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Insulin detemir, does a new century bring a better basal insulin?

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SUMMARY

The treatment of diabetes was revolutionised shortly after the turn of the twentieth century by the extraction and purification of insulin. Methods to protract (i.e. prolong) the action of insulin were developed in the 1930s; little changed in the technology of insulin protraction until the turn of this century when, with renewed interest in the importance of basal insulin in controlling diabetes and thus preventing or delaying complications, technology advanced again. Two new long-acting insulin analogues have come to the market; some may be familiar with insulin glargine, which has been widely used for some years now. This review attempts to describe the novel method of protraction that insulin detemir (launched last summer) employs by albumin binding, to discuss the possible therapeutic benefits of this method of protraction and to describe the findings of studies comparing insulin detemir with other currently available long-acting insulin preparations. The intention of this article is not to review all of the currently available long-acting insulin analogues.

Keywords: Detemir; glucose; insulin; metabolism

The history and treatment of diabetes is discussed below (Table 1) (1–6).

PROLONGING THE ACTION OF INSULIN

Initially, insulin treatment consisted of subcutaneous injections of insulin shortly before meals. In order to avoid multiple injections, a number of attempts were made to prolong the duration of action of insulin or to slow its absorption. Substances used were gum arabic (1923), lecithin (1923) and oil suspensions (1925) (7). These attempts were mostly unsuccessful because of poor stability or side effects at the local injection site.

The first successful insulin preparation with a prolonged action was protamine insulin (8). Here, the principle of protracting the insulin action was to make the insulin less soluble at the neutral pH of tissue fluid. When injected as a suspension, the duration of action was roughly twice as long as that of regular unmodified insulin. Protamine insulin is a complex of the fish protein protamine and insulin. When injected subcutaneously, proteolytic enzymes degrade the protamine, and the insulin is absorbed. A further way of protracting the action of insulin was the so-called lente series. These were preformed in amorphous or crystalline suspensions obtained by the addition of small amounts of zinc ions (9). Since their introduction in the 1950s, the technology of prolonging insulin action has remained relatively unchanged until now.

In the 1990s, the link between metabolic control and development of microvascular complications became firmly established (DCCT) (10). This has led to a renewed interest in long-acting insulins on the basis of a new therapeutic concept. Now, the objective is not avoidance of multiple injections, but the imitation of the physiological secretion of basal insulin in healthy subjects, with additional mealtime insulin requirements taken care of by short-acting insulin bolus injections before meals. This basal bolus concept is the cornerstone of any kind of intensified insulin treatment, which leads to significantly better metabolic control than one or two insulin injections per day can provide (7). However, this therapy is not without its problems; currently available long-acting insulins were recognised not to be good at imitating physiological secretion of basal insulin, they had peaks of action, and they were variable in absorption (11). Therefore, renewed interest in prolonging the duration of action of insulin led to developments along different strategic routes.

It was hoped that proinsulin would increase basal insulin concentrations, but concerns on cardiovascular safety that arose from clinical studies meant that this work was abandoned (12). Proinsulin's metabolite des(64,65)-human proinsulin had an even shorter period of action than NPH insulin and was discontinued (12). Slowing absorption and clearance by strengthening hexameric interactions in the form of cobalt (III)–insulin complex also proved unsuccessful (13). However, increase of the isoelectric point of insulin from

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Table 1 History of diabetes and its treatment

