Insulin detemir: A historical perspective on a modern basal insulin analogue

Luigi Meneghini*a,*, Andreas Lieblb, Martin J. Abrahamsonc

aUniversity of Miami Miller School of Medicine, Miami, Florida, USA
bCenter for Diabetes and Metabolism, Fachklinik, Bad Heilbrunn, Germany
cJoslin Diabetes Center, Harvard Medical School, Boston, Massachusetts, USA

ABSTRACT

Insulin detemir provides prolonged, reproducible blood glucose reduction through a mechanism unique among basal insulins. It was originally studied clinically in predominantly basal + bolus regimens and found to be associated with a low risk of hypoglycaemia compared to insulin NPH, and reduced weight gain compared to other basal insulins. Insulin detemir has been increasingly studied in basal-only insulin regimens in type 2 diabetes, in which an understanding of how to optimize its use has been built incrementally. Glycaemic control and limitation of weight gain tend to be maximized by once-daily (evening) dosing, earlier initiation and careful titration to appropriate fasting glucose targets.

© 2010 Primary Care Diabetes Europe. Published by Elsevier Ltd. All rights reserved.

1. The search for better basal insulins

Until the discovery of insulin in the 1920s, diabetes mellitus was primarily encountered and perceived as a fatal disease, usually occurring in younger individuals. With the classic work of Banting, Best, and others, however, came the prospect of life-saving insulin replacement therapy, which was quickly pressed into clinical service [1]. The initial insulin products were based on extracts from animal pancreata formulated for subcutaneous injection. Such products greatly reduced the incidence of early mortality from diabetic ketoacidosis, but it was soon realized that they were unable to normalize blood glucose. Hence patients still faced the prospect in later life of severe morbidity and early mortality from the complications of chronic hyperglycaemia. A major part of the difficulty in achieving normoglycaemia was the fact that the absorption kinetics of subcutaneously injected insulins poorly matched the secretion patterns of normal physiology [2], in which a low level of ‘basal’ insulin output is supplemented periodically by rapid increases in insulin secretion in response to stimuli such as food intake – a system that matches insulin availability to metabolic need. Indeed, drug development efforts over the last 80 years have focused on modifying and refining the absorption properties of insulin to better match dynamic metabolic needs via predefined kinetic profiles.

When formulated at high concentration to provide a tolerable volume for subcutaneous injection, human (or animal-sourced) insulin self-associates into hexamers that are relatively slow to dissociate and pass from the injection depot through capillary membranes into the circulation [3–5]. The resultant absorption profile resembles neither normal basal insulin secretion nor the very rapid elevation of insulin output seen in the prandial setting [2]. As long ago as the 1930s, therefore, attempts had begun to develop two different kinds of modified insulin – long-acting products with prolonged...
Fig. 1 – The rationale for basal + bolus insulin replacement therapy. Schematic insulin kinetic profiles following subcutaneous injection super-imposed on genuine data showing healthy endogenous insulin concentrations [6]. Solid lines represent refined profiles of analogue products versus human insulin-based products (dotted lines). (From K.S. Polonsky et al. Twenty-four-hour profiles and pulsatile patterns of insulin secretion in normal and obese subjects. J. Clin. Invest. 81 (1988) 442–448. Reproduced with permission from the American Society for Clinical Investigation.)

Absorption to mimic basal insulin output, and rapidly absorbed insulin products that could mimic the prandial response. Together these could be used as a full insulin replacement (‘basal + bolus’) therapy that approximated the natural dynamic blood insulin kinetics (Fig. 1) [6].

The initial approach to modifying insulin kinetics was to manipulate the pharmaceutical vehicle in which animal-derived or recombinant human insulin was formulated, e.g. by altering zinc content or addition of protamine. The limited successes achieved, however, led manufacturers to study modified insulin molecules with altered self-association properties. This research led to the development of today’s modern insulin analogues, with the first to become commercially available being the rapid-acting prandial (or ‘bolus’) insulins, namely insulin lispro and insulin aspart (with insulin glulisine following some years later). Used in a basal + bolus combination with insulin NPH (then the most advanced basal insulin), these analogues were shown, in the late 1990s, to benefit postprandial glucose control when compared with soluble human insulin [2]. This finding was welcomed at a time when postprandial glucose control was emerging as an independent risk factor for cardiovascular disease [7–9]. There was, however, a possible disadvantage to the use of the rapid-acting analogues in basal + bolus regimens with insulin NPH or Lente insulin: the relatively short duration of action of the analogues compared to soluble human insulin (regular insulin) meant these new products contributed relatively little to between-meal insulin levels, obliging compensatory increases to be made to the doses of the accompanying basal insulins [10]. With dose increases came exacerbation of the kinetic limitations of these basal insulins, such as the rather variable absorption profile from injection to injection and the peak in insulin action after about 6 hours. With an unpredictable peak of absorption came an increased risk of hypoglycaemia, this being of particular clinical concern when it occurred during the night following an evening injection. This, in turn, limited the doses and glycaemic targets that patients could safely aspire to, and often forced the addition of a bedtime snack. An important implication was that the potential benefits of the rapid-acting analogues in basal + bolus therapy could only be maximized by developing better basal insulin partners.

