

## Weight-sparing effect of insulin detemir: a consequence of central nervous system-mediated reduced energy intake?

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Insulin therapy is often associated with adverse weight gain. This is attributable, at least in part, to changes in energy balance and insulin's anabolic effects. Adverse weight gain increases the risk of poor macrovascular outcomes in people with diabetes and should therefore be mitigated if possible. Clinical studies have shown that insulin detemir, a basal insulin analogue, exerts a unique weight-sparing effect compared with other basal insulins. To understand this property, several hypotheses have been proposed. These explore the interplay of efferent and afferent signals between the muscles, brain, liver, renal and adipose tissues in response to insulin detemir and comparator basal insulins. The following models have been proposed: insulin detemir may reduce food intake through direct or indirect effects on the central nervous system (CNS); it may have favourable actions on hepatic glucose metabolism through a selective effect on the liver, or it may influence fluid homeostasis through renal effects. Studies have consistently shown that insulin detemir reduces energy intake, and moreover, it is clear that this shift in energy balance is not a consequence of reduced hypoglycaemia. CNS effects may be mediated by direct action, by indirect stimulation by peripheral mediators and/or via a more physiological counter-regulatory response to insulin through restoration of the hepatic-peripheral insulin gradient. Although the precise mechanism remains unclear, it is likely that the weight-sparing effect of insulin detemir can be explained by a combination of mechanisms. The evidence for each hypothesis is considered in this review.

**Keywords:** basal insulin, drug mechanism, weight loss therapy

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### Introduction

Insulin replacement plays a pivotal role in the treatment of people with type 1 diabetes (T1D) and type 2 diabetes (T2D); however, many individuals with diabetes experience adverse weight gain as a consequence of insulin treatment. This, in turn, may impair treatment adherence and impede therapy intensification, with consequent failure to achieve glycaemic goals [1,2]. Weight gain is associated with an increased risk of coronary heart and cardiovascular disease in people with diabetes [3,4], a troubling prospect given that 80–90% of people with T2D are already overweight before insulin replacement [5]. Landmark trials, notably the UK Prospective Diabetes Study [6] and the

Diabetes Control and Complications Trial [7], showed that the cost of improved glycaemic control was considerable weight gain with intensive treatment regimens.

It had previously been assumed that weight gain was an inevitable consequence of insulin therapy [8], but a large body of evidence now indicates that the long-acting basal insulin analogue detemir has both short-term (16 weeks) and longer-term (52 weeks) weight-sparing effects [8–10]. These weight-sparing effects appear to be unique to insulin detemir, and several clinical trials in people with T1D and T2D have reported significantly less weight gain with insulin detemir versus neutral protamine Hagedorn (NPH) or insulin glargine [8–10]. It is important to note that higher doses of insulin detemir were administered in these trials to compensate for its slower onset of action [10,11].

A meta-analysis showed there was significantly less weight gain with insulin detemir compared with insulin glargine [mean difference: 0.91 kg; 95% confidence interval (CI): –1.21 to –0.61], despite a similar degree of glycaemic control and risk of hypoglycaemia in people with T2D [10]. Furthermore, in

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children and adolescents with T1D, the use of insulin detemir did not appear to be associated with adverse weight gain when compared with NPH insulin [12,13]. The proposal that weight-sparing is a novel intrinsic pharmacological property of insulin detemir is supported by the observation that other analogues, including insulin glargine and insulin degludec, do not exhibit this property in clinical trials [14].

Insulin detemir is a long-acting, water-soluble insulin analogue that differs structurally from human insulin in two respects: the attachment of a 14-carbon fatty acid side chain to Lys<sup>B29</sup> and the removal of Thr<sup>B30</sup> [15]. These modifications protract insulin activity via self-association at the injection site and reversible binding to albumin; only the free fraction of the molecule can bind to target insulin receptors (IRs). The degradation of insulin detemir is different from that of other insulin analogues in being partly non-receptor-mediated [16].

Weight gain with insulin therapy is partly attributable to reversal of the negative energy balance associated with glycosuria and partly attributable to potent anabolic effects on peripheral tissues. Furthermore, hypoglycaemia is a stimulus for increased energy intake. The mechanism underpinning the weight-sparing effect of insulin detemir has been studied by several groups that have offered different hypotheses. In the present review, we present the evidence for each of these hypotheses.

### Food Intake Model

Hypoglycaemia is a potent stimulus for energy intake and a plausible model for the weight-sparing effects of insulin detemir, given the documented lower risk of hypoglycaemia with insulin detemir compared with human insulin [9]; however, data from clinical trials comparing insulin detemir and insulin glargine show similar reductions in hypoglycaemia but show weight-sparing only with insulin detemir [10]. Moreover, Davies et al. [17] analysed weight gain data as a function of hypoglycaemia frequency in insulin-naïve people with T2D and found no significant relationship between these two outcomes, suggesting that the weight-sparing effect of insulin detemir must logically involve other mechanisms.

