Intensifying Insulin Therapy in Type 2 Diabetes: Choices & Challenges

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Abstract
Insulin therapy remains the cornerstone of effective diabetes management. Timely intensification of insulin therapy reduces the progression of diabetes and the development of diabetes-related complications. Given that overall hyperglycaemia is a relative contribution of both fasting and postprandial hyperglycaemia, use of basal insulin alone may not achieve optimal glucose control due to its inability to cover postprandial glucose excursions. Intensifying therapy with addition of bolus insulin or switching to premixed insulin is a viable option in patients failing on basal alone therapy. Although the benefits of early insulin treatment are well established, a considerable delay in intensifying insulin therapy in patients with sub-optimal glycaemic control is still observed. Most of the patients and physicians are reluctant to intensify therapy due to the fear of hypoglycaemia, regimen complexity, and increased burden of multiple daily injections. In this context, there is a need for a flexible, alternative intensification option taking into account individual patient considerations to achieve or maintain individual glycaemic targets. An ideal insulin regimen should mimic physiological insulin release while providing optimal glycaemic control with low risk of hypoglycaemia, weight gain and fewer daily injections. The current paper reviews the challenges of insulin intensification in patients with type 2 diabetes mellitus poorly controlled on current treatment regimens.

Introduction

Diabetes is a global epidemic with rising prevalence worldwide. According to the International Diabetes Federation (IDF) there were an estimated 382 million people with diabetes worldwide in 2013 and this number is projected to increase to 592 million by the year 2035, an increase by 55% globally.¹ Figures from a recent Indian Council of Medical Research-India Diabetes (ICMR-INDIAB) study indicate that, in India, there are 62.4 million people with diabetes and 77.2 million with pre-diabetes condition.² The data above clearly suggests that, despite advances in the diagnosis and treatment, the burden of disease remains considerably high in patients with diabetes across the globe.

Diabetes: A Chronic, Progressively Deteriorating Condition

Diabetes is a complex metabolic disorder characterized by hyperglycaemia, arising from insulin resistance and progressive deterioration of beta-cell function.³ However, before clinically meaningful physiological changes manifest as a result of this hyperglycaemia, deterioration of beta-cell function reaches a pathologically advanced state. Data from United Kingdom Prospective Diabetes Study (UKPDS) indicates that by the time diabetes is diagnosed, the pancreatic beta-cell function drops to approximately 50% of normal and steadily declines at approximately 5% per year.⁴ Despite treatment interventions, glycaemic control continues to deteriorate over time suggesting that multiple interventions have to be used with disease progression.⁵,⁶ The beneficial effects of intensive therapy in good glycaemic control was demonstrated in the UKPDS which was a prospective, randomized trial that followed patients with type 2 diabetes mellitus (T2DM) who received either intensive therapy or conventional therapy over a 10-year follow-up period.⁷ The study suggests that intensive glycaemic control is associated with substantial reductions in the risk of both microvascular and macrovascular complications.⁷,⁸ Each 1% reduction in HbA1c is associated with a 37% reduction in microvascular complications, 14% reduction in myocardial infarction (MI), 21% reduction for any endpoint related to diabetes.
and 21% reduction of deaths related to diabetes.\(^7\) Regardless of the importance of tight glycaemic control, several studies have shown that a high proportion of patients who show risk factors for diabetes-related complications do not have an adequately controlled disease.\(^9\)

Inadequate self-management, sub-optimal adherence to treatment regimens and ineffective utilization of existing pharmacotherapies were cited to be the most common difficulties in achieving the desired glycated haemoglobin (HbA1c) levels by patients.\(^10,11\) Therefore early identification and initiation of treatment may be looked in as a basic strategy to achieve optimal glycaemic control in patients with diabetes.