The rapid-acting insulin analogues were followed only a few years later with the development of long-acting basal analogues, insulin glargine and later insulin detemir. Each was developed to provide a prolonged glucose-lowering action following subcutaneous injection, aiming for longer, flatter and more consistent time–action profiles than could be achieved with insulin NPH. Quite different protraction principles were applied for each of the basal analogues. The insulin glargine molecule features a shift of isoelectric point and this is exploited by formulating the drug in a slightly acidic solvent. The pH increase that takes place when the drug is injected into the neutral subcutaneous tissue causes post-injection precipitation, with subsequent slow redissolution and absorption of the precipitate [11].

Insulin detemir derives its prolonged action through an entirely different mechanism. It features a fatty acid side chain that binds the drug reversibly to albumin, both in the subcutaneous tissue and following absorption into the circulation, as well as facilitating hexamer and
The concept of basal + bolus insulin replacement regimens of detemir to ensure 24-hour basal insulin. The early phase 3 studies employed twice-daily dosing diabetes [17] had suggested a mean duration of action isoglycaemic clamp study of insulin detemir in type 1 subjects with insulinopenic type 1 diabetes. As an early insulins, the majority of these early studies were made in rapid-acting analogues such as aspart [10]. To best the analogue as the basal component partnered with detemir, where most of the phase 3 studies assessed therapy defined the initial clinical development of insulin profile.

In terms of their kinetic profiles, comparative isoglycaemic clamp studies of the basal insulin analogues have shown them to have, as expected, more protracted absorption than insulin NPH with relatively reduced peak rates of absorption [16,17]. Repeat-clamp studies have suggested that insulin detemir is also associated with reduced within-subject variability in the kinetic profile from injection to injection in comparison to both insulin NPH [18] and insulin glargine [18,19]; however, the clinical implications of this finding are yet to be defined in patients with type 2 diabetes.

### 2. Detemir determined: Uncovering a clinical profile

The concept of basal + bolus insulin replacement therapy defined the initial clinical development of insulin detemir, where most of the phase 3 studies assessed the analogue as the basal component partnered with rapid-acting analogues such as aspart [10]. To best highlight differences between the clinical profiles of insulins, the majority of these early studies were made in subjects with insulinopenic type 1 diabetes. As an early isoglycaemic clamp study of insulin detemir in type 1 diabetes [17] had suggested a mean duration of action at clinically relevant doses of about 20 hours, most of the early phase 3 studies employed twice-daily dosing regimens of detemir to ensure 24-hour basal insulin coverage. In these trials it became evident that detemir had several clinical advantages over NPH. Firstly, when titrated to achieve similar levels of overall glycaemic control in a series of parallel-group trials, it was found that detemir was associated with a consistently reduced relative risk of nocturnal hypoglycaemia of approximately 30% [10]. A cross-over study in which hypoglycaemia was the primary end point reported a 50% risk reduction (\( p < 0.001 \)) for nocturnal events (and an 18% reduction for all hypoglycaemic events; \( p < 0.001 \)) [20] and a recently published parallel-group study conducted over 2 years reported a 46% risk reduction (\( p < 0.001 \)) for nocturnal hypoglycaemia with detemir despite achieving a significantly lower HbA1c (difference 0.22%; \( p < 0.05 \)) [21]. This represents a considerable improvement in the safety and tolerability profile. The combination of greater safety and better glycaemic control was especially notable when insulin detemir paired with insulin aspart was compared to a human insulin basal + bolus regimen [22]. Here, the analogue regimen resulted in 21% and 55% lower incidences of total and nocturnal hypoglycaemia, respectively, as well as better glycaemic control (a 0.22% difference in HbA1c \( p < 0.001 \) and lower postprandial increments in glycaemia). A second apparent advantage of detemir over NPH, consistent with the results of the repeat-clamp study, was its association with reduced within-subject variability in blood glucose concentration as manifest by consistently lower standard deviations for fasting plasma glucose (FPG) values [10], or by more stable glycaemia during continuous glucose monitoring [23].