### Animal Studies

To explore the relationship between hypoglycaemia, food intake and weight gain, Vasselli et al. [18] continuously monitored food intake over 24 h in mildly streptozotocin-diabetic and intact Sprague–Dawley rats after exposure to a single subcutaneous injection of biologically equivalent doses of insulin detemir (26.25 U/kg) or NPH insulin (15 U/kg). NPH insulin stimulated frank hypoglycaemia during the first 4 h after injection in both normal and diabetic rats, whereas glucose levels remained stable and within the normal range with insulin detemir. There was significantly less cumulative food intake with insulin detemir in the first 12 h after injection and a trend towards less weight gain. In another study, Rojas et al. [19] investigated whether low-dose subcutaneous insulin was associated with body weight and fat mass gain in the absence of confounders such as hypoglycaemia, negative energy balance

and glycosuria in non-diabetic lean [low-fat diet-fed (13.5% fat)] and diet-induced obese [high-fat diet-fed (60% fat)] rats. The study used equipotent doses of insulin detemir (0.5 U/kg) and insulin glargine (0.2 U/kg) with respect to changes in blood glucose in rats. After 4 weeks, insulin detemir significantly reduced cumulative food intake in the high-fat diet-fed group compared with insulin glargine ( $p < 0.001$ ), but this finding was not observed in the low-fat diet-fed group. Similarly, insulin detemir and insulin glargine had a similar effect on body weight and fat mass gain in the low-fat diet-fed group, whereas in the high-fat diet-fed group, insulin detemir significantly attenuated both weight gain and fat mass gain relative to insulin glargine ( $p < 0.05$  and  $p < 0.01$ , respectively). Indirect calorimetry showed no difference in energy expenditure, but 7–10% lower energy intake with insulin detemir resulted in a lesser increase in weight gain and fat mass in the high-fat diet-fed insulin detemir group ( $p < 0.001$ ). In a T2D rat model, Zafar et al. [20] also showed decreased food intake ( $p < 0.05$ ) and weight gain ( $p < 0.05$ ) after 4 weeks of insulin detemir treatment compared with insulin glargine, despite similar glycaemic control. Additionally, they investigated the satiety-reducing effect of insulin detemir, and found lower expression of two hypothalamic appetite-regulating neuropeptides, neuropeptide Y and galanin, with insulin detemir compared with insulin glargine ( $p < 0.05$ ). In marked contrast to other studies in non-diabetic normal weight and overweight rats, which often show insulin-induced hyperphagia and weight gain [21–23], these investigations show that insulin detemir is associated with decreased cumulative food intake and less weight gain in rats even in the absence of hypoglycaemia, and further indicate that inhibitory effects of insulin detemir on appetite are increased in the context of high-fat diets or obesity. Clinical studies have corroborated the negative correlation between weight gain and body mass index (BMI) with insulin detemir treatment, i.e. the lowering/neutral effect of insulin detemir on weight gain is *greater* with increasing BMI [24,25]; however, elucidation of the underlying mechanism requires further research.

### Human Studies

The effect of insulin detemir on reduction of food intake was investigated in a 32-week, randomized, crossover trial in people with T1D ( $n = 23$ ) [26]. Subjects received insulin detemir or NPH insulin as part of a basal-bolus regimen for 16 weeks and then the alternative treatment. Several outcomes were assessed, including total energy expenditure, resting energy expenditure, diet-induced thermogenesis, activity energy expenditure, energy intake, weight change, hypoglycaemia ( $< 3.1$  mmol/l), glycaemic control, and satiety and fuel partitioning-related hormones. Insulin detemir significantly reduced body weight by 0.69 kg compared with a weight gain of 1.7 kg with NPH insulin ( $p < 0.001$ ); this was consistent with the results of several randomized controlled trials in T1D in adults [27–30] and children [12,13]. No differences were reported in energy expenditure, glycated haemoglobin (HbA1c) concentration or rate of hypoglycaemia, but energy intake, based on a 7-day food diary, was significantly lower with insulin detemir than with NPH insulin (2016 kcal/day vs 2181 kcal/day;  $p = 0.02$ ). Interestingly, the subjects ingested

similar amounts of carbohydrate but had a reduced intake of fat and protein when randomized to receive insulin detemir. Overall, despite a limited study population and an open-label design, the findings of Zachariah et al. [26] suggest that the weight-sparing effect of insulin detemir can be attributed to reduced caloric intake. Moreover, the study further confirms that change in energy intake is not linked to hypoglycaemia.