Date	*Name*	*Event*
400 BC	Susrata	Described a mysterious and deadly disease causing increased thirst, enormous urine output (which was attractive to black ants) and wasting away of the body
250 BC	Demetrius of Apamea	Coined the term diabetes from Greek *Dia*, through and *baino*, I flow and *mellita*, a bee
30–90 AD	Areteus of Cappadocia	Wrote 'diabetes is a strange disease, … It consists of the flesh and bones running together into the urine … Its final outcome is death … The patients are tortured by an unquenchable thirst; they never cease drinking and urinating
1674	Thomas Willis	Redescribed the presence of glycosuria and concluded that this must be proceeded by the presence of sweetness in the blood
1774	Matthew Dobson	Demonstrated that the sweetness of urine and serum was due to sugar
1849	Claude Bernard	Working on carbohydrate metabolism linked diabetes with glycogen metabolism
1869	Paul Langerhans	Described small bodies in the pancreas in his thesis. Then developed tuberculosis, left Germany for Madeira, where he died at the age of 40 (4)
Late nineteenth century	Minkowski and von Mehring	Studying digestion and the pancreas. A kennel worker caring for their experimental animals reported to the doctors that their urine was attracting flies, it was discovered the urine had large amounts of sugar (Minkowski denied this version of events). Experimental diabetes had been produced
	Minkowski	Minkowski tried to make an extract of dog's pancreas to treat diabetes, without success
	Caparelli	Discovered that a simple saline extract of pancreas injected directly into the abdominal cavity of dogs had a marked lessening or even disappearance of glucose in the urine
	Bormann	Administered roast pancreas orally, infusions by rectum and subcutaneous injections of raw pancreas extract. One of his patients who received the latter treatment gained 8 pounds in 6 weeks
1898	Blumenthal	Squeezed the juice from raw pancreas and treated it with alcohol to remove the protein, which when administered subcutaneously caused ulcers, but also increased glucose utilisation by 40%
1913	Frederick Allen	' … injections of pancreatic preparations have both proved useless and harmful. The failure began with Minkowski and has continued to the present without interruption … The negative reports have been numerous and trustworthy'. Thought diabetes was a problem of carbohydrate protein and fat metabolism and restricted patients to take as little as 400 calories per day. Survival rates weremonths, but Allen's diets were thought to be the best therapy at the time and were adopted by medical schools and up-to-date practitioners
1901	Eugene Opie	In autopsies of diabetics, destructive changes could be seen in the pancreatic 'islands of Langerhans'
1908	Georg Ludwig Zuelzer	Reduced glycosuria in dogs with the substance called 'acomatrol', which was squeezed juices from pancreatic glands taken from animals at the height of digestion and treated with alcohol. He treated eight patients and successfully reduced their glycosuria

Table 1 Continued

Date	*Name*	*Event*
1911	Georg Zuelzer	His work was funded by a pharmaceutical company. In 1914, his hospital was taken over by the military
	Scott, Starling, Knowlten and Macleod	They also worked extracting and purifying the pancreatic juices, which was interrupted by the World War I.
1920	Barron	Described ligating the pancreatic ducts, which results in atrophy of the exocrine pancreas leaving the islets intact
1921	Banting	Read Barron's article and felt the troublesome digestive enzymes may be circumvented using this technique. Under Professor Macleod at the University of Toronto with the assistance of Best, a medical student. Started ligating ducts in the pancreas of dogs and after the pancreas had degenerated injected extracts of it into depancreatised dogs. They recorded decreased glycosuria but they also were confronted with the problem of preparation and refinement of the extracts of pancreatic tissue. Collip was added with experience gained by several years of devotion to this type of chemistry. They moved on to oxpancreas, with which they discovered that the whole gland when immediately placed in acid aqueous alcohol yielded adequate amounts of insulin. The use of alcohol and acid in the extraction process circumvented the enzyme action
1922	Leonard Thomson	A 14-year-old patient weighing only 64 lb was the first to be given their insulin. He received 7.5 ml in each buttock of 'thick brown muck'. Although his blood sugar and glycosuria fell initially, unfortunately he developed abscesses at the injection sites and became more unwell. The injections were stopped. Six weeks later, he was given Collip's more refined extract, his blood sugar fell and he quickly began to gain weight. Collip's extract was then given to a number of patients with diabetes at the Toronto General hospital; they responded well
1922	Eli Lilly Company	Began to produce insulin commercially

5.4 towards neutrality, thereby causing precipitation or crystallisation at the site of injection, delays absorption and prolongs the effect of insulin (14). The first acid-soluble extended action insulin analogue made by this method was Novosol Basal GlyA21, ArgB27, ThrB30-NH_2-insulin (15), but escalating dose requirements (reduced bioavailability) possibly associated with local inflammatory reactions at the site of injection meant that this insulin was also abandoned.