Because of the natural progression of T2DM, most patients will eventually require insulin. Insulin therapy when used in appropriate doses has the potential to achieve glycaemic control.\(^12\) Timely initiation of insulin can help reverse glucotoxicity and preserve \(\beta\)-cell function for longer than is possible with oral anti-diabetic drugs (OADs) alone.\(^13\) Indeed, increasing evidence suggests that aggressive lowering of glycaemia with insulin therapy in newly diagnosed patients can result in prolonged endogenous insulin secretion and better metabolic control. In T2DM patients after 1 year treatment with insulin, \(\beta\)-cell function was better preserved with increased glucagon-stimulated C-peptide response compared to OADs.\(^14\) Despite the observed benefits of insulin therapy in providing better glycaemic control; often patients and physicians are reluctant to initiate insulin therapy. Concerns regarding weight gain, risk of hypoglycaemia and fear of injections hamper early initiation of insulin therapy in these patients.\(^15\) Furthermore, they require frequent monitoring and are restricted by inconvenient multiple daily injections (MDIs) and lack of flexibility in dosing, prompting patients and physicians to delay initiation and intensification of insulin therapy.\(^16\) The current article reviews the guidelines on initiation and intensification of mealtime insulin and the challenges of insulin intensification in patients with T2DM.

**Insulin Therapy in Diabetes**

Patients with type 1 diabetes mellitus (T1DM) require exogenous insulin replacement from the time of diagnosis whereas patients with T2DM eventually need insulin therapy after the failure of OAD therapy to achieve and maintain glycaemic control.\(^11\) The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) advocate early use of insulin in T2DM patients with poor glycaemic control.\(^11\) In patients with uncontrolled hyperglycaemia using OADs, addition of basal insulin with or without OADs is recommended.\(^11\) Basal insulin provides continuous uniform level of insulin coverage, to regulate glycaemic levels by suppressing excessive glucose production between meals and during sleep. It is also estimated that more than half of people with type 2 diabetes on basal insulin do not achieve target HbA1c.\(^17\) To achieve the HbA1c control, it is required to control both fasting and post-prandial glucose levels, which is also recommended by IDF guidelines.\(^18\) Therefore to counter the progressive decline of glycaemic control, intensification of existing insulin therapy with the addition of glucagon-like peptide-1 (GLP-1) receptor agonist (GLP-1 RA) or mealtime insulin once daily (basal-plus regimen) or switching to pre-mixed insulin twice daily is recommended as the first step of insulin intensification. If blood glucose is still uncontrolled, standard basal-bolus therapy is required (Figure 1).\(^11,19,20\)

**Guidelines for Insulin Initiation and Mealtime Insulin Intensification**

Data from several landmark studies including UKPDS and Diabetes Control and Complications Trial (DCCT), suggests that aggressive management of diabetes and its associated risk factors will lead to a reduction in long-term complications associated with diabetes.\(^8,21\) Intensive insulin therapy can have long-lasting
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Table 1: Summary on the existing guidelines on insulin initiation and intensification

<table>
<thead>
<tr>
<th>Origin</th>
<th>HbA1c targets</th>
<th>FPG targets</th>
<th>PPG targets</th>
<th>Insulin initiation</th>
<th>Insulin intensification</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA/EASD</td>
<td>&lt; 7.0%</td>
<td>&lt; 130 mg/dL</td>
<td>&lt; 180 mg/dL</td>
<td>IA or LA basal</td>
<td>Basal-bolus, Sequential addition of rapid acting analogue or premix</td>
</tr>
<tr>
<td>IDF</td>
<td>&lt; 7.0%</td>
<td>&lt; 115 mg/dL</td>
<td>&lt; 160 mg/dL</td>
<td>LA basal or NPH or BID pre-mix</td>
<td>Multiple daily injections (mealtime and basal)</td>
</tr>
<tr>
<td>AACE/ACE</td>
<td>&lt; 6.5%</td>
<td>&lt; 110 mg/dL</td>
<td>&lt; 140 mg/dL</td>
<td>Basal, premix or basal-bolus. Add Insulin to OADs A1c ≥ 8.5-9.0%</td>
<td>No clear guidance on intensification. T2DMs</td>
</tr>
<tr>
<td>NICE</td>
<td>&lt; 6.5%</td>
<td>n/a</td>
<td>n/a</td>
<td>IA/NPH or premix OD or BID</td>
<td>From basal to BID premix or basal-bolus; or from BID premix to basal-bolus</td>
</tr>
<tr>
<td>CDA</td>
<td>≤ 7.0%</td>
<td>4.0–7.0 mmol/L</td>
<td>5.0–10.0 mmol/L</td>
<td>IA or LA basal</td>
<td>To basal-bolus</td>
</tr>
</tbody>
</table>


Table 1 summarizes different guidelines on glycaemic targets and insulin intensification.

