced weight gain did not occur at the expense of poor control or hypoglycaemia. End-of-trial HbA_{1c} was 6.6% for insulin detemir and 6.5% for NPH, and the number of hypoglycaemic events per patient-year was reduced by 47% with insulin detemir.

There are also indications that insulin detemir reduces weight gain in elderly, adult, and young patients. In a pooled analysis of three phase III, parallel-group trials comparing insulin detemir with NPH, body weight increased less with insulin detemir for both elderly (n = 239, ≥65 years) and younger adult (n = 480, <65 years) patients, with weight difference being −1.0 kg [95% confidence intervals (CI): −1.63, −0.44] for elderly patients and −1.2 kg (95% CI: −1.64, −0.75) for younger adults [34]. Weight was examined for children and adolescents using insulin detemir in a 26-week, multinational, open-label, randomized, parallel-group trial. Children (aged 6–17 years) with type 1 diabetes received detemir (n = 232) or NPH (n = 115) once- or twice-daily (according to pre-trial regimen) and premeal insulin aspart. Participants were generally overweight compared with the BMI norm, but at 26 weeks, BMI decreased towards population norms with insulin detemir, but increased with NPH insulin in young people with type 1 diabetes ($p < 0.0001$).

Basis of the Weight-sparing Effect of Insulin Detemir

The physiological basis for the weight-sparing effect of insulin detemir is an area of active investigation, and the potential mechanisms are not completely understood. One possible explanation is that due to its greater predictability in absorption and action when compared with other basal insulins [35], insulin detemir is associated with less risk of hypoglycaemia, which may reduce the need for defensive snacking by patients who are concerned about hypoglycaemia. This speculation remains to be proved, but it is not without indirect support. For example, reduced incidence of hypoglycaemic episodes (particularly nocturnal episodes), with insulin detemir has consistently been shown across studies, for any level of glycaemic control. This was illustrated by a pooled analysis of four multicentre, randomized phase

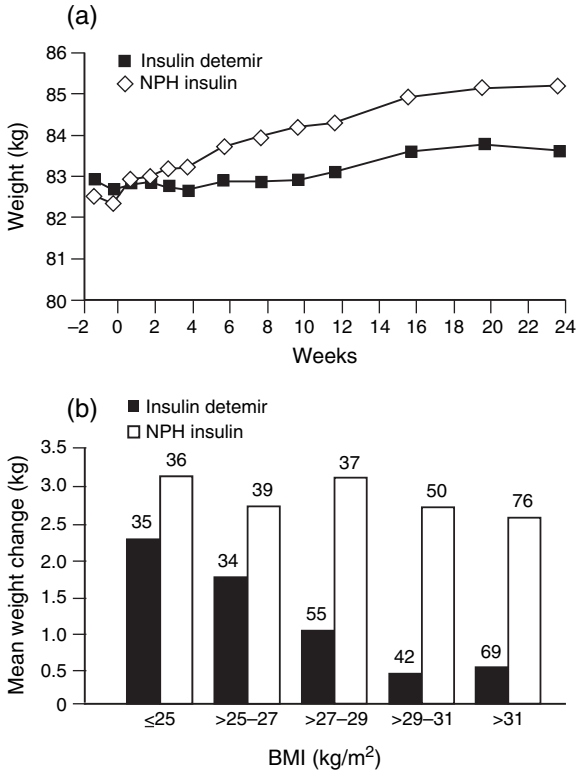

Fig. 3 In a treat-to-target of 475 patients with type 2 diabetes, a difference in weight change between insulin detemir and NPH began to appear early (a) and by 24 weeks, was lowest for patients with highest BMI at entry (b). Reproduced with permission from Hermansen K *et al.* Diabetes Care 2006; **29:** 1269–1274 [32].

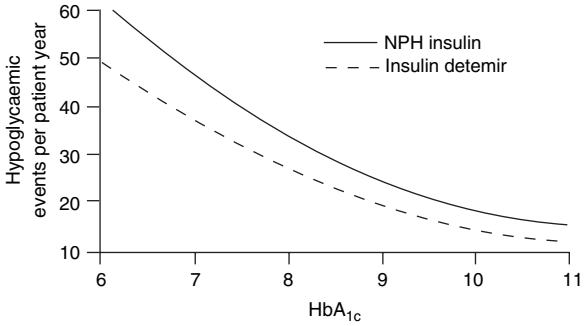

Fig. 4 In a meta-analysis of four phase III trials in type 1 diabetes, insulin detemir led to fewer episodes of hypoglycaemia than NPH at any level of glycaemic control. Reproduced with permission from Russell-Jones D *et al.* Diabetologia 2005; **48** (Suppl. 1): A92 [36].

