Addition of rapid-acting insulin to basal insulin therapy in type 2 diabetes: indications and modalities

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SUMMARY
There are many reasons to believe that in the near future, the treatment of patients with Type 2 diabetes will be characterised by an increased use of insulin therapy. To ensure that insulin regimens are acceptable to patients, and implemented by physicians, they should be as simple and efficient as possible. Simplicity is synonymous with the regimen of once-daily basal insulin glargine given at any time of the day (at the same time each day). With such a strategy, the dose can be adjusted by titrating to target fasting blood glucose values of 5.0 – 7.2 mmol/L (90 – 130 mg/dL). When these targets can no longer be achieved with reasonable doses of long-acting insulin, a rapid-acting insulin analogue should be added at meal times. A step-by-step strategy can be used; it is recommended that initially, a single daily prandial bolus of a rapid-acting insulin analogue is administered before the meal that leads to the highest post-meal blood glucose excursions. Further boluses can be added at other meal times as necessary, i.e., when post-meal blood glucose values remain above 10.0 mmol/L (180 mg/dL) and 7.8 mmol/L (140 mg/dL) at mid-morning and 2h-post-lunch or post-dinner times, respectively. This stepwise strategy may eventually lead to a standard basal–bolus regimen with 3 pre-meal injections of rapid-acting insulin analogues, a potentially small trade-off for achieving fairly-well controlled diabetes.

Key-words: Type 2 diabetes mellitus · Rapid-acting insulin · Timing · Regimens.
Introduction

The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that in type 2 diabetes patients, a decline in beta cell function is inevitable over time despite oral therapy [1]. This suggests that therapy should be adapted as the disease progresses to maintain glycaemic control. The importance of tight glycaemic control has been demonstrated by various prospective studies in which poor control was found to be associated with an increased risk of developing complications including sensory neuropathy [2], microvascular complications [3], stroke [4], myocardial infarction [3-5], macrovascular mortality [6,7] and all-cause mortality [7-10]. Additionally, the landmark Diabetes Control and Complications Trial (DCCT) and the UKPDS have both shown that tight glycaemic control reduces the risk of long term microvascular and macrovascular complications. The UKPDS demonstrated a direct correlation between degree of glycaemic control and both microvascular complications and also myocardial infarction (MI) in patients with type 2 diabetes; for every 1% reduction in HbA1c, a 14% and 37% risk reduction for MI and microvascular complications occurred, respectively [11].

As a direct result of the UKPDS, DCCT and other studies, major associations for diabetes management, including the American Diabetes Association (ADA), American Association of Clinical Endocrinologists (AACE) and the International Diabetes Federation (IDF) Europe, have set strict glycaemic control targets (table I) [12-14]. Unfortunately, these objectives are only achieved in a small proportion of patients [15]. In the third National Health and Nutrition Examination Survey (NHANES III), 1988–1994, only 44.6% of patients with type 2 diabetes met the ADA HbA1c target of < 7.0%, and more than 38% of patients had HbA1c values > 8.0% [16]. An update from the NHANES III survey, 1999–2000, showed that the glycaemic control of the patients had progressively deteriorated over time with the proportion of patients achieving HbA1c < 7.0% falling to 35.8%. A similar deterioration in glycaemic control over time was noted in the UKPDS with the number of patients achieving HbA1c values of < 7.0% dropping from around 50% of patients after 9 years.

Traditionally, initiation of insulin therapy has been recommended in patients with type 2 diabetes when maximum oral therapy no longer provides sufficient control, typically after 10 years of disease progression [17]. Earlier addition of insulin to ongoing oral therapy can significantly improve control, as demonstrated in a sub study of the UKPDS, which showed that early addition of insulin to oral therapy maintained HbA1c levels close to 7% in the first 6 years following diagnosis [18]. However, initiation of insulin therapy is often delayed for several potential reasons, which include the perception that most treatment regimens are complex, and most notably because of patients’ fear of developing hypoglycaemia [19].

