Current guidelines and targets for the management of diabetes mellitus emphasize the importance of intensive treatment regimens to control blood glucose and reduce cardiovascular risk. Ideally, glycaemic control should be as near to normal as practicable for each patient [1,2]. This approach minimizes microvascular complications and assists macrovascular protection, forming a crucial part of the overall medication cocktail to address all recognized vascular risk factors in the diabetic patient.

The primary objective of insulin therapy in the treatment of diabetes is to produce sustained near normal glycemia by replacing or supplementing endogenous insulin secretion in as physiological a manner as possible, postprandially as well as between meals and overnight.

Insulin therapy is increasingly being initiated earlier [3-6], and progressively more aggressive strategies are being employed in an attempt to attain glycaemic control and reduce the risk of diabetes-related complications [4,7-9]. Recently, the ADA and the EASD have proposed a treatment algorithm for T2DM, emphasising the early use of insulin and, in particular, basal insulins for patients inadequately controlled with lifestyle interventions and metformin [10]. However, despite evidence supporting the benefits of the early addition of insulin to Oral Antidiabetic Drugs (OAD) [3,6,11], there are numerous barriers that prevent or delay the initiation of insulin in patients with T2DM, of which fear of hypoglycaemia, weight gain and injections are key factors [12-13].

The ideal insulin therapy would provide good glycaemic control without an adverse impact on patients’ quality of life, by seeking to replicate physiological insulin secretion, thus controlling baseline glucose (basal insulin) by suppression of hepatic gluconeogenesis and, where appropriate, providing postprandial regulation (bolus insulin) to imitate normal glucose homeostasis. There is evidence demonstrating that fasting plasma glucose (FPG) should be the key focus in initial management of patients with poor glycaemic control, while postprandial glycaemia should be targeted in patients with lower HbA1c [14].

A simple and practical approach to implementing basal insulin is to continue OAD therapy and add a single basal insulin dose, titrated according to FPG [11]. Insulin in combination with OADs has been proven to be effective in a systematic review of 20 randomised clinical trials, which confirmed that basal insulin (NPH) plus OAD therapy provided comparable glycaemic control to insulin monotherapy, and was accompanied by an overall reduction in total daily insulin requirement of 43% [15].

Basal insulin therapy utilises the pharmacokinetic properties of long-acting insulin analogues to maintain interprandial and overnight glycemic control without the need for complex multiple dosing. This strategy also allows titration to be accomplished in a safe and simple manner and is an easy ‘first step’ to progressive insulin therapy. As the disease continues to advance, or if more intensive therapy is required to achieve glycaemic targets, the basal insulin dose may be increased, or treatment may be intensified in a simple, logical, step-wise manner to a basal–bolus regimen, by introducing a preprandial fast-acting insulin analogue to control postprandial blood glucose levels.

**LIMITATIONS OF CURRENT BASAL INSULIN THERAPY**

The most relevant pharmacological characteristics of any given insulin – onset of action, peak effect profile, and duration of action – are largely determined by its absorption kinetics from the subcutaneous injection site into the systemic circulation. Under physiological pH, insulin is soluble but has a tendency to aggregate into dimers and hexamers. After subcutaneous injection, insulin is absorbed only in its monomeric form. The dissociation rate of hexamers, therefore, plays a limiting role since these aggregates, as opposed to dimeric and monomeric insulin, are not absorbed into the circulation [16]. These physiochemical properties, which lead to a delay in subcutaneous absorption, have been a problem with the conventional insulin preparations used for basal supplementation [16].

The rate of absorption from the subcutaneous depot varies considerably among certain insulins, such as the intermediate-acting neutral protamine Hagedorn (NPH) and Lente insulins. The consequent day-to-day variability in action and peak effect is responsible for inconsistent and erratic day-to-day outcomes. This is in part a consequence of the fact that these insulins come as a crystal suspension that requires thorough mixing before injection. Variations in the degree to which insulin crystals are solubilized and the extent to which a consistent degree of solubilization is maintained are important factors contributing to the poor reproducibility of NPH and Lente effects.
Another limitation that these two basal supplements demonstrate is a significant peak of action that occurs 4–8 h following their subcutaneous administration, which increases the risk of nocturnal hypoglycemia with evening administration [17]. The subsequent decline of insulin levels can cause early morning fasting hyperglycemia due to the dawn phenomenon or rebound hyperglycemia [18].

**Newer Basal Insulin Analogues**

Newer basal insulin analogues include insulin glargine (glargine) and insulin detemir (detemir).

**INSULIN GLARGINE:**

Glargine was the first long-acting basal insulin analogue to be launched and mimics normal physiological basal insulin concentrations more closely than traditionally available ‘intermediate’ and ‘long-acting’ insulins, such as NPH and insulin ultralente [19, 20].

