Consensus Evidence-based Guidelines for Insulin Initiation, Optimization and Continuation in Type 2 Diabetes Mellitus

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Abstract
The prevalence of diabetes continues to increase despite advances in detection and therapy. Majority of the patients fail to achieve desired glycaemic targets even with maximal tolerated doses of oral anti-hyperglycaemic drugs, necessitating insulin therapy. Although, much attention has been given to early insulin initiation, yet substantial proportion of patients do not achieve glycaemic targets as they fail to initiate or intensify insulin therapy at the appropriate time. The choice of an insulin regimen and timely initiation and intensification of insulin therapy are key factors in achieving optimal glycaemic control. This current consensus guideline developed by a panel of experts aims to provide specific recommendations based on existing guidelines and published data on initiation and intensification of insulin therapy in management of type 2 diabetes mellitus (T2DM) using basal, premixed and basal-bolus insulin regimens in Indian clinical practice. The panel recognized the need to upgrade the existing guidelines for management of T2DM and endorsed recommendations that are in line with Indian insulin guidelines.

Introduction
Type 2 diabetes mellitus (T2DM) is characterized by progressive loss of insulin secretion from β-cells and increasing insulin resistance driven by obesity. It is estimated that, by the time diagnosis is done, most patients with T2DM had lost more than 50% of their β-cell function which steadily continues to decline at approximately 3-5% per year. Overtime, even with multiple oral anti-diabetic drugs (OADs) patients fail to achieve or maintain glycated haemoglobin (HbA1c) levels. However, accumulating evidence suggests that the decline in β-cell function may be slowed or even reversed, particularly if addressed early in the course of the disease. Nevertheless, the prevalence of diabetes continues to increase despite advances in detection and therapy.

Prevalence of diabetes: Global and India
According to recent estimates from International Diabetes Federation (IDF), approximately 382 million people worldwide in the 20-79 year age group had diabetes mellitus (DM) in 2013 and by 2035 this number is going to increase to approximately 592 million (7.8%). DM is a major health concern in Asian countries with more than 60% of the world’s diabetic population living in Asia. Prevalence of DM and impaired glucose tolerance is high for all Asian countries and is expected to increase further in the next two decades. According to IDF, 65.1 million Indians are affected by diabetes making them the second largest population in the world; this number is expected to reach 109 million by year 2015. New figures from a recent Indian Council of Medical Research-India Diabetes (ICMR-INDIAB) study indicate that there are already 62.4 million people with diabetes and 77.2 million people with pre-diabetes. The prevalence of diabetes varies from 9% to 16.6% in different regions, with higher prevalence rates in the southern region of India. Studies over the period 1990-2000, indicate a rising trend in diabetes from 5% to 15% and 2% to 5% among urban and rural populations, respectively.

T2DM: Need for insulin
Glycaemic control is the cornerstone of the management of T2DM. Generally comprehensive lifestyle management combined with metformin monotherapy is the recommended initial therapy for patients with T2DM. However, majority of patients (>50%) fail to achieve target glucose levels even with maximal doses of monotherapy, requiring intensification of therapy by addition of one or more pharmacological agents including insulin. When intensifying the existing therapy, physicians need to elucidate the role of beta cells in insulin secretion to the patients newly diagnosed with diabetes and convince them for intensive insulin therapy. Besides, physician should also consider patient-related issues such as previous co-morbidities, presence of uncontrolled symptomatic hypoglycaemia and obesity while prescribing insulin.

Existing guidelines for T2DM
Several international, national and regional guidelines are available for diabetes management to facilitate physicians and patients by providing step-wise treatment algorithm for management of T2DM. They include American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD), American Association of Clinical Endocrinologist (AACE), National Institute of Clinical Excellence (NICE), International Diabetes Federation (IDF) and Indian National Consensus Group (INCG) guidelines. Although, the recommended glycaemic target varies somewhat among the guidelines, the overall aim is to guide physicians in identifying components of diabetes care, general treatment goals, and tools to evaluate the quality of care. Based on results from large randomized trials, most of the guidelines emphasise on aggressive management of diabetes and associated risk factors for prognosis in T2DM.