Initiating basal insulin

Basal insulin replacement therapy is used to control the 24-hour post absorptive glucose profiles overnight and during fasting and interprandial periods. A single daily injection of basal insulin, such as insulin glargine, given at any time of the day but at the same time each day along with continued use of oral antidiabetic agents leads to significant improvements in HbA1c levels. This is due to lowering of fasting hyperglycaemia resulting in a beneficial carryover effect on glycaemic levels throughout the day. It has been hypothesised that basal insulin improves overnight and fasting glucose control at such a level that glucotoxicity is decreased, allowing oral agents to exert their full effect on modulating and increasing insulin secretion for mealtime control [20]. The addition of a long-acting insulin to ongoing oral therapy can significantly improve control, particularly when following a treat-to-target regimen whereby the insulin is titrated to a fasting glucose target. Under this treatment concept, oral therapy is continued and a single bedtime injection of a long-acting (basal) insulin analogue is added; using a simple algorithm, the insulin is systematically titrated, seeking a defined target such as blood glucose levels. Using this type of regimen presents several advantages: the first one is obvious since it serves to reduce the number of insulin injections to a minimum. The second one is to reduce the frequency of blood glucose self monitoring to a single daily test pre-breakfast; such monitoring can be sufficient when the injection of insulin glargine is before dinner or at bedtime. The third advantage lies in the fact that the adjustments of insulin doses are easier, the goal of the treatment being to achieve pre-breakfast plasma glucose levels below a given target; in the treat-to-target trial [21] and in the LANMET trial [22], this was < 5.6 mmol/l (100 mg/dL).

In order to reach such targets, it is usually recommended to increase the insulin dose progressively, without decreasing despite monotherapy treatment with metformin, insulin or sulfonylurea. After three years, approximately 50% of patients were achieving the HbA1c < 7.0% compared with around 25% of patients after 9 years.

### Table I

<table>
<thead>
<tr>
<th>Glycaemic control parameters from current guidelines.</th>
<th>ADA</th>
<th>AACE</th>
<th>IDF Europe</th>
</tr>
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<tbody>
<tr>
<td>HbA1c (%)</td>
<td>&lt; 7.0</td>
<td>≤ 6.5</td>
<td>≤ 6.5</td>
</tr>
<tr>
<td>Fasting plasma glucose, mmol/l (mg/dL)</td>
<td>5.0 – 7.2</td>
<td>&lt; 6.1</td>
<td>&lt; 6.1 (110)</td>
</tr>
<tr>
<td>2 hour postprandial glucose, mmol/l (mg/dL)</td>
<td>&lt; 10.0</td>
<td>&lt; 7.8</td>
<td>&lt; 7.5 (135)</td>
</tr>
</tbody>
</table>

ADA = American Diabetes Association; AACE = American Association of Clinical Endocrinologists; IDF = International Diabetes Federation.
being concerned about the upper limit of maximal doses used. Having employed this method, Yki Järvinen in the LANMET study demonstrated that this objective can be achieved [22]. However, it must be noted that the insulin doses used were rather high, with a daily average of 70 units and maximal doses approaching 200 units per day. As a consequence, the investigators reported noticeable gain in body weight in their patients, the increment in body weight being generally equal to 2 kg for each 1% decrement in HbA1c levels [23]. This relationship described by Yki Järvinen [23] was confirmed by computing and averaging the results observed in several other randomized trials [21,22,24-27]. The results of this analysis (figure 1) indicate that this relationship is observed whatever the insulin regimen used. For instance, treatments with once-daily insulin glargine or NPH insulin and once- or twice-daily premix insulin or thrice-daily rapid insulin analogues at each premeal period produce a similar relationship between weight and insulin or thrice-daily rapid insulin analogues at each premeal used. For instance, treatments with once-daily insulin glargine or other long-acting insulin analogues combined with a reinforcement of dietary recommendations and thus of patients’ dietary behaviour.