Glargine is an analogue of regular human insulin (RHI) produced by recombinant DNA technology. The primary structure of glargine differs from RHI in two ways [21]: (1) two arginine residues are added to the C-terminus of the B-chain, which alters the isoelectric point (from pH 5.4 to 6.7), making the molecule less soluble at the physiological pH of subcutaneous tissue; and (2) the asparagine residue at position 21 in the A-chain of RHI is replaced with a neutral glycine residue (Fig. 1), which stabilises the molecule, to limit deamidation and dimerisation at the acidic pH of 4.0 at which glargine is formulated.

Upon injection into the subcutaneous space (pH 7.4), the acidic glargine solution is neutralised and glargine forms an amorphous suspension, resulting in delayed absorption and an extended duration of action compared with NPH [19, 22]. The absorption of glargine is slower than that of NPH in healthy volunteers [20] and in patients with T2DM [22]. NPH demonstrates a peak of concentration 4–8 h after administration, while the absorption of glargine from the injection site is relatively constant with no prominent peak in plasma insulin concentration in healthy male volunteers [20]. These properties mean that glargine mimics normal physiological basal insulin concentrations more closely than traditionally available ‘intermediate’ and ‘long-acting’ insulins, such as NPH and insulin ultralente [19, 20]. The smooth, long-acting time–action, 24-h profile of glargine is dose-dependent and offers true once-daily dosing and a reduced incidence of hypoglycaemia compared with NPH in the majority of patients with T2DM [23, 24].

In principle, glargine can be given by once-daily subcutaneous injections at any time of the day, although bedtime is usually preferred. Several studies have reported similar or slightly improved glycemic control with glargine compared with once- or twice-daily NPH. However, glargine therapy resulted in fewer episodes of nocturnal hypoglycaemia and less weight gain [25-27].

**INSULIN DETEMIR**

Detemir was the second long-acting analogue launched and also offers advantages over NPH for patients with T2DM [28, 29].

Detemir is produced by recombinant DNA technology; the amino acid threonine in position 30 of the B-chain of RHI has been omitted, and myristic fatty acid attached to the ε-amino group of amino acid lysine B29 in order to obtain long-acting properties (Fig. 2) [30]. The prolonged action of detemir is mediated by the strong self-association of detemir molecules at the injection site and albumin binding via the fatty acid side-chain [31].

Studies in patients with Type 1 diabetes (T1DM) have demonstrated that detemir has a slower, more prolonged absorption over 24 h and a flatter time–action profile compared with NPH [32, 33] and, in clinical practice, detemir is typically administered twice daily. An isoglycaemic clamp study in patients with T1DM showed that the duration of action of detemir is dose-dependent; the mean duration of action ranges from 5.7 to 23.2 h at doses of 0.1–1.6 units/kg [33]. At equipotent doses of detemir and NPH, the duration of action of detemir is estimated to be approximately 4 h longer compared with that of NPH (determined by interpolation of results from two different detemir doses) [33]. The peak of action of detemir is dose-dependent. This property has potential implications for detemir titration, as peaks of insulin action may be associated with an increased risk of hypoglycaemia, and is a consideration that should be taken into account when switching from once daily to twice daily administration of detemir (discussed below). In contrast, the smooth, long-acting time–action profile of glargine shows no pronounced peak of action and is not dose-dependent, offering true once-daily dosing and a reduced incidence of hypoglycaemia compared with NPH in the majority of patients with T2DM [23, 24].

A direct comparison of the pharmacokinetic and pharmacodynamic properties of glargine and detemir has recently been conducted in a 2-week study of 24 patients with Type 1 diabetes [34]. Findings

### Figures

**Fig. 1:** The amino acid structure of insulin glargine showing the key amino acid modifications that result in the protracted duration of action.

**Fig. 2:** The amino acid structure of insulin detemir showing the key modifications that result in the protracted duration of action.
Table 1: Receptor binding, metabolic and mitogenic potency of currently used insulin analogs versus human insulin

<table>
<thead>
<tr>
<th>Insulin type</th>
<th>Insulin receptor affinity</th>
<th>Metabolic potency</th>
<th>IGF-1 receptor affinity</th>
<th>Myotogenic potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human insulin</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Lispro</td>
<td>84 ± 6</td>
<td>82 ± 3</td>
<td>156 ± 16</td>
<td>66 ± 10</td>
</tr>
<tr>
<td>Aspart</td>
<td>92 ± 6</td>
<td>101 ± 2</td>
<td>81 ± 9</td>
<td>55 ± 22</td>
</tr>
<tr>
<td>Glargine</td>
<td>86</td>
<td>60 ± 3</td>
<td>641 ± 51</td>
<td>783 ± 13</td>
</tr>
<tr>
<td>Detemir</td>
<td>~18 - 46</td>
<td>~ 27</td>
<td>16 ± 1</td>
<td>~ 11</td>
</tr>
</tbody>
</table>

generally agreed with the once-daily dosage of glargine and twice-daily dosing of detemir commonly used in clinical practice as, while both long-acting insulin analogues had a similar onset of action, the end of action was earlier with detemir. This report is, however, in contrast to another recent study comparing detemir and NN344 (both albumin-bound insulin analogues) with glargine in 27 patients with T2DM [35]. In this instance, detemir was found to have a similar time–action profile and duration of action to glargine, suggesting that detemir may also be well-suited to a once-daily regimen.