Rationale/need for India specific guidelines
Despite evidences supporting the early initiation of insulin to achieve optimal glycaemic control, yet substantial proportion of patients do not achieve glycaemic targets as they fail to intensify insulin therapy. Many patients and physicians are...
reducing reluctance to begin insulin treatment owing to significant concerns about weight gain, hypoglycaemia and changes in lifestyle. Although several guidelines have been published for the management of T2DM, due to confounding biases and non-applicability of these guidelines in Indian scenario, these cannot be widely used in Indian clinical practice. This current consensus guideline aims to provide specific recommendations based on published data for proper management of T2DM and justified for use according to routine Indian clinical practice.

Methodology

A systematic review of literature from medical databases was conducted to provide the best possible evidence base for the recommendations. Existing guidelines, meta-analyses, systematic reviews and key cited articles relating to the medical condition were reviewed by a group of doctors and recommendations relevant to Indian scenario were framed. The recommendations were discussed at the National Insulin Summit, held in August 2013 by an expert panel of physicians, endocrinologists and key opinion leaders. At this summit, recommendations for each section of the guidelines, and overall recommendations were agreed upon. Where there was little or no evidence, the committee relied on experience, judgement and consensus to make their recommendations. The consensus document was drafted and circulated for further feedback from the participants and others who could not attend.

Grading system

The current consensus guidelines have been developed in accordance to the AACe protocol for standardized production of clinical practice guidelines. Recommendations are organized by topic and are assigned evidence level (EL) ratings on the basis of the quality of supporting evidence all of which have also been rated for strength. Recommendations are based on clinical importance and graded as A (strongly recommend), B (intermediate), C (weak) and D (not evidence based), those are coupled by four intuitive levels of evidence: 1, 2, 3, 4. The evidence levels have been positioned on the basis of available evidence to be used for grading recommendations as follows:

- “1”: Meta-analysis of randomized controlled trials, randomised controlled trials
- “2”: Meta-analysis of nonrandomized prospective or case-controlled trials, nonrandomised controlled trial, prospective cohort study, retrospective case-control study
- “3”: Cross-sectional study, surveillance study (registries, surveys, epidemiologic study, retrospective chart review, mathematical modelling of database), consecutive case series, single case reports
- “4”: No evidence (theory, opinion, consensus, review, or preclinical study)

Insulin Therapy in T2DM

Traditionally, insulin treatment for T2DM is usually started when the initial oral therapy, in double or triple combination and at the maximum tolerated doses fails to achieve optimal glycaemic control. However, recent guidelines recommend initiation of insulin early in the course of disease, especially in patients with HbA1c > 9% as it is unlikely to achieve glycaemic targets with the use of oral agents alone. Data from a recent meta-analysis indicate that, short-term intensive insulin therapy for 2-3 weeks have favourable outcomes on recovery and maintenance of beta-cell function and protracted glycaemic remission, besides increment in HOMA-B (β-cell function) and decrease in HOMA-IR (insulin resistance) improving the underlying pathophysiology in early T2DM. While baseline body mass index and fasting plasma glucose (FPG) were considered to be important clinical predictors to identify these patients. The current consensus recommendations are in line with ADA/EASD and IDF guidelines for insulin management in T2DM.

Recommendations

- It is recommended to initiate insulin when HbA1c is more than 9% even after treatment with maximum tolerated dose of two or three OADs (Grade A; EL 4).
- In newly diagnosed T2DM patients with higher body mass index and lower FPG, short-term intensive insulin therapy for 2-3 weeks is recommended for favourable outcomes on recovery and maintenance of beta-cell function and protracted glycaemic remission (Grade A; EL 1).

Initiation of insulin therapy-general strategy

Timely initiation of insulin therapy is crucial for optimal glycaemic control and improved patient outcomes. Although most physicians agree that insulin is an effective approach in treating diabetes, many still consider it a last resort due to the fear of hypoglycaemia and weight gain to their patients. The choice of insulin regimen depends on several factors such as type of diabetes, duration of diabetes, baseline and current HbA1c levels, age, existing comorbidities, ability to adhere to medical instructions, number of injections, hypoglycaemia, weight gain and frequency of monitoring.

Both AACE/ACE and ADA/EASD guidelines recommend initiating insulin therapy with basal insulin. The general concept is to first correct the fasting hyperglycaemia with one injection of basal insulin, and then address postprandial hyperglycaemia, if needed, with other insulin options. Similarly, IDF recommends initiation of insulin with either basal insulin or premixed insulin when first line and second-line therapies fail to achieve glycaemic target of HbA1c < 7.0%. INCG guidelines suggest initiation of insulin therapy with premixed insulin in newly diagnosed patients with FPG values > 150 mg/dL, PPG values > 200 mg/dL and HbA1c > 8.5%.