On the basis of the same concept, a di-arginylinsulin analogue known as insulin glargine was developed that had a much slower and more reproducible rate of subcutaneous absorption than NPH insulin (16), resulting in slower onset and extended hypoglycaemic effect. An additional phenol molecule bound to the hexamer of crystalline insulin glargine might further contribute to its protracted action. The variation in plasma glucose and insulin concentrations between patients is less when insulin glargine is used compared to ultralente insulin (17,18).

INSULIN DETEMIR

Physical and Chemical Properties

Insulin detemir is produced by a process including recombinant DNA technology using *Saccharomyces cerevisiae* and chemical synthesis. The molecular formula is $C_{267}H_{402}N_{64}S_6$ and the molecular weight is 5916.9 Da. In comparison to human insulin, the amino acid residue at position B30 has been omitted, and a 14-C fatty acid chain has been attached to position B29. The molecule is lipophilic due to the fatty acid chain. By adding zinc to the formulation, the molecule is stabilised, and hexamers are formed making it hydrophilic and thereby soluble in water (19,20) (Figure 1).

Pharmacology

Like native insulin, insulin detemir exists predominantly as hexamers in the presence of zinc and phenol. The fatty acid side-chains contribute to the aggregation of hexamers, which results in delay in dissociation into monomers, and thereby may delay systemic absorption (21,22). In monomeric state, the 14-C fatty acid chain attached to position B29 binds to the fatty acid-binding sites of albumin in the subcutis, which further delays absorption into the bloodstream (21,22,23).

Formulation

There have been three formulations of insulin detemir used during its clinical development program. Formulation A was the first and contained 600 nmol/ml insulin detemir and glycerol as an isotonic agent. One dosing unit was defined as 6 nmol, the same as in current human insulin products. Formulation B contained 1200 nmol/ml insulin detemir and had mannitol as isotonic agent. One dosing unit was defined as 12 nmol. The final formulation of insulin detemir, formulation

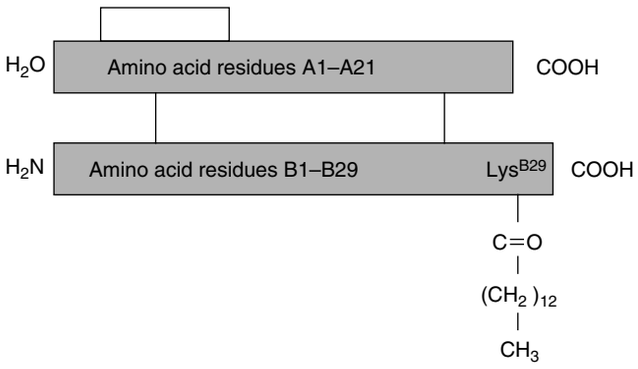

Figure 1 Schematic structure of insulin detemir

C, contains 2400 nmol/ml, one dosing unit being defined as 24 nmol. This is the formulation currently marketed.

The constituents in formulations B and C are insulin detemir, phenol, m-cresol, mannitol, disodium phosphate, sodium chloride, zinc (as zinc acetate), hydrochloric acid, sodium hydroxide and water for injections. Both formulations are clear and colourless and are at pH 7.4 [Investigator's Brochure, Soluble, Basal Insulin Analogue Insulin Detemir (NN304)].

Efficacy Pharmacology

The receptor-binding properties of insulin detemir have been studied using soluble human insulin receptors and the human hepatoma cell line HepG2. The affinity of insulin detemir for the insulin receptor was about 18–46% relative to human insulin using soluble receptors 20, 24 and 27% (when corrected for albumin binding) using HepG2 cells. Correction for albumin binding is necessary to get a measure for the receptor affinity, when assay buffers containing albumin are used, as only free (non-albumin bound) insulin detemir is available for binding to the receptor.