A third potential advantage that had not been anticipated, but which was seen in every phase 3 study in patients with type 1 diabetes, was that use of detemir caused significantly less weight gain than insulin NPH. This weight advantage was of particular potential interest in type 2 diabetes.

### 3. Changing needs with insulin therapy in a changing diabetic landscape

Even while the development of insulin analogues was taking place, a sea-change in the global face of diabetes was gathering pace. In recent decades the incidence and prevalence of type 2 diabetes has increased to such an extent that it has become one of the predominant health-economic problems of the early 21st century, and now represents more than 90% of all cases of diabetes mellitus [24]. The rise in type 2 diabetes has followed a global rise in obesity. In the USA, for example, the prevalence of obesity doubled between the years 1980 and 2004. It is now estimated that approximately one-third of US citizens are clinically obese, with a further third overweight (body mass index [BMI] >25-30 kg/m²) [25]. In this same interval, the prevalence of diabetes in adults rose from approximately 5% to 9%, with 81% of this increase accounted for by individuals with BMI >30 kg/m² [26]. The high prevalence of overweight adults with type 2 diabetes (often associated with co-morbidities) is a growing health-economic concern in all regions of the world [27,28]. Worryingly, as sedentary habits and over-eating perpetuate down through the generations, type 2 diabetes is occurring with increasing incidence in adolescents and children [29-31].

While the clinical development and evaluation of insulin products in recent years has often continued to focus on the treatment of type 1 diabetes, there are several important consequences of this rise in type 2 diabetes that affect today’s clinical requirements of insulin therapy.
3.1. The new needs: Insulin for the people
The sheer scale of the problem means that responsibility for disease management can no longer remain in the domain of specialists. The locus of care is forcibly shifting to primary care, with a growing recognition of the need to empower patients to self-manage their type 2 diabetes, and provide their physicians with appropriate skills and resources. However, persuading patients to take responsibility for insulin injection therapy is a confidence-building exercise that needs to overcome deeply ingrained psychological barriers, while enabling the primary care provider to efficiently and confidently implement insulin management strategies [32]. In particular, anxiety often arises out of preconceptions about injection pain, treatment complexity, implications of insulin therapy, and the risks and experience of hyperglycaemia. Under these circumstances, insulin regimens that are demonstrably simple, safe and painless are clearly desirable.

3.2. The new needs: Insulin supplementation rather than replacement
With residual beta-cell function, as is generally the case in early type 2 diabetes, exogenous insulin need not be introduced as full replacement therapy, but rather as supplementation therapy using a simple regimen. Supplemental insulin may help reduce the pressure of chronic hyperglycaemia that contributes to the decline in beta-cell function, by relieving glucotoxicity and temporarily enabling some recovery of the endogenous insulin response, especially soon after diagnosis [33,34].

Regarding early insulin supplementation strategies, there continues to be some controversy over whether it is clinically better to correct fasting hyperglycaemia using only basal insulin, or whether to lower post-prandial excursions by supplementing the prandial insulin response [35,36], which is often compromised in type 2 diabetes [37]. It is now increasingly clear that basal insulin supplementation alone can lower HbA1c to guideline target levels in many patients for a determined period of time, using a regimen that is very simple and relatively safe, provided it is initiated early enough [35,38]. With progression of beta-cell dysfunction, the regimen can be intensified as needed after the patient has gained experience and acceptance of injecting insulin.