From these apparently simple considerations, there arises the question of why, in most patients, the problem of weight gain remains. The first reason is that approximately 50% of patients remain totally unconcerned by dietary issues [15]. However, even for those who strive to make some dietary changes, weight gain is commonly observed. This phenomenon can be partly explained by analysing the results from a variety of studies [21,22,24,25,27] (figure 2). For example, when the increments in body weight and decrements in HbA1c are plotted against the insulin doses used in several randomized studies [21,22,24,25,27], firstly we see that the weight gain remains relatively low (+ 2 kg) and secondly that reductions in HbA1c levels are rapid and linear (- 0.5% decrease in HbA1c for each increment in insulin dose equal to 0.1 unit/kg body weight/day) as long as the insulin dose remains below 0.5 unit/kg body weight/day. Above this threshold, body weight steadily increases and the improvement in terms of HbA1c decreases is less substantial (- 0.5% decrease in HbA1c for each increment of insulin dose equal to 0.2 unit/kg body weight/day). For that reason, in our clinical practice we usually recommend that, in patients with type 2 diabetes, a total daily dose of ≥ 0.5 unit/kg of body weight should not be enforced with insulin glargine or other long-acting insulin analogues when such insulin preparations are used once-daily. This clinical attitude is in agreement with the remarks made by Hirsh in a recent review article [29]. According to our observations and to Hirsh’s remarks, basal insulin alone has the capability to reduce HbA1c to less than 7% i.e. to the target as defined by the ADA standards of medical care for patients with diabetes [12], provided that baseline levels are below 9%. In this situation, most patients achieve the target with less than 0.5 unit/kg body weight/day since every increment of insulin dose equal to 0.1 unit/kg body weight/day results in a 0.5% decrease in HbA1c. In contrast, in those patients who exhibit baseline levels of HbA1c higher than 9–10%, two therapeutic approaches can be proposed. The first one involves the progressive increase in the dose of the long-acting insulin analogue to achieve HbA1c < 7%. This strategy requires large insulin doses since above the threshold of 0.5 unit/kg/day every 0.5% additional decrement in HbA1c is obtained with a 0.2 unit/kg/day increase in insulin dose. Therefore, it is not surprising that after several weeks of treatment such strategies necessitate the administration of a mean total daily dose of long acting insulin analogue as high as 1 unit/kg/day. As a consequence, and as illustrated in figure 2, weight continues to increase when the 0.5 unit/kg/day threshold has been exceeded. For that reason, the second choice would be to

![Equation of Yki-Järvinen: \( \Delta HbA1c = -1\% \rightarrow \Delta weight = +2kg \)](image-url)

**Figure 1**
Relationship between decrements in HbA1c (delta HbA1c) and weight gain (delta weight) in patients with type 2 diabetes treated with different insulin regimens. (Isosceles triangles = ref 21; right angle triangles = ref 22; squares = ref 24; rhombuses = ref 25; crosses = ref 26; circles = ref 27; black figures are shown for addition of insulin glargine; open figures are shown for addition of NPH insulin or rapid-acting insulin analogue).
limit the dose of basal insulin and to add prandial boluses of rapid analogues as soon as the glycaemic targets have not been reached with reasonable doses of a once-daily injection of a long-acting insulin analogue.

Adding preprandial insulin to basal insulin therapy

As stated previously, increasing the dose of long-acting insulin analogue indefinitely does not represent an appropriate therapeutic approach once the threshold daily dose has been achieved. For this reason, specific interventions targeting both fasting plasma glucose and postprandial glucose can provide an alternative by mimicking the complex daily pattern of physiological insulin secretion. Such intervention can result in tight glycaemic control with overall daily insulin doses that remain below 1 unit/kg/day, i.e. below the upper limit that commonly defines the insulin resistant state. When switching patients with type 2 diabetes from a long-acting basal insulin alone to basal insulin plus prandial insulin, it is important to simplify treatment regimens as much as possible in order to promote treatment adherence, but this should not be at the expense of glycaemic control. While intensive insulin therapy has been shown to be optimal in patients with type 1 diabetes, recent evidence has emerged showing that one major prandial glucose excursion occurs daily in patients with type 2 diabetes especially after breakfast, at mid-morning [30]. This suggests that adding a single daily prandial injection before the meal of the day that produces the largest postprandial glucose excursions may further improve glycaemic control in patients with type 2 diabetes.