Insulin binding/dissociation kinetics were studied using Chinese Hamster ovary cells overexpressing the insulin receptor (CHO-hIR cells). Insulin detemir dissociates about three times faster from the insulin receptor than human insulin (24). Activation of the insulin receptor tyrosine kinase (IRTK) was studied using CHO-hIR cells. Insulin detemir was approximately 9.5% as potent as human insulin in stimulating IRTK activity (corrected for albumin binding) (24).

The insulin-like growth factor-1 (IGF-1) receptor-binding properties of insulin detemir were examined using soluble human IGF-1 receptors and using HepG2 cells. The affinity of insulin detemir for the IGF-1 receptor was determined to be 16% relative to human insulin using soluble receptors and to be 41% (corrected for albumin binding) using HepG2 cells (24).

Pharmacokinetics and Protein Binding

The albumin-binding properties of insulin detemir have been extensively studied using an immobilised human serum albumin preparation (19,25). The binding constant of insulin detemir for HAS was determined to be 2.4×10^{-5} M-1 at 23 °C and 1.0×10^{-5} at 37 °C in this assay system. On the basis of this binding constant, insulin detemir is estimated to be 98.4% albumin bound in plasma (37 °C, 0.6 mM albumin), which is consistent with *in vitro* studies using ^{125}I-labelled insulin detemir in human plasma which determined the plasma protein binding (98.8%) of insulin detemir.

The interaction between albumin binding of insulin detemir, fatty acids and selected drug substances including warfarin, acetylsalicylic acid, diazepam, phenylbutazone, valproic acid, ibuprofen, tolbutamide and glibenclamide was also examined *in vitro* using the immobilised human serum albumin preparation (25). Insulin detemir binds to the fatty acid-binding sites of the albumin molecule, but is independent of binding of the first equivalent of fatty acid. The binding of insulin detemir to immobilised human serum albumin preparation was independent of the binding of drugs in the two major binding pockets located in domains IIA and IIIA of the albumin molecule. None of the tested drugs competed with the albumin binding of insulin detemir at clinically relevant drug to albumin-concentration ratios. In conclusion, the *in vitro* studies do not suggest any clinically relevant albumin-binding interactions.

Mitogenicity

The biological effects of insulin are both metabolic and mitogenic. The metabolic potency was evaluated by measuring stimulation of lipogenesis in primary mouse adipocytes. Insulin detemir stimulated lipogenesis with a potency of approximately 29% of human insulin (corrected for albumin binding) (24). This is consistent with the relative affinity to the insulin receptor.

The mitogenic potency of insulin detemir was evaluated using Chinese Hamster ovary cells, K1 strain (CHO-K1), human mammary cancer fibroblasts (MCF-7 cells) and human osteosarcoma cells B10 (Saos/B10 cells), respectively. The mitogenic potency of insulin detemir was determined to be approximately 9% (CHO-K1), 14.6% (MCF-7) and 11% (Saos/B10) relative to human insulin after correction for albumin binding (24). Taken together, the *in vitro* pharmacology studies indicate that insulin detemir is less potent than human insulin in binding to insulin and IGF-1 receptors and in stimulating metabolic and mitogenic responses.

COULD DETEMIR HAVE ADVANTAGES OVER CURRENT INSULIN PREPARATIONS?

Effects on Glucose Metabolism

Some consider that current insulin replacement regimens have disadvantages. In normal physiology, insulin is released from

the pancreas into the portal circulation, exerting direct effects on the liver. In this 'first pass', the liver extracts up to 60% of the insulin delivered to it, and the remainder is dispersed into the systemic circulation. In consequence, hepatocytes are exposed to insulin concentrations three to four times higher than the other target organs for insulin, adipose tissue and muscle. Pharmacologically, insulin is delivered into a subcutaneous depot and absorbed into the systemic circulation through which it is distributed in approximately equal concentrations throughout the body. The normal portal/peripheral insulin gradient is lost, resulting in relative peripheral hyperinsulinaemia and underinsulinisation of the liver.