### Central Nervous System Hypothesis

Several lines of evidence show that insulin signalling in the brain plays a key role in weight control. IRs are abundant in satiety and appetite-controlling regions of the brain, such as the hypothalamus [31], and downregulation of brain IRs has been associated with hyperphagia [32] and impaired insulin-mediated suppression of endogenous glucose production [33]. Furthermore, direct injection of insulin into the brain reduces food intake [34]. Obesity is associated with CNS insulin resistance [35], and studies using intranasal insulin, which effectively bypasses the blood–brain barrier, have shown that central insulin action is associated with peripheral insulin sensitivity [36,37], increased satiety and improved weight control [38–40]. It therefore remains attractive to hypothesize that the reported differences in food intake and weight gain with insulin detemir are likely to be, at least in part, mediated via central pathways.

### Animal Studies

Hennige et al. [41] hypothesized that insulin signalling in the brain may be different with insulin detemir compared with human insulin. They examined this with a study of the impact of insulin detemir (2.4 mmol/l) versus human insulin (0.6 mmol/l) on the insulin signalling cascade in both brain (hypothalamic and cerebrocortical regions) and peripheral (liver and muscle) tissues in C57Bl/6 mice. Insulin detemir was injected via a non-clinically relevant route directly into the inferior vena cava to avoid the effect of altered subcutaneous absorption kinetics. In muscle and liver, both insulin detemir and human insulin displayed equal activation/phosphorylation of the IR signalling cascade at several time points ranging from 2 to 30 min post-injection, suggesting that insulin detemir does not alter peripheral IR signalling kinetics; however, in hypothalamic tissue, activation/phosphorylation of both the IR and the IR substrate 2 was significantly elevated, and occurred earlier, with insulin detemir than with human insulin. Similar results were obtained in cortical tissue. Insulin signal transduction via the IR and IR substrate 2 has previously been shown to be involved in the regulation of appetite and body mass [35,42]. Concurrent measurements in brain activity, using electroencephalography (EEG), showed that enhanced cerebral insulin signalling with insulin detemir did indeed modulate cortical electrical activity (a significant increase in delta activity was reported). Total insulin concentration from brain extracts was significantly greater with insulin detemir versus human insulin, suggesting more efficient transport across the blood–brain barrier with insulin detemir. Consistent with these findings, a recent study by Begg et al. [43] showed that insulin detemir is actively transported into the cerebrospinal

fluid. Conversely, another study, using different methodology, showed that insulin detemir did not cross the blood–brain barrier and that therefore any central effect would be mediated indirectly [44]. Thus, the question of whether, and if so under what conditions, insulin detemir crosses into the brain parenchyma remains unresolved; however, the findings clearly indicate enhanced and more rapid effects on the CNS with insulin detemir than with human insulin.

In another animal-based study, Vasselli et al. [45] investigated the feeding- and body weight-inhibitory effects for 5 days after single equimolar doses of insulin detemir or regular human insulin administered directly via microinjection into the brain (third ventricle) of normal Sprague–Dawley rats. Although both treatments reduced food intake significantly over 2 days [by 20–35% compared with the control ( $p < 0.01$ )], the reduction was significantly greater with insulin detemir than with regular human insulin ( $p < 0.01$ ) and was dose-dependent using 0.5, 1.0 and 2.0 mU/rat (corresponding to doses of regular human insulin of 4.0, 8.0 and 16.0 mU/rat). Similarly, a concurrent reduction in body weight of 4–10% was reported with both treatments over 5 days ( $p < 0.01$ ), yet the magnitude of the effect was also significantly greater with insulin detemir than with regular human insulin ( $p < 0.01$ ) for the first 2 days. Whole-body energy expenditure was significantly increased with insulin detemir after 72 h compared with the control ( $p < 0.01$ ), but this effect was not observed for regular human insulin. Finally, both types of insulin significantly reduced the respiratory quotient over 2 days, but again, the effect of insulin detemir was significantly greater ( $p < 0.05$ ) than that of regular human insulin. These data consistently support the hypothesis that insulin detemir has more robust inhibitory effects than human insulin on food intake, weight gain and energy expenditure, which persist when delivered directly to the brain.

Moore et al. [46] investigated the effects of insulin detemir and insulin glargine on hepatic glucose production and the CNS using a two-step hyperinsulinaemic-euglycaemic clamp procedure in dogs. They reported no difference in hepatic glucose metabolism between the two insulin analogues; however, phosphorylation in the liver, but not the hypothalamus, of Akt (protein kinase B or PKB) and signal transducer and activator of transcription 3 (STAT3), two insulin signalling components associated with gluconeogenesis and glycogenesis, was greater with centrally administered insulin detemir than with insulin glargine. Although energy intake and weight gain were not measured in this study, the findings suggest that there are differences in the central regulation of glucose metabolism between insulin detemir and insulin glargine.