3.3. The new needs: Insulin with less weight gain
A third consideration of importance in the management of patients with type 2 diabetes is weight control. There are several reasons why this is important. Patients with type 2 diabetes are very often overweight, which contributes to the pathophysiology of the disease (via several mechanisms including insulin resistance) as well as to the difficulty in treating hyperglycaemia [39]. Furthermore, deliberate non-adherence to insulin therapy as a way of controlling weight has long been recognized in adolescent females with type 1 diabetes [40,41], but has also been reported in patients with type 2 diabetes [42]. Being overweight is independently associated with an increased risk of cardiovascular disease, and can also contribute to increased mortality in patients with type 2 diabetes [43]. The prognostic implications of small amounts of weight gain above ideals in adulthood have not been well studied, but projections based on epidemiological data suggest that even small excesses of weight gain may increase cardiovascular risk to a clinically meaningful extent [43,44]. Hence, it is important to avoid every kilogram of gain beyond a patient’s ideal weight if at all possible. Indeed, diet and exercise form the cornerstone of therapy throughout the course of type 2 diabetes, with patients encouraged to strive for a healthier body weight and greater physical activity. When drug intervention is required, metformin and the newer incretin-based therapies are often used because of their ability to lower blood glucose without weight gain, indeed with the prospect of some weight loss with glucagon-like peptide-1 (GLP-1) analogues. With traditional insulin therapies, however, it becomes difficult to improve glycaemic control while avoiding weight gain. Theoretically, much of the weight gain so often seen with exogenous insulin therapy must derive from the unphysiological kinetics and distribution of insulin when delivered subcutaneously, as well as from resolution of glycosuria [39]. This implies that insulin products engineered to have kinetic properties that minimized weight gain would clearly be desirable in the treatment of type 2 diabetes.

3.4. New needs, new regimens: The birth of ‘BOT’
It was against this background, of a rising incidence of type 2 diabetes and the consequent changing needs with regard to insulin therapy, that insulin analogues first entered clinical use. Some of the properties of the new basal insulins, glargine and detemir, seemed well suited to type 2 diabetes. For example, an early clamp study to determine the kinetic profile of insulin glargine [16] suggested it had a very flat profile (reminiscent of continuous subcutaneous insulin infusion) with a duration of action of nearly 24 hours. Subsequent clamp studies of glargine have tended to report rather less flat profiles [45], but they have confirmed glargine (and detemir) to give a more prolonged and less peaked action profile than insulin NPH, fostering the view that glargine could be used as a once-daily basal insulin carrying a lower risk of hypoglycaemia than NPH. There was, therefore, the prospect that a basal insulin could be given in the evening and safely titrated to achieve fasting normoglycaemia and possibly target levels of
HbA1c [46,47]. This idea was tested in the ‘treat-to-target’ trial by Riddle and colleagues [46] where once-daily glargine or NPH were added to oral antidiabetic drug (OAD) therapies in a cohort of insulin-naïve patients with type 2 diabetes with a mean FPG of 190–200 mg/dL, and a mean baseline HbA1c of 8.6%. Rather than there being a dose titration phase followed by a maintained dose phase as was usual in insulin trials at this time, insulin doses were continually titrated over 24 weeks according to an algorithm based on FPG and hypoglycaemia, targeting an FPG of 5.6 mmol/L. Both insulins lowered mean HbA1c to 7.0%, with about 58% of patients reaching this level of control. Insulin glargine was associated with significantly fewer hypoglycaemic episodes than insulin NPH (9.2 versus 12.9 events/patient/year; p<0.005 for all confirmed events ≤72 mg/dL [4.0 mmol/L]), especially nocturnal hypoglycaemia (3.1 versus 5.5 events/patient/year; p<0.001 for confirmed events ≤72 mg/dL [4.0 mmol/L]), with few reported severe hypoglycaemia events in either arm (2.5% versus 1.8% of patients taking insulin glargine or insulin NPH, respectively). There was no advantage for glargine over NPH in terms of efficacy as reflected by HbA1c (6.96 versus 6.97%, respectively; NS) or weight gain (3.0 versus 2.8 kg, respectively; NS). This study clearly showed that with some attention to blood glucose monitoring and dose adjustment, the simple addition of once-daily basal insulin to OADs could safely bring the majority of patients to guideline-recommended HbA1c targets, and the concept of ‘basal + oral’ therapy (BOT) as an insulin initiation regimen in type 2 diabetes became widely adopted. Combined with the initial publications on the kinetics of insulin glargine, the Riddle treat-to-target study established the notion of a peakless, long-acting ‘once daily for all’ insulin therapy for type 2 diabetes with popular appeal among primary care prescribers and patients hitherto wary of the perceived complexity and risks of insulin therapy. Perhaps surprisingly, the relative success of once-daily intermediate-acting insulin NPH in the original treat-to-target study was often overlooked. Less surprising was a subsequent analysis of the Riddle study data that revealed that patients with lower baseline glycaemia achieved the lowest HbA1c levels at study end [47], further contributing to the discussion regarding the optimal time (blood glucose level) at which to initiate BOT [46].

4. Detemir in type 2 diabetes: Dispelling the myths and discovering the secrets of success

4.1. The twice-daily legacy

Early studies of detemir in type 2 diabetes collectively supported a lower risk of hypoglycaemia, as well as a 50% reduction in weight gain, when compared to insulin NPH [48–50]. Moreover, the relative advantage of insulin detemir over insulin NPH in terms of weight gain increased with increasing BMI [49,51,52]. These were encouraging findings that indicated detemir was a good choice of basal insulin for overweight people with type 2 diabetes.