Capillary endothelial cells in adipose and muscle limit the transfer of insulin detemir from the circulation into the extravascular extracellular space (21), whereas in the liver, the sinusoids are lined by highly fenestrated epithelial cells, between which there are large gaps. The sinusoids also have no basal lamina. Because of this, no significant barrier exists between blood plasma in the sinusoid and the hepatocyte plasma membrane (26). Insulin detemir can therefore pass freely to this 'space of Disse' (the perisinusoidal space) (27,28), thus exposing hepatocytes to insulin detemir possibly resulting in a greater effect of this insulin analogue on the liver than on the peripheral tissue. Additional support for this hypothesis comes from a novel insulin analogue that binds to thyroid hormone-binding proteins which has been shown to have a greater effect on the liver compared to peripheral tissues (29).

Studies comparing similar subcutaneous doses of detemir and NPH using stable isotopes and euglycaemic clamp conditions have compared the effects of these two insulins on hepatic glucose output and peripheral glucose uptake. Researchers have found small differences with detemir having greater effect on hepatic glucose output and less effect on peripheral glucose uptake than NPH in subjects without diabetes (30), with type 1 diabetes (31,32) and subjects with type 2 diabetes (33). The differences found in these studies were in spite of similar glucose-infusion profiles. The subtle differences in action of these two insulins giving detemir a more physiological action, i.e. greater hepatic and lower peripheral effect, potentially give rise to a new explanation of the differences found in hypoglycaemia rates and weight gain found in the large multicentre studies. It is hoped that these actions may also result in less development of microvascular complications, as will be discussed later. More research in this area is needed.

Variability

Blood glucose variability correlates with mean glycaemic exposure and risk of hypoglycaemia (34), and also with mortality (35). Somogyi (36) observed that the blood glucose and glycosuria of diabetic patients often showed wide fluctuations even when both carbohydrate content of the diet and insulin dose are unchanged.

With conventional crystalline suspensions of insulin, some of this can be explained by poor mixing techniques, with variations in the actual concentration of insulin injected varying in one study from 5 to 214% (37). Studies have shown that fluctuations in absorption rate are the main cause for unpredictable insulin activity, accounting for as much as 80% of the variability in the action of NPH insulin or insulin lente (38). Lauritzen et al. (39) injected subjects with radiolabelled NPH insulin over a 12-day period; they found that absorption varied greatly from full to only 19% on some doses. Chen et al. (40) also observed large variations in absorption of NPH insulin after subcutaneous injection, with 50% of the original dose of insulin found at the injection site for around 12 h on one day, and around 96 h on another in the same patient. Luzio et al. (41) also describe large variations in insulin absorption rates, with 50% absorption between 7 and 18.2 h for NPH, and 10.2 and 42 h for glargine. There is also considerable variation in the absorption of NPH depending on the site of injection (42), and the time of day that that site is used (40).

Insulin detemir uniquely among the long-acting insulin analogues does not form a precipitate at the site of injection, and this property has been considered to be of key importance in eliminating a potential source of variability (43). It is also likely that plasma albumin binding may buffer the effect of short duration changes in the depot absorption rate, thereby limiting the pharmacodynamic variability (44). This favourable action was found in a study reported by Heise et al. (45), and Bott et al. (46) compared the pharmacokinetic and pharmacodynamic profiles, and within-subject variability of NPH, detemir and glargine in patients with type 1 diabetes. Subjects received four identical doses of insulin on four different dosing days (18). Subjects were randomised to each insulin. In this study, reproducibility of the glucose-infusion rate curves were analysed, and it was found that the probability of reproducibility was worst for NPH insulin, followed by glargine, and that detemir had the most reproducible curve. The coefficient of variation for pharmacodynamics as observed by glucose-infusion rate and pharmacokinetics as assessed by insulin concentration area under the curve was significantly lower with detemir than NPH and glargine.