CONTROVERSIES OF BASAL INSULIN ANALOGUES

Insulin Analogues and Cancer

Insulin and IGF-1 receptors recognise the terminal part of the insulin B chain and extensions into the C chain differently. Modification of B26–B30 regions of the B chain increases IGF-1 receptor binding, as does modification of the B10 residue and extension of the B chain by addition of arginine residues [36]. Changes at both sites have additive effects, in that AspB10DiArg insulin, used for experimental purposes only, produces a 90-fold increase in binding to the IGF-1 receptor on human mammary epithelial cells (HMECs). Insulin glargine (A21Gly,B31Arg,B32Arg human insulin) also contains arginine residues at positions B31 and B32, together with a glycine substitution at A21; Insulin detemir; B29Lys (ε-tetradecanoyl),desB30 human insulin carries a fatty acyl chain attached to the end of the B chain. The ability of analogues to stimulate HMEC growth generally correlates with their ability to bind to the IGF-1 receptor, but prolonged interaction with either receptor also appears necessary for stimulation of mitotic activity [37].

Kurtzhals and colleagues used a variety of systems, including human osteosarcoma cells, to compare receptor affinities (Table 1) and mitogenic potencies of the insulin analogues in current clinical use, and found that insulin glargine has a six–to eightfold increase in receptor affinity and mitogenic potency compared with human insulin [36].

Insulin glargine is partially degraded at the injection site, yielding two bioactive products known as M1, which lacks the diarginine residues at B31 and B32, and M2, which has additional deletion of the threonine at B30. Both products retain the glycine substitution for asparagine at A21. These are therefore closely similar to, but not identical with, human insulin [38,39] and their mitogenicity appears to be low [39]. All three forms (unchanged insulin glargine, M1 and M2) enter the circulation. Further degradation of insulin glargine to M1 occurs on exposure to serum, probably mediated by carboxypeptidase enzymes [39]. These observations suggest that insulin glargine behaves to some extent as a prodrug, generating bioactive breakdown products both at the site of injection and within the circulation. It follows that insulin glargine may be less mitogenic in vivo than in vitro, but the studies suggest considerable inter-individual variation, and a substantial proportion of the insulin injected will, on present evidence, reach the cells in the form of unaltered glargine.

A large observational study suggested that use of insulin glargine is, after adjustment for dose, associated with a possible increase in tumour risk in humans [40]. The major finding of this analysis was a strong correlation between insulin dose and cancer risk, regardless of insulin type. Dose for dose, however insulin glargine appeared to carry a higher risk of cancer than human insulin.

A Swedish study revealed that those on insulin glargine alone, have a higher risk of breast cancer than those on insulins other than insulin glargine, with an RR of 1.99 (95% CI 1.31–3.03), all other cancer risks being equal [41].

INSULIN GLARGINE AND RETINOPATHY

A further safety concern requiring human studies arose when one of the early clinical trials [26] was reported to have observed a threefold increase in retinopathy progression with insulin glargine compared with human insulin [42]. Since IGF-1 has a role in normal retinal vascular function and disease [43], this observation raised the possibility that insulin glargine might also have mitogenic effects on the vascular endothelium. The FDA required prospective comparative studies of retinopathy progression in patients taking human and glargine insulins in 1999 [44] and this work was finally culminated [45]. Reassuringly, this analysis was entirely negative.

SUMMARY

- Basal analogues provide an improved balance between control and tolerability when compared to traditional basal insulins.
- In basal-bolus therapy, a waning of effect is evident in a considerable percentage of patients. These individuals are likely to do better if the basal dose is split between two injections per day. If this is done, the basal insulin dose is likely to rise, but the bolus dose may be reduced to compensate.
- Nocturnal hypoglycaemia is likely to be reduced if the basal insulin dose is split between morning and evening, or given as a morning injection titrated to a pre-dinner glucose target.
- Basal analogues can be added once daily to OADs to initi-
ate insulin in type 2 diabetes and, provided baseline control is not too poor, can be titrated to achieve guideline HbA₁c targets.

- There appears to be a limit of achievement with basal only insulin therapy (plus OAD) and this is likely due to the failure of this approach to adequately limit the postprandial PG rises that characterize type 2 diabetes. The actual limit of achievement is largely determined by glycaemic control at baseline.

- While splitting the basal dose can improve control and reduce nocturnal hypoglycaemia, if the insulin is titrated by fasting and pre-dinner targets, the total dose tends to rise disproportionately to the reduction in HbA₁c if no provision is made for postprandial glycaemic control.

Although there is clearly more to be learned about their use, the arrival of glargine and detemir is nevertheless welcome for, even if their optimal use is not as straightforward as originally hoped, they undoubtedly offer the potential to achieve an improved balance between glycaemic control and tolerability in clinical practice.

Further lessons to be learned from future studies should enable physicians to use these new tools to even greater effect.

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