The initial studies of detemir in type 2 diabetes carried over the twice-daily dosing schedules that had been used in the type 1 diabetes trials, even though once-daily NPH had been shown to be effective in BOT in the original Riddle treat-to-target trial. It might also be noted in this context that the duration of action of subcutaneously injected insulin is dose-dependent [17], and that type 2 diabetes patients typically require higher doses than patients with type 1 diabetes as a consequence of greater weight and lower insulin sensitivity. In retrospect, twice-daily dosing was therefore unnecessary, but the first study of detemir in a treat-to-target BOT regimen, reported by Hermansen et al. [49], compared twice-daily insulin detemir with twice-daily insulin NPH. This study produced substantial improvements in HbA1c in previously insulin-naïve patients, with a decrease over 24 weeks of 1.8% from a baseline of 8.6% with detemir, and of 1.9% from a baseline of 8.5% with NPH (NS between groups). The relative risks for overall and nocturnal hypoglycaemia were respectively reduced by 47% and 55% with detemir (p<0.001), although absolute event numbers were small with both insulins. Weight gain of 1.2 kg with detemir over this time was significantly lower than the 2.8 kg gain seen with NPH (p<0.001).

Tolerability and weight advantages over NPH, with equivalent glycaemic control, were therefore clearly shown for detemir in a BOT regimen, but with twice-daily dosing, which had less popular appeal than once-daily dosing. Furthermore, the first head-to-head trials comparing the two basal analogues in type 2 diabetes [53,54] compounded the perception that detemir tended to require twice-daily dosing by comparing once-daily glargine against dosing algorithms for detemir that would allow a switch from once- to twice-daily dosing, these differing regimens reflecting product labelling at that time. In the meantime, however (and notwithstanding the facts that insulin NPH had already been shown to be effective in BOT given once daily [46], and that insulin detemir had a longer duration of action than insulin NPH [17]), evidence began to accumulate that the kinetic profiles of detemir and glargine were actually rather similar [45], contrary to some of the popular perceptions that were developing. Indeed, one clamp study in patients with insulin-requiring type 2 diabetes showed near identical time–action profiles (including duration of action) for detemir and glargine at clinically relevant doses (Fig. 2) [19]. Based on these data, once-daily detemir should be expected to make an effective BOT regimen.

This was first formally tested in a BOT treat-to-target regimen by Philis-Tsimikas and colleagues [50], where
Fig. 2 – Pharmacodynamic profiles of the basal insulin analogues detemir and glargine at clinically relevant doses in insulin-treated type 2 diabetes patients [19]. (From O. Klein et al., Albumin-bound basal insulin analogues (insulin detemir and NN334): comparable time–action profiles but less variability than insulin glargine in type 2 diabetes. Diabetes Obes. Metab. 9 (2007) 290–299. Reproduced with permission of Blackwell Publishing Ltd.)

morning or evening administration of insulin detemir were compared to each other, and to evening administration of insulin NPH. Although the final HbA1c values (7.4−7.5% across groups) in this 20-week study were not as low as those achieved in the Hermansen study, the baseline mean of ~9.0% was higher and the magnitudes of HbA1c reduction (approximately −1.5% to 1.7%) were similar to those of the earlier treat-to-target BOT studies. As previously demonstrated, the insulin detemir group had less hypoglycaemia and weight gain in comparison to insulin NPH. This study further supported the concept that the final HbA1c achievable using only basal insulin is largely determined by baseline HbA1c; hence, the suggestion had been made that patients in poor or failing control were likely to require intensification of the regimen to include mealtime bolus insulin [47]. Indeed, when studies of the addition of basal insulin to OADs are considered together, it becomes apparent that the mean level of HbA1c reduction is in the order of −1.5% [55]. This implies that to reach a target HbA1c <7.0% using BOT, the basal insulin should be initiated before HbA1c rises above about 8.5%. Of course, a basal-only insulin regimen can still be introduced in patients with poorer control with the expectation of significant improvement in glycaemic control. This can be regarded as an effective regimen with which to establish patient confidence in insulin therapy. Nevertheless, the expectation should be for subsequent intensification of the regimen.