Recommendations

- Both premixed insulin and basal insulin can be considered as a start insulin in patients with T2DM (Grade A; EL 1).
- When FPG is high consider initiating insulin therapy with basal insulin.
- When both FPG and PPG are high consider initiating insulin therapy with premixed insulin.

Better PPG control in insulin-naïve Asian subjects

In India, premixed insulin is the preferred mode of initiating and intensifying therapy as recommended in the Indian premix guidelines. Studies indicate that PPG is higher among Asians in response to a realistic carbohydrate load compared to Caucasians, even in patients with low body mass index. Given that elevated PPG levels are a substantial contributor to daytime hyperglycaemia, targeting PPG control becomes crucial in achieving optimal glycaemic control. Evidence suggests that in insulin-naïve Asian subjects with T2DM inadequately controlled with OADs, once-daily premixed insulin achieved better glycaemic control compared to basal insulin. Mean self-monitoring of blood glucose (SMBG) at bedtime was significantly lower with premixed insulin than basal insulin.
In T2DM patients initiating insulin therapy with premixed recommendations are in line with inCG guidelines. Compared to human premixed insulin, the current consensus control, reduced risk of hypoglycaemia and weight gain. The current consensus recommendations are in line with INCG guidelines.

**Recommendations**

- In T2DM patients initiating insulin therapy with premixed analogue insulin than premixed human insulin is recommended for low risk of hypoglycaemia (Grade A; EL 1). Moreover, premixed insulins have been shown to be superior in decreasing PPG with an added advantage of lower risk of hypoglycaemia and greater treatment satisfaction compared to human premixed insulin. The current consensus recommendations are in line with INCG guidelines.

**Initiation with basal insulin therapy**

In clinical practice, the most popular scheme for starting insulin therapy in T2DM is the addition of once daily (OD) basal insulin to the oral therapy. Evidences indicate several benefits to using basal insulin analogues (insulin detemir and insulin glargine) over intermediate-acting human insulin (neutral protamine Hagedorn (NPH) including better glycaemic control, reduced risk of hypoglycaemia and weight gain. Moreover basal insulin analogues have been associated with lower within-patient pharmacokinetic properties of insulin degludec are preserved in subjects with renal impairment and hepatic impairment.

Insulin degludec can be administered anytime in the day and is recommended as once daily basal insulin analogue. Insulin degludec is a flat and stable glucose-lowering profile and nocturnal hypoglycaemia was reduced by 55% (P < 0.001) with basal analogue insulin compared to basal human insulin. Insulin degludec is a new basal insulin analogue with a unique mode of protraction by forming multi hexamers in subcutaneous space. It has a flat and stable glucose-lowering effect making it an ultra-long acting basal insulin analogue with half-life of more than 25 hours (twice as long as that for insulin glargine) and duration of action beyond 42 hours. Insulin degludec has a more consistent and evenly distributed metabolic effect across a 24-hour dosing interval than insulin glargine. Moreover, its day-to-day variability is considerably lower than insulin glargine (up to four times). The ultra-long pharmacokinetic properties of insulin degludec are preserved in subjects with renal impairment and hepatic impairment.

Most of the guidelines including IDF, ADA/EASD, NICE and Chinese Diabetes Society, recommend initiation of insulin therapy with basal insulin. The current consensus recommendations are in line with IDF, ADA/EASD, NICE guidelines for initiation of basal insulin therapy.

**Intensification of Insulin Therapy**

The traditional approach of hyperglycaemia management follows the sequence of lifestyle modification, monotherapy, combination therapy with OADs, and finally treatment with insulin. This results in recurrent failure glycemic control in patients with T2DM due to the substantial glycaemic burden carried for years, before therapy is intensified (Figure 1). Thus, it is prudent to choose interventions that effectively lower hyperglycaemia and keep glycaemic levels as near to normal as possible. At this point, insulin supplementation is required in order to achieve glycaemic control.

**Existing guidelines on intensification**

Several guidelines including ADA, EASD, IDF, AACE, NICE and INCG recommend insulin intensification for the treatment of diabetes to facilitate good glycaemic control. Patients initiated on basal insulin may be intensified to either basal-bolus therapy or premixed insulin BID. Similarly those initiated on OD premix insulin therapy may be intensified to BID or TID, which may be an intensified to basal-bolus therapy (Figure 2).