### Human Studies

Food intake is regulated by glucose, amino acids, hormones, neuropeptides and trophic factors in the hypothalamus, and insulin is now well established as an adiposity signal acting within the brain and CNS to influence energy homeostasis through food intake and body weight [47,48]. Although it is difficult to assess the effects of insulin on the human CNS it has been suggested that insulin acts through the cerebral cortex [49] and studies have demonstrated reduced

cerebrocortical response to hyperinsulinaemia in non-diabetic, obese subjects [49]. Interestingly, Tschritter et al. [50] demonstrated that intravenous insulin detemir treatment restored the cerebrocortical insulin response in a two-step hyperinsulinaemic-euglycaemic clamp procedure. In the first step of the clamp, insulin detemir and human insulin were administered as a bolus (30 and 6.25 mU/kg, respectively), followed by an infusion period (0.5 and 0.25 mU/kg/min, respectively); in the second step, bolus values were 90 and 17.75 mU/kg and infusion values were 2.0 and 1.0 mU/kg/min, respectively. In normal overweight subjects, insulin detemir significantly increased beta activity observed on EEG compared with human insulin ( $p = 0.001$ ), while similar blood glucose concentrations were maintained with both treatments throughout the experiment [50]. This effect was similar to that observed with human insulin in lean subjects and is in accord with the findings of Hennige et al. [41]. There is widespread acceptance that non-esterified fatty acids (NEFA) can mediate insulin resistance, and study results suggest that the reported insulin-mediated reduction in CNS activity in obese people may be associated with elevated levels of NEFA [51]. Studies have shown that insulin-mediated cerebrocortical activity is reduced in the presence of elevated NEFA, and monounsaturated fatty acids promote insulin-mediated cortical activity [52,53].

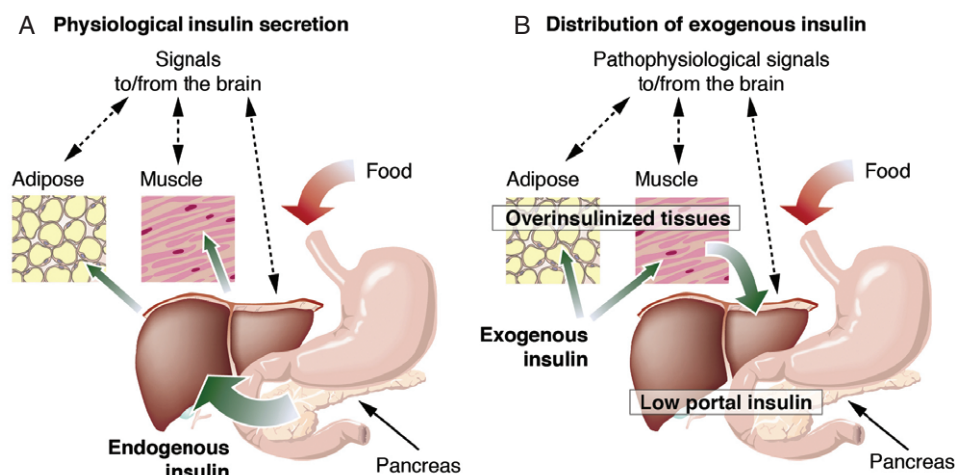
The acute effects of human insulin (17.75 mU/kg) and insulin detemir (90 mU/kg) on frontocortical EEG direct current potentials were studied in healthy subjects using two hyperinsulinaemic clamps followed by a steady 90-min infusion [1.0 (human insulin) vs 2.0 (insulin detemir) mU/kg/min] [54]. Consistent with the study design of Tschritter et al. [50], insulin detemir induced similar peripheral effects with both treatments. Food intake was also assessed by offering a standard meal 20 min after insulin infusion from which subjects could eat *ad libitum* for 50 min. A more negative direct current potential level was reached with insulin detemir compared with human insulin  $\sim 15$  min after bolus injection ( $p = 0.02$ ), despite similar blood concentrations and hormone levels (leptin, glucagon, plasma adrenocorticotrophic hormone and serum cortisol). Moreover, food intake was significantly decreased in the test meal with insulin detemir compared with human insulin, by  $\sim 300$  kcal ( $1559.79 \pm 138.72$  kcal with human insulin vs  $1256.78 \pm 82.41$  kcal with insulin detemir;  $p = 0.04$ ). Given that peripheral effects were comparable in this study, the results suggest that systemic mediators are not the cause of the decreased caloric intake.