With the discrepancy in results between the Hermansen and Philis-Tsimikas studies, there was still some discussion about the suitability of a once-daily detemir regimen. The next study to be published that shed light on the issue was a 52-week head-to-head comparison of detemir and glargine by Rosenstock and colleagues [53]. Interpretation of data from this study is complicated by the fact that unequal dose titration algorithms were used to reflect differences in the product labelling at this time. Thus, glargine was given once daily in the evening and titrated against a fasting glucose target of ≤6.0 mmol/L. However, patients receiving detemir were to be switched to twice-daily dosing if, with once-daily evening dosing, their pre-dinner plasma glucose was >7.0 mmol/L and their fasting glucose was <7.0 mmol/L, or limited by nocturnal hypoglycaemia. A second pre-dinner glucose target (≤6.0 mmol/L) was then applied for titration of the morning dose. The effect of this algorithm was that 55% of detemir-treated patients were switched to twice-daily dosing over the course of the study, with most switches made within the first 12 weeks. Interestingly, a retrospective audit of blood glucose data showed that had this algorithm been applied appropriately, and in both insulin groups, then 87% and 81% of glargine- and detemir-treated patients, respectively, would have been switched to twice-daily dosing [56].

Evidence from the Rosenstock study actually suggested there were no advantages to be gained from adding a second dose of insulin detemir. On the contrary, while patients completing on once-daily detemir gained less weight than those on once-daily glargine (2.3 versus 3.9 kg; p < 0.001) this advantage was lost in recipients of twice-daily detemir (3.7 kg). In addition, recipients of twice-daily detemir completed the study on nearly double the insulin dose of those completing on once-daily detemir (1.0 versus 0.52 U/kg), but without any apparent gain in glycaemic control (HbA1c decreased by about 1.5% to 7.1% in both cases); this finding fuelled speculation that detemir had a relatively low dose potency. Of course, patients were not randomized to once- or twice-daily detemir so it could have been that clinical outcomes would have been worse had the option of twice-daily use not been available. However, the longitudinal effect of a switch from once- to twice-daily detemir in this study was retrospectively evaluated in an unselected cohort who made the switch at week 12...
Fig. 3 – Effect of switching from once- to twice-daily basal insulin dosing in a basal + oral therapy regimen on glycaemic control and insulin dose. Data (on file, Novo Nordisk, Bagsvaerd, Denmark) are from a subset of patients all switched from once-daily to twice-daily detemir at week 12 in the study reported by J. Rosenstock et al. [53].

(Fig. 3) (data on file). This group had been on once-daily detemir long enough for it to have impacted on HbA1c so the opportunity was provided to monitor insulin dose and blood glucose trajectories in response to the change in dosing frequency. While the dose nearly doubled after switching, there was little further decrease in HbA1c. Therefore, these patients gained little from the switch to twice-daily dosing; instead they increased injection number and insulin unit consumption. This same pattern was also seen in the ADAPT™ study of insulin detemir in type 1 diabetes when patients on basal + bolus therapy switched from once- to twice-daily basal dosing before a follow-up assessment [57]. Furthermore, a longitudinal analysis of 52-week data from the observational PREDICTIVE™ study [58] again showed that switches from once- to twice-daily basal insulin dosing led to dose increases without corresponding gains in glycaemic control in basal-bolus treated type 1 and type 2 diabetes and in BOT-treated type 2 diabetes. The observation of higher doses without better glycaemic control associated with completion on twice- versus once-daily detemir was also seen in a clinical trial of basal + bolus therapy in type 2 diabetes [54].

The likely mechanism responsible for the dose discrepancies between once- and twice-daily basal insulin dosing was explained by Devries and colleagues [55] who highlighted similar patterns in studies of other basal insulins including glargine. In short, when patients are switched from once- to twice-daily dosing in the setting of a treat-to-target algorithm, the fasting glucose target remains the same so the evening dose is unlikely to decrease. In order to titrate the second (morning) insulin dose, an additional pre-dinner blood glucose target is deployed. Thus, the number of injected insulin units is quickly elevated. It is intuitive to think that the total blood glucose lowering effect of an injection of insulin will be proportional to the dose given. In fact, the reality is far more complicated than this, as implied in the data presented in Fig. 3 where it is clear that a doubling of total basal insulin dose resulted in very little further change in HbA1c. As well as the total dose, the rate and timing of the appearance of insulin in the circulation in relation to food ingestion (and counter-regulatory responses) influence the glucose-lowering effect achieved. This was demonstrated 20 years ago in a study of patients with type 2 diabetes where an identical total unit dose of insulin was administered in three different infusions that varied in duration and timing in relation to a standard meal test [59]. This study showed the effect of the insulin dose on the area under the postprandial glucose curve to vary greatly, with a rapid infusion timed to coincide with food absorption having the greatest effect.