**Intensification with basal-bolus therapy**

Although initiating basal insulin in T2DM patients results in significant improvement in glycaemic control, therapy eventually needs to be intensified with the addition of prandial insulin to achieve desired glycaemic control. Randomized clinical trials investigating the efficacy of basal-bolus regimen have reported significant improvement in HbA1c, less weight gain, lower rates of hypoglycaemia and less within-person variation in blood glucose than basal human insulin or all human basal-bolus regimen.

In a study comparing efficacy and safety of all analogue versus all human basal-bolus therapy in T2DM patients, despite similar reduction in HbA1c (0.65% and 0.58% respectively), the
basal-bolus analogue regimen was associated with a significantly lower within-person variation in self-measured fasting plasma glucose (FPG) (SD: 1.20 versus 1.54 mmol/L, P < 0.001) and lower body weight gain (0.51 versus 1.13 kg, p = 0.038) than with all human basal-bolus regimen. The risk of nocturnal hypoglycaemia was 38% lower with all analogue basal-bolus regimen than with all human basal-bolus regimen. The current consensus recommendations are in line with ADA/EASD guidelines and published data from clinical trials.

**Recommendations**

- All analogue basal-bolus regimen may be considered as all human basal-bolus regimen for similar reduction in HbA1c with reduced risk of nocturnal hypoglycaemia, less weight gain and lower day-to-day within-person variability in FPG (Grade A; EL 1).

**Table 1: Titration Algorithm for BIAsp 30 based on FPG values**

<table>
<thead>
<tr>
<th>FPG values</th>
<th>Dose change</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4.4 mmol/L</td>
<td>&lt; 80 mg/dL</td>
</tr>
<tr>
<td>4.4–6.1 mmol/L</td>
<td>80–110 mg/dL</td>
</tr>
<tr>
<td>6.2–7.8 mmol/L</td>
<td>111–140 mg/dL</td>
</tr>
<tr>
<td>7.9–10.0 mmol/L</td>
<td>141–180 mg/dL</td>
</tr>
<tr>
<td>&gt; 10.0 mmol/L</td>
<td>&gt; 180 mg/dL</td>
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</tbody>
</table>

**Table 2: Comparison of recommendations from current consensus guidelines and existing guidelines**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AACE</th>
<th>ADA/EASD</th>
<th>IDF</th>
<th>NICE</th>
<th>INCG</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glycaemic targets</strong></td>
<td>HbA1c &lt; 9.0</td>
<td>HbA1c ≤ 6.5</td>
<td>HbA1c ≤ 7.0</td>
<td>HbA1c ≤ 7.0</td>
<td>HbA1c ≤ 7.0</td>
</tr>
<tr>
<td>FPG: &lt; 110 mg/dL</td>
<td>FPG: &lt; 110 mg/dL</td>
<td>FPG: 70–130 mg/dL</td>
<td>FPG: &lt; 115 mg/dL</td>
<td>FPG: &lt; 110 mg/dL</td>
<td></td>
</tr>
<tr>
<td>PPG: &lt; 180 mg/dL</td>
<td>PPG: &lt; 140 mg/dL</td>
<td>PPG: &lt; 180 mg/dL</td>
<td>PPG: &lt; 160 mg/dL</td>
<td>PPG: &lt; 180 mg/dL</td>
<td></td>
</tr>
</tbody>
</table>

**Initiation with basal insulin therapy**

- When FPG is high (> 150 mg/dL), consider initiation with basal analogue insulin.
- When HbA1c ≤ 8.0% initiate OD at 0.1–0.2 U/kg body weight; When HbA1c 8–10% initiate at 0.2–0.3 U/kg body weight and based on degree of hyperglycaemia initiate at 0.1–0.2 U/kg body weight.

**Initiation with premixed insulin therapy**

- When both FPG and PPG are high (> 150 mg/dL and > 200 mg/dL respectively), initiate in patients requiring simpler regimen or finding difficulty with basal-bolus therapy.
- Intensify basal or premixed insulin therapy to basal-bolus therapy; Consider prandial insulin when PPG is high.

**Intensification with basal-bolus therapy**

- Consider all analogue basal-bolus regimen; Regular SMBG levels 2 hours after meals is recommended.
- Intensify from OD to BID/TID; Split the OD dose into equal breakfast and dinner doses (50:50); when intensifying BID to TID up titrate lunch dose and down titrate morning dose.
- No recommendation available.