Van Golen et al. [55] conducted a randomized, 12-week crossover study in people with T1D comparing the effect of basal-bolus treatment with insulin detemir versus NPH insulin (insulin aspart as prandial insulin) on brain regions associated with regulating appetite. Positron emission tomography (PET) scans were used to measure cerebral blood flow (CBF) and cerebral glucose metabolism ( $CMR_{glu}$ ). At the end of the study, insulin detemir had decreased body weight by 0.7 kg, whereas NPH insulin had increased body weight by 0.6 kg ( $p = 0.02$ ); the HbA1c (7.4%), daily insulin dose (basal insulin 25.9–26.5 IU/day), rate of perceived hyperglycaemia and rate of hypoglycaemia were similar in the two groups. CBF, measured

during a resting, fasting condition, was significantly higher with insulin detemir in most appetite-related brain regions than with NPH insulin [e.g. left insula:  $0.40 \pm 0.07$  (NPH insulin) vs  $0.44 \pm 0.09$  (insulin detemir) ml/cm<sup>3</sup>/min ( $p = 0.04$ ); right thalamus:  $0.38 \pm 0.06$  (NPH insulin) vs  $0.43 \pm 0.08$  (insulin detemir) ml/cm<sup>3</sup>/min ( $p = 0.04$ )]; these findings remained after adjusting for HbA1c, glucose and insulin levels. No differences were observed in  $CMR_{glu}$  in appetite-related predefined regions. Although it is difficult to determine whether the increase in CBF was a cause or a consequence of the reported weight loss, decreased CBF has previously been shown to be associated with weight gain [56,57].

Another study, however, in which a hyperinsulinaemic-euglycaemic clamp procedure was used, showed that insulin had no effect on CBF when healthy subjects and subjects with impaired glucose tolerance were compared [58]. Van Golen et al. [59] further studied the weight-sparing effect of insulin detemir by assessing the impact on food-related activation in brain regions associated with appetite regulation. As part of the study design described above, they used functional magnetic resonance imaging (fMRI) to measure brain region-specific activation in networks linked to motivation, reward and cognitive control in response to food pictures. Indeed, previous fMRI studies have shown that obese subjects' brains display hyperactivation in these brain regions [60] and that reactivity to high-calorie food pictures can predict weight gain [61]. The results reported by Van Golen et al. [59] consistently showed a decrease in body weight with insulin detemir ( $-0.7$  kg) and an increase with NPH insulin (0.5 kg;  $p = 0.007$ ), with similar effects on HbA1c, insulin dose, rate of perceived hyperglycaemia and rate of hypoglycaemia. Insulin detemir treatment resulted in significantly lower brain activation in bilateral insula, a region associated with processing food choices, when pictures of food versus non-food items were viewed ( $p \leq 0.05$ ). In the bilateral insula, the fMRI signal with NPH insulin was positively associated with change in body weight, suggesting that NPH insulin increases food-related activity in a manner that promotes weight gain, whereas no increase was seen with insulin detemir.

Overall, the results of the studies above support the hypothesis that the weight-sparing effect of insulin detemir could be underpinned by direct or indirect effects on the CNS. Enhanced CNS activity measured via substrate phosphorylation, EEG, magnetoencephalography, fMRI and PET scans in preclinical or clinical models with insulin detemir, compared with human insulin, was consistently reported in the absence of changes in peripheral metabolism, although it is plausible that changes may have been missed as a result of the study design. The process through which insulin detemir mediates this effect on the CNS is unclear, but several groups postulate that albumin-bound insulin detemir enhances active transport across the blood–brain barrier, which consequently raises brain tissue concentrations [41,54,55]; however, this remains an unresolved issue. These studies were conducted in normal subjects or in individuals with T1D, and there is a scarcity of data in T2D. Unfortunately, it is difficult to extrapolate these results to T2D given its completely different pathophysiology,



**Figure 1.** Normal and pathophysiological distribution of insulin. In normal physiology (A), the liver is exposed to greater insulin concentrations than peripheral tissues. In people with diabetes (B), exogenous insulin is administered into the systemic circulation; thus, the liver is relatively underinsulinized and peripheral tissues are overinsulinized.

including both more profound peripheral and central insulin resistance.

### Hepatoselective Hypothesis

Based on the evidence provided above, insulin detemir is consistently observed to enhance CNS activity and this effect may be associated with its weight-sparing mechanism; however, in parallel with this evidence, other studies have shown that insulin detemir may exert a relative hepatoselective effect on the liver versus peripheral tissues compared with human insulin or insulin glargine [46,62,63].

In normal physiology, insulin is secreted from pancreatic  $\beta$  cells into the portal circulation [64]. Hepatocytes are thus normally exposed to three to four times greater insulin concentrations than peripheral tissues such as muscle and adipose tissue. In people with diabetes, however, exogenous insulin is administered subcutaneously into the systemic circulation and therefore the normal portal/peripheral insulin gradient is lost, creating a situation where the liver is relatively underinsulinized and peripheral tissues overinsulinized (Figure 1); however, it is not known which pathophysiological signals to and from the brain are related to this peripheral overinsulinization. The latter increases glucose uptake and lipogenesis while reducing lipolysis, thus contributing to the weight gain typically associated with exogenous insulin therapy [65]. In contrast to the systemic circulation, where the vascular endothelium is essentially impermeable to insulin, the portal circulation in the liver is sinusoidal with large pores. It has been suggested that large insulin analogues might gain easier access to the liver through the portal sinusoidal pores and have relatively less effect in the periphery [66]. Insulin detemir, because of its large size, may help to restore the portal/peripheral gradient [66].