This favourable action may result in lower frequencies of unpredicted hypo- or hyperglycaemia. A study reported by Pieber et al. (32,47), looking at duration of action, pharmacodynamic profile and between subject variability of insulin detemir in subjects with type 1 diabetes, found a linear dose–response relationship for pharmacokinetic and pharmacodynamic properties of detemir. It reported a longer duration of action at a dose of 0.4 μ/kg (20 h) than NPH at a dose of 0.3 iμ/kg (13 h). They also reported less variation between subjects.

WHAT THE STUDIES HAVE SHOWN

Hypoglycaemia

Hypoglycaemia is a common problem encountered in the treatment of diabetes. In one study of 411 patients with type 1 diabetes (48), patients had 1.8 episodes of mild hypoglycaemia per patient per week, and 0.027 episodes of severe hypoglycaemia per patient per week. Others have suggested that people with diabetes have an average of two episodes of symptomatic hypoglycaemia a week (49,50), and an estimated 2–4% of deaths of people with diabetes are attributable to hypoglycaemia (51). Socially, this causes problems to patients with diabetes, with around three times the percentage of people with type 1 diabetes being refused car insurance than those without diabetes (52). In the DCCT and UKPDS (10,53), studies rates of severe hypoglycaemia were higher for a given HbA1c in conventionally treated patients than those on intensive treatment regimes; however, those on intensive treatment regimes were more likely to have more frequent hypoglycaemia. Hypoglycaemia seems to be the price to be paid for improving rates of progression to complication.

Duration of diabetes is associated with decreases in the hormonal response to hypoglycaemia (54). This can lead to a vicious circle of hypoglycaemia, causing impaired physiological responses to hypoglycaemia, causing reduced awareness to hypoglycaemia, causing increased vulnerability to further episodes, and thus more hypoglycaemia.

All counter-regulatory hormone responses to hypoglycaemia increase hepatic glucose output either directly alone or in combination with an indirect effect by the stimulation of lipolysis (47), and some also decrease peripheral glucose uptake. In normal physiology, these defence mechanisms are appropriate, as insulin is released into the portal circulation and has its first effects at the liver, and the liver is essential in the production of glucose to support brain metabolism (55). In type 1 diabetes, insulin is administered by subcutaneous delivery, it circulates peripherally first, controlled by pharmacokinetics, with peak actions occurring 1–8 h after injection (47). This does not resemble physiological insulin profiles of a normal 24-h day and is unable to respond to changing insulin need (56,57). In this situation, the liver is relatively underinsulinised, and peripheral tissue overinsulinised. Counter regulation exerts itself primarily at the liver; suppression of hepatic glucose output is thus easily overcome, as in these circumstances, the liver is relatively underinsulinsed; however, the peripheral over insulinisation presents a more difficult obstacle. It could be argued that greater counter regulation has to occur to prevent a further fall in plasma glucose and maintain the brain's glucose supply. This may cause later hyperglycaemia as a result of the sustained release of counter-regulatory hormones and their prolonged duration of action which may be a factor in the overall deterioration in glycaemic control seen in patients with frequent hypoglycaemia.

Thus, an insulin analogue exerting greater effects on the liver than the periphery has the potential to reduce hypoglycaemic episodes and may reduce weight gain through less snacking to avoid hypoglycaemia. Conversely, it can be argued that an insulin that has a greater effect on the liver, would oppose the counter-regulatory hormones more effectively, and this would exacerbate hypoglycaemia. This, however, makes less physiological sense, as the counter-regulatory hormones are likely to overcome effects on hepatic glucose output and are less likely to overcome effects on peripheral glucose uptake.