**Mealtime Insulin Intensification**

Insulin intensification is essential to minimize patient’s exposure to chronic hyperglycaemia albeit not exacerbating the risk of hypoglycaemia, while achieving individualized fasting, postprandial, and HbA1c targets. Overall glycaemic control (or HbA1c level) is contributed by both fasting plasma glucose.
(FPG), addressed by basal insulin, and postprandial glucose (PG) addressed by prandial insulin. Simply increasing basal insulin dose may still result in inadequate glycaemic control because the mealtime insulin response remains uncovered exposing the patient to high PPG levels after every meal. Moreover, if a meal is missed affecting the inter-meal insulin levels, the patient may have a risk of hypoglycaemia (Figure 2). 28 Therefore, PPG control should be covered either by using premixed insulin analogues which provides both basal and mealtime insulin coverage or basal-plus/bolus therapy i.e. addition of prandial insulin to basal insulin dose at mealtime instead of increasing basal insulin dose.

One of the options for prandial coverage is the basal-plus regimen involving addition of a pre-meal rapid-acting insulin analogue to ongoing basal insulin. Therefore addition of a prandial insulin injection before the meal to counter postprandial glycaemic excursions is a logical first step in progressing insulin therapy. This approach allows more gradual intensification of insulin therapy to full basal-bolus therapy if glycaemic targets are not achieved. In a study by Davidson et al., patients uncontrolled on basal insulin alone were randomized to receive rapid-acting insulin once, twice or three times daily. The study reported non-inferior reductions in HbA1c with once or twice daily rapid-acting insulin to 3 times daily (95% CI: -0.39; 0.36 and -0.30; 0.43, p > 0.5 for both). However, more patients met the target HbA1c with 3 pre-prandial injections (46%) than with 2 injections (33%) or 1 injection (30%). 29 Similarly, when stepwise addition of bolus insulin was compared with full basal-bolus regimen in patients with T2DM inadequately controlled on basal insulin and OADs, non-inferiority of stepwise regimen to full basal-bolus regimen in glycaemic control was observed after 32 weeks (HbA1c mean treatment difference = 0.14 [95% CI: -0.02; 0.30], p = 0.0876). 30 In a study on treatment intensification, stepwise addition of bolus insulin (insulin aspart) either with largest meal (SimpleSTEP) or meal with the largest prandial glucose increment (ExtraSTEP) to patients inadequately controlled on once daily basal insulin (insulin detemir) and OADs was associated with a significant reduction in HbA1c (approximately 1.2% in both groups). 31

Premixed insulin is also an alternative option for insulin intensification to achieve or maintain glycaemic targets over time. A retrospective, observational study compared treatment intensification with insulin glargine + rapid-acting insulin (basal-bolus regimen) or switching to premixed insulin in T2DM patients uncontrolled on basal insulin glargine. 32 The study reported intensification with basal-bolus or premixed insulin was similar in HbA1c reduction from baseline (basal–bolus −0.79%, premixed −0.71%; p = 0.6455), proportion of patients achieving HbA1c target of <7.0% (15.5 and 13.7%, respectively, p = 0.5956) and the incidence of hypoglycaemia events (21 and 35 events/100 patient-years, respectively, p = 0.2033). 32

**Barriers for Intensification**

Reports from real life data (based on UK THIN database) that evaluated treatment patterns in T2DM patients receiving basal insulin therapy indicated that a large proportion of patients (59.8%) remained on basal insulin through a 2.9 year follow-up period despite higher HbA1c levels. 33 In patients who changed therapy, the reasons for intensification/switch included increasing HbA1c values and longer duration of diabetes, indicating a gap between clinical need and insulin intensification in real-world clinical practice. 33 Although the benefits of early insulin use in maintaining glycaemic control are well established, there are barriers to timely intensification of treatment for both physicians and patients with diabetes. 35,36