In the first human study to explore the relative effects of insulin detemir on liver and peripheral tissue, Hordern et al. [62] conducted a 16-h euglycaemic clamp procedure (blood glucose clamped at 4.0–5.5 mmol/l) in healthy subjects. They

compared the effects of insulin detemir and an equipotent dose of NPH insulin on the hepatic glucose rate of appearance ( $R_a$ ), peripheral glucose rate of disposal ( $R_d$ ), glycerol  $R_a$  and NEFA concentrations. Their findings showed that the baseline-adjusted  $R_a$  was significantly lower with low-dose insulin detemir compared with NPH insulin (mean difference: 0.25 mg/kg/min; 95% CI: 0.05–0.44;  $p < 0.05$ ), while there was no significant difference in  $R_d$  suggesting a greater suppression of endogenous hepatic glucose production with comparable peripheral effect on glucose uptake with insulin detemir. They also showed less suppression of NEFA, indicating that insulin detemir was exerting smaller antilipolytic effects than NPH insulin. The results of this study suggested that insulin detemir preferentially targets the liver and may partially restore the normal portal/systemic gradient seen with endogenous insulin secretion. In another study, Smeeton et al. [63] investigated the relative effects of insulin detemir and NPH insulin on glucose metabolism during an innovative hypoglycaemic protocol in which they allowed a gradual fall in plasma glucose to hypoglycaemic levels. Endogenous glucose production and peripheral glucose uptake measurements were recorded for each participant at every 0.5 mmol/l interval of glucose ranging from 7.0 to 2.5 mmol/l. No differences were reported in rates of hypoglycaemia, counter-regulatory hormone concentrations or NEFA levels between insulin detemir and NPH insulin; however, insulin detemir produced greater suppression of hepatic glucose output ( $p = 0.001$ ) and lower stimulation of peripheral glucose uptake ( $p = 0.005$ ) relative to NPH insulin.

Overall, these findings confirm that insulin detemir does indeed have a greater relative effect on the liver and less of an effect on peripheral glucose uptake compared with NPH insulin. These results indicate partial restoration of the normal portal/peripheral insulin gradient with insulin detemir. Also of note, a recent study in healthy subjects demonstrated preferential hepatic versus peripheral action of a novel, large basal insulin analogue (insulin peglispro) compared with insulin glargine. Initial results suggest that this insulin is

**Table 1.** Strengths and weaknesses of weight-sparing hypotheses.

	Strengths	Weaknesses
<b>Food intake hypothesis</b>	<ul style="list-style-type: none"> <li>Conclusive demonstration of lower energy intake with insulin detemir vs human insulin</li> <li>Demonstration that hypoglycaemia is not responsible for the weight-sparing effect of insulin detemir</li> </ul>	<ul style="list-style-type: none"> <li>Conditions studied in animals not necessarily transferable to humans</li> </ul>
<b>CNS hypothesis</b>	<ul style="list-style-type: none"> <li>Findings consistent between human and animal data, and between intravenous and subcutaneous injection data</li> <li>Similar effects shown with different brain activity measurement tools</li> <li>Results fit with the energy intake data</li> </ul>	<ul style="list-style-type: none"> <li>Reporting of acute effects only – lack of long-term studies</li> <li>Several studies use a non-clinically relevant route of insulin administration (intravenous)</li> <li>Findings of Banks et al. [44] suggest that insulin detemir cannot cross the blood–brain barrier</li> <li>Potential peripheral signals may affect central mechanisms, but these were attenuated by the experimental design</li> <li>Lack of functional metabolic data in T2D</li> <li>Exact mechanism remains unclear</li> </ul>
<b>Hepatosselective hypothesis</b>	<ul style="list-style-type: none"> <li>Conclusive evidence that insulin detemir is hepatoselective</li> <li>Consistent results in animal and human data</li> <li>Complements the findings associated with the CNS hypothesis</li> <li>Another hepatoselective analogue causes weight-sparing effects</li> </ul>	<ul style="list-style-type: none"> <li>Concurrent brain activity not measured</li> <li>Food intake not measured</li> <li>Lack of functional metabolic data in T2D</li> </ul>
<b>Fluid retention hypothesis</b>	<ul style="list-style-type: none"> <li>Attempt to link the weight effects of insulin detemir with change in fluid retention</li> </ul>	<ul style="list-style-type: none"> <li>Only one study has explored this hypothesis</li> <li>Long-term clinical trial data suggest that weight loss is progressive</li> <li>Confounding effect from the difference in HbA1c with insulin detemir</li> <li>No significant difference reported in sodium excretion</li> <li>Inconsistent with other evidence</li> </ul>

CNS, central nervous system; HbA1c, glycated haemoglobin; T2D, type 2 diabetes.

also weight-sparing [67]. This provides further evidence that hepatoselectivity may indeed be an important mechanism contributing to the weight-sparing effect of insulin detemir.