The treat-to-target concept

An ideal insulin replacement therapy should mimic the physiological insulin secretion of normal individuals that occur in response to 24-hour fasting glucose levels and also post-absorptive and postprandial glucose profiles [31,32]. Under an ideal treat-to-target regimen in patients with type 2 diabetes, basal insulin would be titrated to specific targets, following which, in poorly controlled patients, prandial insulin will be added and titrated to specific targets. This would provide an individualized program of therapy for each patient with the aim of improving glycaemic control and reducing episodes of hypoglycaemia. The treat-to-target approach has been tested in overweight patients with inadequate glycaemic control (HbA1c > 7.5%), whose basal insulin was titrated to a target fasting plasma glucose value of ≤ 5.6 mmol/l (100 mg/dL). This treatment regimen successfully achieves glycaemic control (HbA1c < 6.5–7%) in approximately 60% of patients [21]. In the remaining 40%, a once-daily injection of a long-acting analogue fails to achieve these objectives. In these patients, two clinical situations can be identified: as mentioned above, the first one corresponds to those patients who exhibited very poor control at baseline, i.e. HbA1c > 9–10% prior to any insulin treatment. The second situation is related to patients who meet fasting glucose targets but who keep HbA1c levels within a range between 6.5 and 7.5%. In such patients it has been demonstrated that postprandial glucose excursions are the major contributor to overall hyperglycaemia [33]. In order to increase the percentage of patients who achieve both fasting and postprandial objectives and, consequently, HbA1c targets, it seems that the addition of boluses of rapid-acting analogues to basal insulin might represent an adequate therapeutic strategy. Various studies have been conducted where basal and both basal and bolus insulin [21-27,29,34,35,36] have been titrated to achieve blood glucose targets as defined by different associations [12-14].

The ADA provides recommendations on HbA1c levels and pre-prandial glycaemic goals, which are set within a
5.0–7.2 mmol/L (90–130 mg/dL) range [12]. The ADA recommendations also indicate that consideration of postprandial glucose excursions should be limited to patients who are not meeting HbA1c goals but who do not have postprandial glucose values within the recommended range. It is suggested that in these individuals, postprandial values (1–2 hours after the start of a meal) should be controlled so that average postprandial glucose values are < 10.0 mmol/L (< 180 mg/dL). Furthermore, by using a 4-point diurnal glycemic profile, we have observed that the glucose peaks after breakfast are higher than after lunch whatever the clinical and therapeutic status of the patient [30]. This indicates that postprandial glucose targets used for treat-to-target titration should be higher after breakfast, with suggested peak glucose values of < 10.0 mmol/L (< 180 mg/dL) at post breakfast time and < 7.8 mmol/L (< 140 mg/dL) at post lunch time [37]. However, it is difficult to define universal recommendations since they may vary between countries due to different eating practices [38,39].

Pre-mixed insulin

Twice-daily injection of pre-mixed insulin is commonly used, particularly in Europe. Use of pre-mixed insulin twice daily can sometimes be problematic since such insulin regimens do not provide an adequate physiological replacement of insulin in all patients, particularly in those who suffer from severe endogenous insulin deficiency. Furthermore, the inflexibility of dosing with pre-mixed insulin is one of the additional failures of such insulin preparations, since they do not allow individualized basal-bolus adjustments, which thus increases the difficulties associated with implementing treat-to-target regimens [34].

Separate administration of preprandial and basal insulin

The classic ‘basal-bolus’ regimen comprises basal insulin with a separate injection of preprandial insulin at each mealtime. This provides the most physiological insulin replacement strategy. However, patients may find the transition from basal insulin plus oral therapy directly to basal insulin plus three daily prandial insulin injections difficult. Patients may find this regimen of multiple injections more complex and there is an increased potential for non-compliance. More gradual transitioning to a prandial insulin may be more acceptable to patients with type 2 diabetes on a basal-prandial regimen; however, this should not be at the expense of glycaemic control. Incorporation of prandial insulin into a treatment regimen could begin with one prandial insulin injection per day before the meal that produces the largest postprandial glucose excursion. Further injections can be gradually introduced at other pre-meal times as required. This provides a “stepping stone” to intensive basal–bolus therapy. An ongoing trial named OSIRIS (Opposing Step-by-step Insulin Reinforcement to Intensified Strategy) is based on this stepwise approach of introducing bolus insulin, whilst taking into account that postprandial blood glucose excursions are not equivalent during the day. Patients with type 2 diabetes are to receive a single bolus dose of insulin glulisine at the time of their most hyperglycaemic meal, followed by a second and potentially third dose if they fail to achieve glycaemic control targets over time. This is to be compared with a standard basal-bolus regimen combining basal insulin with three bolus injections.