Most patients are reluctant to intensify insulin regimen as they are often limited by lower flexibility in dosing, as seen with premixed insulins or burden of MDIs perceived with basal-bolus regimens. 37,38 Moreover these regimens require frequent SMBG (as with basal-bolus regimen) or adherence to a consistent meal schedule (as with premixed insulin regimen). 19

Hypoglycaemic symptoms in patients are reported to be associated with lower treatment satisfaction, insulin adherence and health related quality of life. 39,40 Aggressive glycaemic control also increases the risk of hypoglycaemia, which increases patient’s anxiety and fear for the treatment. 20 An observational study reported that fear of hypoglycaemic episodes (severe: 58%, mild or moderate: 43%) lead to modification of prescribed insulin dose by T2DM patients. 41 Needle phobia or injection-related anxieties affect patient compliance to insulin treatment resulting in poor glycaemic control. 42,43 Fear of hypoglycaemia restricts the physician also in insulin intensification. Physicians (> 70%) reported that they would treat patients more aggressively if there were no concerns of hypoglycaemia with insulin therapy. 44

Pain and inconvenience associated with MDIs and SMBG also contribute to non-adherence to insulin regimen. 45,46 MDIs along with the frequency of insulin administration are considered quite burdensome for patients treated with insulin. 47,48 Physicians also
delay intensification of insulin therapy based on perceived inconvenience, pain and weight gain of their patients.48-51 Another perceived burden of insulin therapy for a patient is to plan life around the number of injections to be administered which may interfere with his/her daily life activities.52

For most patients with diabetes from India, physicians play an important role in managing T2DM by intensifying insulin regimens. Though most physicians believe that insulin is the most effective agent in achieving glycaemic goals in patients with T2DM, there is notable reluctance among physicians, specifically primary care physicians (PCPs) in timely intensification of insulin therapy in these patients.53 Similarly, patients are concerned about the hypoglycaemic risk, weight gain, and needle pain with insulin therapy.52,54 Most of the physicians (98%) believe that insulin intensification is essential in maintaining the target glycaemic control in patients with T2DM and > 76% agreed that once the patients learn to intensify insulin they will start using the therapy.53 While 30% of PCPs never/rarely intensify insulin, compared to 4% of specialists (p < 0.0001), the MODIFY study demonstrated that lack of experience (49%) and lack of time to educate patients (49%) are the main barriers faced by physicians in the intensification of insulin. It was also observed that physicians have a misconception that patients would not cope-up with insulin intensification.55 This kind of misconception may be discouraging for an Indian patient with diabetes, who solely depends on physician’s advice on insulin intensification. Low knowledge on diabetes management and low rate of physician recommendations influence the use of self-monitoring devices by patients with diabetes.56 Taken together, all these physician barriers contribute to delay in insulin initiation and intensification, leading to poor glycaemic control and development of complications in patients with T2DM.

Conclusion

Early initiation and intensification of insulin prevents prolonged exposure to hyperglycaemia and reduces the risk of associated complications. An ideal regimen attempts to mimic physiological, both basal and postprandial insulin secretion facilitating in the achievement and sustaining of good glycaemic control. As recommended by several guidelines, insulin therapy is initiated with basal insulin or premixed insulin and intensified with addition of bolus insulin or switching to premixed insulin when glycaemic targets are not achieved with optimal doses of basal insulin. While insulin therapy is the cornerstone for effective management of diabetes, several patient and physician related barriers such as fear of hypoglycaemia, weight gain, inflexibility in dosing and burden of MDIs have hampered the initiation and/or intensification of insulin therapy to achieve desired glycaemic targets. In light of this, there is a demand for a flexible, alternative treatment intensification option taking individual patients into consideration to achieve glycaemic control and overcome barriers related to MDIs of insulin with reduced number of daily injections, low risk of hypoglycaemia and with less consequences of delayed or missed insulin dose.

References


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