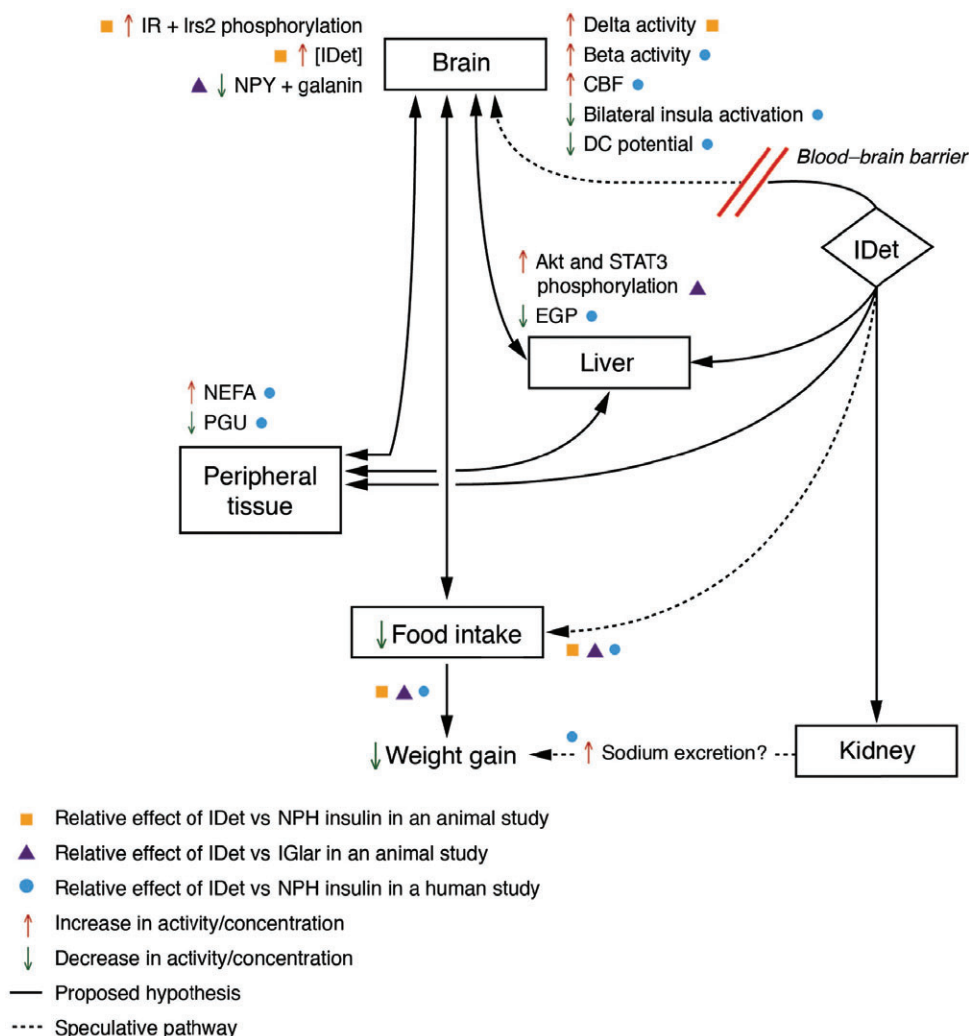
### Fluid Retention Hypothesis

Fluid retention is another potential cause of increased body weight. The fluid retention hypothesis suggests that insulin-induced tubular sodium resorption contributes to increased exchangeable sodium, increased hyperfiltration and volume expansion in people with diabetes [68]; however, the albumin-binding property of insulin detemir could prevent the normal insulin-induced decrease in glomerular filtration rate (GFR), thus reducing weight gain. This hypothesis has not been investigated in animals. In a randomized, open-label, 8-week crossover study in people with T2D, Hendriksen et al. [69] investigated the effect of insulin detemir versus NPH insulin on urinary sodium excretion, body weight and extracellular volume. Insulin detemir was associated with a significant reduction in body weight (0.8 kg) and lean body mass (0.8 kg) compared with NPH insulin ( $p < 0.01$  and  $p < 0.05$ , respectively). There was no significant reduction in extracellular volume. Remarkably, the authors reported that the change in weight with insulin detemir occurred as early as 1 week from starting study treatment ( $p < 0.001$ ) and that this change was accompanied by a non-significant and transient increase in urinary sodium excretion. These

observations were taken to suggest that insulin detemir may reduce body weight by reducing fluid retention. No differences were reported in GFR, 24-h blood pressure measurements or hormone levels (plasma aldosterone, plasma N-terminal-pro brain natriuretic peptide and renin) after the treatment period. Of concern, however, HbA1c was not comparable between the two groups: it increased from 7.6% at baseline to 8.2% with insulin detemir while it was maintained at 7.6% with NPH insulin. Insulin detemir was again associated with weight loss in this study; however, it is difficult to reconcile the 1-week findings with those of the large, randomized clinical trials that compare insulin detemir with NPH insulin, in which weight loss occurred progressively. Furthermore, the results in terms of fluid retention and kidney function reported here may be, at least in part, a consequence of poorer glycaemic control. This finding needs corroboration from other clinical studies, with equivalent glycaemic targets between insulin detemir and comparator insulin. Based on the available evidence, we conclude that the fluid retention hypothesis is unlikely to be a significant factor in the weight-sparing actions of insulin detemir.