III trials of detemir (n = 1180 patients) vs. NPH insulin (n = 810 patients) in adult type 1 diabetes [36]. Hypoglycaemia was defined by blood glucose <2.8 mmol/l (approximately 50.4 mg/dl) [plasma glucose <3.1 mmol/l (approximately 55.8 mg/dl)]. The relative risk of hypoglycaemia was 22% lower for insulin detemir than NPH ($p < 0.001$), regardless of HbA_{1c} level achieved (figure 4) [36].

Despite this favourable safety profile, and although the reduced fear of hypoglycaemia could hypothetically be associated with decreased defensive snacking, it is unlikely fully to account for the weight-sparing effect of insulin detemir. Some support for this is provided by the fact that insulin glargine similarly reduced hypoglycaemia compared with NPH in a treat-to-target study [37] that used a similar protocol to the detemir study discussed previously [32]. In the glargine/NPH treat-to-target trial, however, there was a weight gain of 3 kg within 24 weeks in both insulin treatment groups [37].

The weight-sparing advantage of detemir would appear to be unique to this analogue because comparisons between insulin glargine and NPH have tended to show no between-group differences in weight outcomes. For example, in the Riddle treat-to target study [37], weight gain in the NPH group was identical to that reported in our own study at 2.8 kg [32], while recipients of glargine gained a mean 3.0 ± 0.2 kg. Nevertheless, direct comparisons of detemir with glargine are awaited with interest. To date, only two such studies have been reported, and these only in abstract form. The findings are difficult to interpret due to discrepancies in the dosing regimens between treatments. In a study of twice-daily insulin detemir vs. once-daily insulin glargine used in basal-bolus therapy for type 1 diabetes, detemir was associated with half the level of weight gain of insulin glargine (0.5 vs. 1.0 kg), but this difference did not reach statistical significance [38]. In another study where once- or twice-daily detemir was compared with once-daily glargine in basal + oral therapy, weight gain was significantly lower with detemir, but overall was atypically high in comparison with other studies using similar protocols (3.0 vs. 3.9 kg, for detemir and glargine, respectively; $p = 0.012$) [39].

Other factors potentially accounting for the weight-sparing effect of insulin detemir might be sought in the properties of the analogue that show differences to other insulins. Insulin detemir is the first therapeutic insulin analogue to be engineered using acylation with a fatty acid to enable reversible albumin binding [40]. This property retains insulin detemir in the injection depot and represents a unique mechanism of protraction, which produces a more consistent pharmacokinetic and pharmacodynamic profile compared with other basal insulins, such as NPH or insulin glargine [35]. In the circulation, insulin detemir is 98% bound to plasma albumin, and it is possible that this results in a different profile of distribution to target tissues, compared with other

exogenously administered insulins. For example, one way in which insulin detemir might act differently, with implications for weight gain, is in the extent of its effect on the liver. Suppression of HGO is essential for maintaining normoglycaemia, and it requires much higher concentrations of insulin than exist in the peripheral circulation. Physiologically, this becomes possible because high concentrations of insulin are released in pulses from pancreatic β cells directly into the portal circulation. Thus, portal insulin levels may be as much as 10-fold higher than insulin concentrations measured in the peripheral blood [9,41]. Peripheral insulin concentrations, nevertheless, are able to remain within physiological limits because up to 60% of pancreatic insulin is extracted by hepatocytes in the first pass through the liver, prior to insulin being dispersed into the systemic circulation. In the diabetic state, the high portal concentrations necessary to suppress HGO must be achieved through exogenous administration of insulin into the peripheral circulation (i.e. via subcutaneous injection or continuous subcutaneous insulin infusion). Thus, peripheral tissues, such as adipose tissue, are exposed to a relative hyperinsulinaemia because they encounter the exogenously administered insulin before the concentration can be reduced by hepatic extraction. This, in turn, increases peripheral glucose uptake, increases lipogenesis, and decreases lipolysis–all of which would be expected to result in weight gain.