Flexibility of dosing around mealtimes

Through the 1990’s, regular human insulin (RHI), a short-acting form of human insulin, became the prandial insulin of choice; however, such preparations do not have an ideal pharmacokinetic profile for controlling postprandial excursions. Indeed, RHI administration is followed by an initial delay of 30 minutes, a peak in plasma insulin levels at 1–2 hours, with a return to basal levels taking 6–8 hours. Therefore, a key disadvantage of RHI is the requirement of administration 30–45 minutes prior to eating, which necessitates mealtime planning, can be restrictive for patients, and can lead to poor patient compliance. In one study evaluating the RHI injection-meal interval of diabetic patients, 62% of patients admitted to injecting their prandial insulin less than 15 minutes before a meal [40]. Furthermore, use of RHI is associated with patient variability as the onset of action of RHI after subcutaneous administration is influenced by the dose and concentration of RHI, the site and depth of injection, and subcutaneous blood flow [41]. For that reason, regular insulins are progressively being replaced by rapid-acting analogues. With the newer insulin preparations, the physiological prandial insulin response begins 10 minutes after the start of a meal, peaks at 60 minutes and returns to normal levels after 2–3 hours.

The insulin analogues insulin lispro (lispro [Lys B28, Pro B29]), insulin aspart (aspart [Asp B28]) and insulin glulisine (glulisine [Lys B3, Glu B29]) have several advantages over RHI. Studies have suggested that insulin analogues can provide better metabolic control but without an accompanying increase in risk of hypoglycaemia [42,43], and in some cases a reduction in hypoglycaemia, including severe hypoglycaemia [44,45]. Furthermore, the analogues have a lower tendency to form into hexamers, which results in a more rapid onset of action and shorter duration of action, thereby providing a more physiological prandial insulin replacement than RHI (table II) [46–48]. This allows patients to have greater flexibility in their eating patterns and encourages compliance since rapid-acting insulin analogues are usually administered immediately prior to a meal.
Table II

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Onset of action</th>
<th>Peak in activity</th>
<th>Duration of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analogues</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lispro</td>
<td>5 – 15 min</td>
<td>1 hour</td>
<td>4 – 5 hours</td>
</tr>
<tr>
<td>Aspart</td>
<td>5 – 15 min</td>
<td>1 hour</td>
<td>4 – 5 hours</td>
</tr>
<tr>
<td>Glulisine*</td>
<td>5 – 15 min</td>
<td>1 hour</td>
<td>4 – 5 hours</td>
</tr>
<tr>
<td>Human insulin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td>0.5 – 1 hours</td>
<td>2–4 hours</td>
<td>6 – 10 hours</td>
</tr>
</tbody>
</table>

*This analogue was recently approved in the USA and EU.

Conclusions

Rapid-acting insulins provide the most physiological form of postprandial insulin supplementation, and when added to basal insulin in patients with type 2 diabetes, can bring even relatively well controlled patients much closer to target. Therapy must be acceptable to patients but not at the expense of glycaemic control. Therefore, strategies which allow flexible dosing and gradual initiation of a rapid-acting insulin analogue to basal insulin therapy in patients with type 2 diabetes may achieve this as it is more acceptable to patients and could result in improved glycaemic control with relatively low doses of insulin over the day time. This would be a real advantage for preventing oesinsulinisation and thus an excess of weight gain i.e. the two consequences that are usually observed in insulin resistant patients with type 2 diabetes after initiation of insulin treatments following secondary failure of ongoing oral antidiabetic treatments.

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ERRATUM

In the Consensus and Guidelines section of issue n°6/2005 of Diabetes & Metabolism, the first name of Dr Schwarz was misspelled. On the cover and on the first page 606 of the article “Pre-diabetes essential action: a European perspective” it should read P Schwarz and not EH Schwarz. The correct reference is:

The editor asks the author to excuse this error due to technical problems in data transfer.