### Summary

The results of the studies presented above show that to understand the weight-sparing effect of insulin detemir one must consider the impact of insulin detemir on the finely tuned interplay of efferent and afferent signals between muscle, brain,



**Figure 2.** Diagram showing the weight-sparing effect of insulin detemir. Insulin detemir exerts direct and/or indirect effects on several interlinked tissues that control its lowering/neutral effect on weight gain. Akt, protein kinase B; CBF, cerebral blood flow; DC, direct current; EGP, endogenous glucose production; IDet, insulin detemir; IGLar, insulin glargine; IR, insulin receptor; Irs2, insulin receptor substrate 2; NEFA, non-esterified fatty acid; NPH, neutral protamine Hagedorn; NPY, neuropeptide Y; PGU, peripheral glucose uptake; STAT3, signal transducer and activator of transcription 3.

liver, renal and adipose tissues. Given the complexity of these pathways and the somewhat contradictory findings of some studies, it is challenging to define a unifying mechanism that underpins the weight benefit reported with insulin detemir in clinical trials. Based on the presented evidence, the effect of insulin detemir on weight gain is unlikely to be explained by just one of the hypotheses discussed, but by a combination of them. The strengths and weaknesses of each hypothesis are presented in Table 1. It has been consistently shown that insulin detemir reduces energy intake, and it appears that this shift in energy balance is not associated with a lower incidence of hypoglycaemia. Insulin detemir may regulate satiety by direct action in the CNS, by indirect central stimulation by peripheral mediators and/or via a more physiological counter-regulatory response to insulin through restoration of the hepatic-peripheral insulin gradient; however, it is clear that the weight-sparing mechanism of insulin detemir is mediated by a CNS-mediated reduction in satiety and energy

intake. We conclude that changes in fluid retention are unlikely to contribute to this mechanism. A summary of the putative pathways and signals involved in regulating the weight-sparing effect of insulin detemir are shown in Figure 2.

A clinically important aspect of insulin detemir's effect on weight is the observation in clinical trials of a greater magnitude of change with increasing BMI. The findings above suggest this may be mediated via restoration of normal cerebral activity in response to insulin detemir; however, this has not been conclusively linked to improved weight control, nor has it been demonstrated in individuals with diabetes. Further research into this effect is certainly warranted to elucidate further the potential role of insulin detemir in controlling weight gain in overweight and obese people with diabetes.

The advantageous effects of insulin detemir on satiety and weight gain are an important therapeutic benefit in the management of diabetes, particularly given that the effects seem to be greatest in those with highest BMI. Further investigation to

understand the weight-sparing effect of insulin detemir is warranted, and may have important therapeutic implications for the design of future insulin analogues. Finally, we conclude that the weight-sparing properties of insulin detemir are mediated directly or indirectly through CNS-mediated reduced energy intake.

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## Conflict of Interest

D. R.-J. has received research funding, advisory board and speaker honoraria from Lilly, Novo Nordisk, Sanofi, Pfizer, AstraZeneca, Sandoz, Boehringer Ingelheim and Takeda. T. D. has received honoraria for speaking engagements, and consulting or grant support for the conduct of studies or scientific meetings from Abbott, AstraZeneca, Sanofi, Bayer, Roche, Boehringer, BMS, Lilly, Medtronic, DexCom, Novo Nordisk and Convatec. K. H. has received research funding from Novo Nordisk and honoraria from Novo Nordisk, AstraZeneca, Eli Lilly, Sanofi-Aventis, Cilag-Janssen, Boehringer Ingelheim and Takeda. K. N. has received investigator-initiated research support, and has been a principal investigator on Novo Nordisk-supported trials. K. R. has received research support from Novo Nordisk in relation to the paediatric and adolescent trial of insulin detemir referenced in this article, and travel support in relation to attendance at an advisory board meeting about insulin detemir and weight management. N. T. has received research funding and honoraria from, and conducted clinical trials on behalf of, Novo Nordisk and Eli Lilly. J. R. V. has received funding for studies cited in the text from Novo Nordisk, and is currently an Advisory Board member for Novo Nordisk for insulin detemir. B. Y. and H. U. H. have no competing interests to declare.

All authors were involved in the outline, structuring, writing and review of the article, and approved the version to be published.

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