**Intensification with premixed insulin therapy**

- Intensify from OD to BID/TID; Split the OD dose into equal breakfast and dinner doses (50:50); when intensifying BID to TID up titrate lunch dose and down titrate morning dose.
- Intensify therapy if already using premixed insulin from OD to BID or from BID to TID.
- Intensify from OD to BID, when HbA1c > 8.5%.
  - If HbA1c > 7% and FPG > 100 mg/dL, titrate from OD to BID till FPG levels < 100 mg/dL.

**Abbreviations**: ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes; AACE, American Association of Clinical Endocrinologist; IDF, International Diabetes Federation; NICE, National Institute of Clinical Excellence; INCG, Indian National Consensus Group; HbA1c, Glycosylated haemoglobin; FPG, Fasting plasma glucose; PPG, Postprandial plasma glucose; OD: Once daily; BID: Twice daily; TID: Thrice daily; SMBG, self-monitoring of blood glucose.
insulin OD or BID for the need of short-acting insulin before meals or change to a regimen of mealtime plus basal insulin, if blood glucose control remains inadequate.\(^4^4\)

INCG guidelines recommend titration of premixed insulin therapy from OD to BID, if HbA1c > 8.5%.\(^2^7\) Similarly, if a patient on premixed insulin (OD or BID) has within-target pre-meal blood glucose but HbA1c > 7%, intensification of premixed insulin to BID or TID should be considered.\(^4^5\) When the total daily dose of insulin in an OD regimen exceeds 20 U, the regimen should be intensified to BID such that the dose is distributed as two thirds in morning and one third in evening. However when the single dose exceeds 30 units, the dose can be split into two equal doses, which reduces the chance of hypoglycaemia.\(^4^6\) The current consensus recommendations are in line with INCG guidelines.

**Recommendations**

- When intensifying premixed insulin therapy from OD to BID, it is recommended to split the OD dose into equal pre breakfast and pre dinner doses when total insulin dose crosses 30 units (50:50) and doses titrated as per the algorithm given in Table 1 (Grade A; EL 4).\(^4^5\)
- When intensifying premixed insulin from BID to TID, consider adding 2–6 U or 10% of total daily BIAsp 30 dose before lunch which may require down titration of morning dose (-2 to 4 U) (Grade A; EL 4).\(^4^5\)

**Premixed insulin vs. basal plus therapy**

Clinical evidences indicate that modern insulin analogue regimens, adjusted to post prandial glucose targets, enable a majority of people with T2DM to reach HbA1c ≤ 7.0% after failure of OADs and OAD-basal insulin therapy.\(^5^7\) Data from a 24-week, open-label, multinational, superiority trial comparing basal plus vs. premixed insulin in 923 insulin-naïve T2DM patients uncontrolled on OADs suggest that more number of patients treated with premix insulin achieved superior HbA1c reduction from baseline (P = 0.008), superior mean plasma glucose reduction from baseline (P = 0.024) and more patients reached HbA1c < 7% compared to basal plus therapy (27.9% vs. 19.3%).\(^3^8\)

**Recommendations**

- In insulin-naïve patients with T2DM, premixed insulin regimen twice daily may be considered similar to basal plus regimen to achieve target HbA1c (≤ 7%) without the risk of hypoglycaemia (Grade A; EL 1).\(^3^8\)

**Summary**

T2DM is a chronic condition, which requires proactive escalation of therapy, including early advancement to combination therapy and/or insulin use. The choice of an insulin regimen and the timing of initiation and optimization of insulin therapy are key factors in achieving optimal glycaemic control. Several simple and practical algorithms are available to guide patients and physicians through a step-by-step process of initiating and advancing insulin therapy. However, practical considerations involved with initiation and optimization of insulin therapy have to be more carefully dealt to achieve glycaemic goals without the risk of hypoglycaemia and weight gain. Based on the best clinical observations and recommendations from existing guidelines and protocols for insulin therapy in T2DM, the current consensus recommendations have been developed which are summarized in Table 2.

**Proposed Algorithm for Initiation and Intensification of Insulin Therapy in Patients with Type 2 Diabetes Mellitus**

Based on the consensus guidelines developed for initiation and intensification of insulin therapy in patients with type 2 diabetes mellitus, an algorithm has been proposed (Figure 3).

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**References**