Collectively, the BOT treat-to-target studies have taught us that while clinically important improvements can be safely achieved with these regimens, there is a limit to what basal insulin can achieve in isolation when
added to OADs (−1.5% reduction in HbA1c when baseline values ≤ 9%) and once reached this cannot be extended by dividing or increasing the dose. On the contrary, twice-daily dosing results in less efficient use of basal insulin, and, in the case of detemir, attenuation of any relative weight benefit. The conclusion is therefore that basal insulin is best given once daily in type 2 diabetes, and that subsequent intensification when needed is best achieved by adding bolus insulin, not a second basal dose. Of note is that in most BOT studies, most of the glycaemic-lowering effect was achieved with approximately 0.4–0.7 units/kg/day. Since HbA1c is a function of both fasting and postprandial glucose control, it follows that optimal glycaemic control, once basal insulin replacement has been appropriately implemented, will ultimately require separate interventions to address both fasting and postprandial glucose excursions.

4.2. Power to the patients

As noted previously, however, another of the ‘new needs’ of insulin therapy is that the regimen should be simple to self-manage. The BOT ‘treat-to-target’ approach had achieved excellent results in clinical trials, but there was some doubt that patients could be relied upon to operate the aggressive continuous titration entailed in these regimens. Simplification of titration algorithms for patient use was first published in the AT.LANTUS study, in which a very large cohort of patients were randomized into either physician-led or self-led titration groups, both targeting an FPG of ≤ 5.5 mmol/L [60]. The self-led titration group actually achieved better HbA1c reduction in this study. Patients adding glargine to one OAD reduced their HbA1c by −1.3% with physician-led titration and by −1.5% with self-titration (p = 0.03) [61]. The respective improvements when glargine was added to more than one OAD were −1.5% and −1.8% (p = 0.001), and severe hypoglycaemia occurred only rarely.

The concept of patient-led titration was also adopted for insulin detemir in a study that tested a very simple dose titration concept [62], which was named the ‘303 algorithm’ because patients adjusted the basal insulin by either increasing or decreasing it by 3 units (every 3 days), or leaving it unchanged if FPG levels were above, below or at target range, respectively. This approach was compared to ‘standard-of-care’ physician-led dose adjustment. Once again the patient-led algorithm achieved results at least as good as standard care (HbA1c reduction −1.1 versus −1.0%; p = 0.09 in insulin-naïve patients) [62,63].

A final observation of clinical relevance from the treat-to-target (and other) studies was that detemir was consistently associated with lower rates of nocturnal hypoglycaemia than insulin NPH, despite similar FPG values. This observation likely reflects the later occurrence of Cmax for detemir that had been previously observed in comparative clamp studies [17]. Indeed, these latter data indicate that the Tmax of detemir (at doses of 0.4–0.8 U/kg) occurs at about 8.6–9.3 hours whereas that for insulin NPH (at 0.3 U/kg) occurred at 6.1 hours. Following evening administration, then, it seems likely that the Cmax of detemir might well coincide with patients’ pre-breakfast fasting glucose assessments, whereas NPH might have peaked a couple of hours earlier (Fig. 4). The implication was that detemir (and presumably glargine) could be tolerably titrated using lower FPG targets than hitherto utilized – indeed, targets that might precipitate nocturnal hypoglycaemia if attempted with insulin NPH. Ironically, while common FPG targets had been set in comparative clinical trials in an attempt to make equitable assessments, it could have been the case that the FPG targets used were more appropriate for NPH than the basal analogues, hence differences in clinical profile went under-estimated.

Fig. 4 – Implications of insulin kinetics on fasting plasma glucose (FPG) targeting and risk of nocturnal hypoglycaemia. A hypothetical schematic showing how a later insulin Tmax following evening injection would permit a more ambitious FPG target to be set.
4.3. Pulling the lessons together in the TITRATE study