A study reported by Russell-Jones et al. (58,59) compared once-daily nocturnal injection of detemir and NPH in a 6-month multicentre randomised controlled trial. They found that 6 months of treatment with insulin detemir resulted in slight lowering of HbA1c, lowering of fasting plasma glucose, less fluctuation in blood glucose levels especially at night, less nocturnal hypoglycaemia in the last 5 months of treatment and a relative decrease in weight in comparison to the group treated with NPH.

Vague et al. (60) reported the efficacy and tolerability of detemir compared to NPH in a basal bolus regime using aspart as the bolus insulin. They also reported that detemir had similar metabolic control judged by HbA1c, but found a lower within-subject variation in fasting blood glucose, a flatter and more stable blood glucose profile during the night, a lower risk of hypoglycaemia, a relative decrease in weight gain and a good safety profile.

De Leeuw et al. (61) reported a study using NPH or detemir as a twice-daily basal regime and using aspart as the bolus insulin. Again, it was found that detemir had similar glycaemic control over 12 months, a significantly lower risk of hypoglycaemia and a significant and favourable weight reduction in comparison to NPH.

Pieber et al. (62) reported a study using a basal bolus regime with aspart as the bolus insulin and twice-daily basal injections of detemir or NPH. The NPH was given at breakfast and bedtime, in one detemir arm detemir was given as the NPH, and in the other, it was given at breakfast and at suppertime. Compared to NPH, detemir provided significantly lower fasting plasma glucose in both arms, significantly lower within-subject variation in both arms and less weight gain, thus suggesting that detemir may be administered more flexibly than NPH.

Home et al. (63) reported a similar study with type 1 subjects randomised to receive their bolus insulin in a basal bolus regime as either NPH morning and bedtime, detemir morning and bedtime or detemir 12 h apart. Again, they found detemir produced significantly lower fasting plasma glucose, lower within-subject variability, lower nocturnal hypoglycaemia, less weight gain and flexible administration.

Haak et al. (64) reported a study with type 2 individuals using a basal bolus regime with aspart as the bolus insulin and twice-daily NPH or detemir. They found lower risk of hypoglycaemia, less weight increase and similar glycaemic control. Hermansen et al. (65) compared an analogue basal bolus regime of twice-daily detemir (morning and bedtime) with aspart as the bolus insulin to a human insulin regime of twice-daily NPH (morning and bedtime) with actrapid as the bolus insulin. Subjects had type 1 diabetes and were randomised in an open label trial for 18 weeks. They found that the analogue regime lowered HbA1c more than the human insulin regime and caused less nocturnal hypoglycaemia.

Insulin and Weight Gain

Studies have confirmed that insulin therapy is often associated with weight gain. Both the DCCT (10) and UKPDS (53) showed increased weight gain in their intensively treated group. Hathout et al. (66) has shown weight gain in patients previously treated with intensive insulin regimes switching to continuous subcutaneous insulin infusions. Studies have shown that decreasing HbA1c levels by 2.5% is associated with a gain of 5 kg in a year and that weight gain is more common in women than men (67). Four putative mechanisms for weight gain are better glycaemic control leading to decreased glycosuria, the anabolic effects of insulin increasing fat storage, defensive eating habits against hypoglycaemia and decreased metabolic rate with less energy expenditure. DCCT found that those who had had a severe hypoglycaemic episode gained more weight over 12 months (10), suggesting evidence in favour of defensive eating patterns. In favour of the anabolic effects of eating, insulin-associated weight gain occurs in both fat and lean tissue with significantly higher percentage body fat, and fat-free mass in the intensively treated group of DCCT than in the conventional group.