Very preliminary, but nevertheless, provocative findings suggest that insulin detemir may have some advantages over other basal insulins with respect to the balance between hepatic vs. peripheral action, due to its high degree of albumin binding. In a 16-h euglycaemic clamp study, the effect of equipotent doses of insulin detemir and NPH were studied in healthy volunteers to evaluate the effect on hepatic glucose production, peripheral glucose disposal, and lipolysis [42]. This suggested a preferential hepatic effect for insulin detemir compared with NPH. By contrast, insulin detemir was less effective than NPH at reducing nonessential fatty acid concentrations (mean difference, −0.10 mmol/l, $p < 0.02$), suggesting a greater peripheral effect for NPH, and potentially enhanced lipogenesis compared with insulin detemir.

Taken together, these findings could indicate that insulin detemir has the potential to create a more physiological insulin profile in terms of its effect in both hepatic and peripheral target tissues, thereby minimizing peripheral lipogenesis and maximizing suppression of HGO. This hypothesis remains to be proved.

Additionally, several *in vivo* studies in both mice and humans have suggested that insulin detemir may have specific, enhanced central nervous system (CNS) effects, compared with human insulin, which may also account for some of the weight-sparing effect [43,44]. For example, studies in mice indicate that insulin receptor substrate 2 (IRS-2) phosphorylation in the hypothalamus occurs earlier and is more marked after exposure to insulin detemir than human insulin [43]. In another laboratory study, which involved 10 overweight people with normal glucose tolerance, magnetoencephalography was used to measure magnetic fields in the brain under three conditions: after a hyperinsulinaemic euglycaemic clamp with insulin detemir; after a hyperinsulinaemic euglycaemic clamp with human insulin; and after a saline infusion [44]. Results indicated that insulin detemir stimulated cortical activity in the beta band, whereas human insulin had no effect. This finding is consistent with the growing recognition that insulin signalling in the brain is essential for regulation of adiposity, and that, in the CNS, insulin actually works to oppose weight gain by transmitting satiety signals [45]. Indeed, it has recently been speculated that impairment in this signalling system and/or insulin resistance in the CNS might be involved in the pathophysiology of weight gain and type 2 diabetes–the so-called 'neurocentric model of diabesity' [46]. It can be speculated that the fatty acid residue or albumin-binding properties of insulin detemir might facilitate distribution into the brain because the lower albumin concentrations in the CNS compared with peripheral circulation would promote a higher unbound fraction; this would help to normalize the impaired satiety signal.

It is important to emphasize that preliminary findings, suggesting differential effects of insulin detemir on hepatocytes and in the CNS, remain to be confirmed with further studies to clarify the precise mechanisms by which insulin detemir limits or prevents weight gain in diabetes. New theories about the regulation of satiety and appetite point to a prominent role of blood glucose dynamics and CNS demands for blood glucose in stimulation of meal initiation [47,48]. Thus, the physiological actions of exogenous insulin will necessarily play an increasingly important role.

From the perspective of patients who are struggling with the decision to start or intensify insulin therapy, the well-documented weight-sparing effect of insulin detemir should provide some encouragement that, although minor weight gain is not unusual, clinically significant weight gain need not be inevitable. Earlier and more aggressive use of hypoglycaemic therapies in type 2 diabetes may, in the future, also help to mitigate some of this increase in weight by ensuring that patients do not achieve large disparities between actual HbA_{1c} and

recommended targets as they progressively intensify their therapy regimen.

Conclusion

Insulin detemir has consistently shown an overall weight-sparing effect in randomized, controlled clinical trials involving people with type 1 and type 2 diabetes. Furthermore, this weight-sparing effect persists over time, and is magnified in people who are the most obese, and therefore most at risk for the adverse consequences of insulin-associated weight gain. Although the precise mechanisms remain to be confirmed, it is likely that unique structural and ensuing pharmacological properties of insulin detemir at least partly explain its weight-sparing effect. Reduced weight gain occurs even when insulin detemir is used without concurrent OADs. Given these findings, insulin detemir may be a particularly useful basal insulin and has a role in the management of insulin-associated weight gain, which is of concern to patients and health care professionals.

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