The various lessons learned across the treat-to-target studies were ultimately combined in the design of the TITRATE study [38], in which insulin detemir was given once daily to insulin-naïve patients who were asked to self-titrate it using the 303 algorithm. The cohort inclusion criteria in many ways represented the ideal target group for BOT insulin initiation: patients were required to be sub-optimally controlled on OADs, with an HbA1c not exceeding 9.0%. The cohort was also generally well suited to the choice of detemir, having a mean baseline BMI in excess of 33 kg/m². Due to the recognized low risk of hypoglycaemia, patients were randomized to one of two FPG target groups, with these targets set lower than in previous studies (4.4–6.1 mmol/L and 3.9–5.0 mmol/L). In this study, addition of once-daily detemir tolerably achieved the American Diabetes Association (ADA) guideline target of HbA1c <7.0% in the majority of patients, without weight gain in the majority of patients. Patients randomized to the lower FPG target decreased their HbA1c from a baseline mean of 8.0% to 6.8% after 20 weeks, whereas HbA1c for patients randomized to the less aggressive FPG target decreased from 7.9% to 7.0% (p < 0.01, between groups). In total, 64.3% and 54.5% of the lower and higher target groups, respectively, achieved HbA1c <7.0% (p < 0.05, between groups). The respective detemir doses at the end of the study were 0.57 and 0.51 U/kg, and overall rates of hypoglycaemia were low at 7.73 and 5.27 events/subject/year, respectively, with just one major hypoglycaemic event reported in the 3.9–5.0 mmol/L target group.

5. Future directions

The TITRATE study seems to illustrate the optimal way of using detemir as initial insulin therapy in type2 diabetes. Data from this and other studies have led to a change in the European product labelling, which now recommends once-daily dosing for insulin detemir. The safety profile of insulin detemir is being further explored in ongoing studies designed to verify our current understanding and extend our clinical experience with the use of detemir in pregnancy and in very young children. A head-to-head treat-to-target comparison with glargine is also underway, which will involve equitable once-daily dosing algorithms in a cohort similar to that used in the TITRATE study, and it is hoped this trial will clarify the relative merits of these products with regard to glycaemic control, safety and weight management once and for all.

Also in need of resolution is the mechanism(s) underlying the unique profile of detemir with regard to weight change. There are two primary hypotheses as to why weight gain is relatively reduced with detemir, and there are some preliminary data in support of each of these. One suggests that detemir has a relatively greater effect on the liver than upon adipose tissues, and hence has a more natural pattern of tissue distribution than subcutaneously injected human insulin [39,64], and the other suggests that detemir might restore impaired insulin-mediated satiety signals in the central nervous system [65,66]. A series of metabolic studies are investigating this issue further – a better understanding of the pharmacological mechanisms could help in the identification of patients most likely to gain benefit from the choice of detemir.

Finally, it is important to acknowledge that while the development of insulin therapy over the last few decades has been a story of gradual refinement, there is still a long way to go with regard to delivering tolerable and highly effective therapy for our patients with insulin-deficient diabetes. Lessons learned in the clinical development of detemir may, however, help to produce future insulin analogues that are refined still further. In particular, detemir may pave the way for the development of analogues that have even more physiologic profiles with regard to prolonged and reproducible action, and the avoidance of hypoglycaemia and weight gain.

Acknowledgements

All authors have been involved throughout the development of the manuscript, from initial concept to providing final approval. The meeting upon which this manuscript is based was funded by Novo Nordisk. Novo Nordisk was involved in the selection of faculty for this meeting, who were paid an honorarium for speaking. The authors thank Murray Edmunds, Watermeadow Medical, UK, for writing assistance in the development of this manuscript; this assistance was funded by Novo Nordisk. Novo Nordisk was involved in the selection of faculty for this meeting, who were paid an honorarium for speaking. The authors thank Murray Edmunds, Watermeadow Medical, UK, for writing assistance in the development of this manuscript; this assistance was funded by Novo Nordisk, who also had a role in review of the manuscripts for scientific accuracy.

Conflict of interest statement

Luigi Meneghini has received funding for research from Novo Nordisk, sanofi-aventis and Medtronic Minimed, has acted as a consultant to Novo Nordisk, is a member of an advisory board for Novo Nordisk, and is a member of a speaker bureau for Novo Nordisk, Eli Lilly and sanofi-aventis. Andreas Liebl has received honoraria for presentations from Eli Lilly, MSD, Roche, and Novo Nordisk, and is a member of advisory boards for Eli Lilly, MSD, Roche, and Novo Nordisk. Martin J. Abrahamson is a member of an advisory board for Novo Nordisk, and is a member of a speaker bureau for Novo Nordisk, Merck, Eli Lilly and Amylin.
References

(303 Algorithm) for insulin detemir in patients with type 2 diabetes—results of the randomized, controlled PREDICTIVE™ 303 study, Diabetes Obes. Metab. 9 (2007) 902–913.