As discussed above, an insulin analogue exerting greater effects on the liver than the periphery has the potential to reduce hypoglycaemic episodes and may reduce weight gain through less snacking to avoid hypoglycaemia. Others suggest that peripheral hyperinsulinaemia increases peripheral glucose uptake and lipogenesis and decreases lipolysis, contributing to the weight gain associated with insulin therapy (4). Alternatively, Kruszynska et al. (68) investigated the effects on carbohydrate metabolism of peripheral insulin delivery compared to portal insulin delivery. They found that hepatic glycogen concentrations are lower in rats receiving insulin into the systemic circulation compared to those rats receiving insulin via the portal circulation. Others have shown that sensors in the liver to increases in intracellular ATP concentrations, affecting eating behaviour via signals transmitted via vagus afferents from the liver to the brain (69–71). The control of eating behaviour remains a highly complex and controversial subject with many factors having been shown to influence it. Nonetheless, some or all of these theories may help to explain the differences described in this paper in weight gain found in patients using detemir compared to NPH (72).

A study reported by Standl et al. (73,74) compared subjects with type 1 diabetes using a basal bolus regime of either NPH or detemir for 1 year (and using actrapid as the bolus insulin). Again, it was a multicentre randomised parallel group study. They found that detemir resulted in similar glycaemic control to NPH based on HbA1c and fasting blood glucose measurements, but less nocturnal hypoglycaemia. The patients in this study also lost weight compared with baseline using detemir, but gained weight compared with baseline if using NPH. Subjects in this study also found good safety and tolerability with detemir.

OTHER POTENTIAL BENEFITS

Growth Hormone (GH) and Insulin-Like Growth Factor (IGF-1) and Microvascular Complications

IGF-1 has a three-dimensional structure similar to insulin. Insulin-like growth factor-1 negatively feeds back to decrease the secretion of GH. In subjects with diabetes, IGF-1 levels are at the low end of the normal range or suppressed; this is more pronounced in patients with poor control. Growth hormone levels are raised throughout the day with increased frequency and pulsatility and exaggerated response to stimuli. Clearance of GH remains normal, so levels are raised secondary to increased release. This too is more pronounced in patients with poor control (75). Delivery of insulin via the portal system influences hepatic IGF-1 production. In rats, intraperitoneal insulin given to mimic portal insulin increases IGF-1 mRNA expression and systemic IGF-1 levels (76). Griffen et al. (77) also provided evidence that insulin delivered via the portal circulation is more effective than systemic insulin at restoring IGF-I levels in diabetic rats. These observations indicate that insulin and GH are required for full expression of hepatic IGF mRNA and that intraperitoneal insulin is more potent than subcutaneous insulin at stimulating hepatic IGF-1 synthesis. Subcutaneously delivered insulin leads to unphysiologically low portal insulin, and this may explain why, despite intensive subcutaneous insulin therapy, circulating IGF-I levels in diabetic patients remain either low or at best low normal (78). Low levels of IGF-1 are sensed at the pituitary/hypothalamus level, and GH is hypersecreted. This will lead to a distorted GH/IGF-1 axis with raised GH and inappropriately low IGF-1. Changes in GH levels have been implicated in the development of microvascular complications, particularly retinopathy but also nephropathy (79). Low levels of circulating IGF-1 have also been implicated to be associated with neuropathy (80). Some authors have suggested that relative underinsulinisation of the liver may play an important role in the development of microvascular

complications (81–83). Speculation therefore suggests that an insulin that has greater effect at the liver may be associated with reduced frequency of microvascular complications.

CONCLUSION

In summary, the treatment of diabetes was revolutionised at the beginning of the last century, insulin technology then remained remarkably unaltered until the latter parts of that century. Large multicentre trials, however, demonstrated the importance of strict glycaemic control, and there was renewed interest in providing insulins that work in more physiological way. Detemir is one of these new insulins developed to provide a basal insulin supply. From the studies summarised above, it appears to have advantages over other current basal insulins; whether these advantages are a result of its differences in action or from reduced variability is not known. Now that detemir has been launched for treatment, it is hoped that these well-publicised advantages may be observed in everyday clinical use.

CONFLICT OF INTEREST

Professor Russell-Jones has been paid honoraria for lectures by Novo Nordisk, and Dr SVM Hordern has completed an MD thesis, researching differences in effect on glucose and lipid metabolism between insulin detemir and NPH insulin. This study was funded by Novo Nordisk.

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