Consensus statement on Choice of Insulin Therapy in Type 2 diabetes

Jothydev Kesavadev¹, Rajesh Rajput², Mathew John³, Anand Kumar Annamalai⁴, PV Rao⁵

Abstract

Type 2 diabetes has reached epidemic proportions and is a major public health problem affecting all classes of the societies. Tight glycaemic control is the need of the hour to prevent complications of diabetes, although many options are available for the same, insulins occupies the key therapeutic option for optimal glycaemic control.

The aim of this consensus group convened during the National Insulin Summit 2015, Puducherry, was to focus on the choice of insulin therapy for the optimal glycaemic control. The choice of insulin varies from physician to physician and different types of insulins like, premix, basal and prandial are available to choose from. Many organizations have provided guidelines and recommendations for initiation and intensification of insulin therapy. Scientific published literature and major clinical guidelines were reviewed and summarized. The choice of insulin therapy for initiation and intensification options was discussed in the consensus meeting. Consensus recommendations have been drafted for choice of insulin therapy for initiation and intensification. These can aid clinicians in choosing the appropriate insulin therapy for managing patients with type 2 diabetes.

Background/Introduction

Type 2 diabetes has grown in epidemic proportion in the last decade. The trends for the future, both for India and the world as a whole, are alarming. Achieving tight glycaemic goals can help reduce diabetes related mortality and morbidity. The effective management of hyperglycaemia has therefore attained top priority in the overall disease management.

Current evidence supports the fact that maintaining glycaemic targets close to normal has demonstrated beneficial effects on micro- and macro-vascular disease in a setting of type 1 and type 2 diabetes. It is also now clearly proven that tight glycaemic control early in the natural history of disease can have lasting benefits on both micro- and macro-vascular complications, famously termed as “metabolic memory” or “Legacy effect”.¹

Available antidiabetic drugs include insulin as the most potent injectable therapy. Insulin is the oldest of the currently available treatment options in type 2 diabetes.² When used adequately, insulin is the most effective glucose lowering agent (Figure 1). The introduction of modern insulin analogues has also contributed to further improvements in patient outcomes with better glucose control and convenience to patients and lower risk of hypoglycaemia. Table 1 summarizes the list of insulins currently available for the management of diabetes.³

However, despite the benefits, market surveys show that only about 33000 physicians prescribe insulin and as compared to more than a lakh prescribers of OADs.⁴,⁵

In order to facilitate and draw the attention of physician community towards optimal deployment of insulin therapies in routine care of type 2 diabetes, a group of experts from across India held a consensus meeting at National Insulin Summit (NIS), November 2015. The objectives of the meeting were to: 1. identify

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<table>
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<tr>
<th>Insulin</th>
<th>Onset of action (h or Min)</th>
<th>Peak action (h or min)</th>
<th>Duration (h)</th>
<th>Comments</th>
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<tbody>
<tr>
<td>NPH</td>
<td>1.5</td>
<td>4.0-12</td>
<td>24</td>
<td>Greater nocturnal hypoglycaemia risk compared with other basal insulins</td>
</tr>
<tr>
<td>Human premix 30/70 (30% regular human insulin + 70% NPH)</td>
<td>0.5</td>
<td>2-8</td>
<td>Up to 24</td>
<td>Control both fasting &amp; post prandial glucose</td>
</tr>
<tr>
<td>Human premix 50/50 (50% regular human insulin + 50% NPH)</td>
<td>0.5</td>
<td>2-8</td>
<td>Up to 24</td>
<td>Provides higher concentration of short acting insulin to cover high prandial excursions</td>
</tr>
<tr>
<td>Glargine</td>
<td>2-4</td>
<td>No peak</td>
<td>Up to 24 hours</td>
<td>Once daily dosing</td>
</tr>
<tr>
<td>Detemir</td>
<td>2</td>
<td>No peak</td>
<td>16-24</td>
<td>Better postprandial control compared with human premix</td>
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<tr>
<td>Lispro 75/25</td>
<td>0.25-0.5</td>
<td>1.3</td>
<td>12-24</td>
<td>Provides higher concentration of short acting insulin to cover high prandial excursions</td>
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<tr>
<td>Lispro 50/50</td>
<td>0.25-0.5</td>
<td>1.3</td>
<td>12-24</td>
<td>Provides higher concentration of short acting insulin to cover high prandial excursions</td>
</tr>
<tr>
<td>Aspart 70/30</td>
<td>10-20 min</td>
<td>1-4</td>
<td>Up to 24</td>
<td>Better postprandial control compared with human premix</td>
</tr>
<tr>
<td>Aspart 50/50</td>
<td>10-20 min</td>
<td>1-4</td>
<td>Up to 24</td>
<td>Provides higher concentration of short acting insulin to cover high prandial excursions</td>
</tr>
<tr>
<td>Regular</td>
<td>0.5</td>
<td>1.5-3.0</td>
<td>8</td>
<td>More postprandial hypoglycaemia than rapid-acting analogues</td>
</tr>
<tr>
<td>Lispro, aspart, glulisine</td>
<td>0.1-0.25</td>
<td>0.5-1.5</td>
<td>3-5</td>
<td>Can dose closer to meal and with better postprandial control compared with regular insulin</td>
</tr>
<tr>
<td>Degludec</td>
<td>1-2</td>
<td>No peak</td>
<td>&gt;42</td>
<td>Peakless insulin with lower hypoglycaemia, lesser glycemic variability and more dosing flexibility than other basal insulins</td>
</tr>
<tr>
<td>IDEgAsp</td>
<td>10-20 min</td>
<td>1-4</td>
<td>&gt;24 hours</td>
<td>Distinct &amp; separate action of both basal &amp; prandial components</td>
</tr>
</tbody>
</table>

Table 1: Summary of the available insulin formulations

Methods

Classification of insulin therapies is presented in Table 1 and the group identified following situations to propose recommendation by consensus: Initiation of insulin therapy with basal insulins or premix insulins, insulin initiation at diagnosis and intensification of insulin therapy with premix insulins or by basal bolus therapy.

Each situation was subsequently evaluated for relevant and published clinical and epidemiological evidence as well as defined place in guidelines/algorithms from national and global professional associations. These evaluations were then factored into the national context based on personal experience and common therapy practices in India. The final proposed consensus recommendation captured the collective outcome of the above process in easily implementable steps and understandable language.

Insulin Therapy Situation 1: Insulin Initiation with Basal Insulins

Current place in Guidelines/Recommendations: Initiation with basal insulins

ADA (American Diabetic Association) 2015 and ADA /EASD consensus recommends basal insulin alone, as the most convenient initial insulin regimen, beginning at 10 U or 0.1–0.2 U/kg, depending on the degree of hyperglycemia. The consensus statement published by AACE (American Association of Clinical Endocrinologists) recommends that patients with A1C >8.0%, patients on two or more oral antidiabetic drugs (OADs) or on GLP-1 therapy, and patients with long-standing T2DM are unlikely to reach their target A1C with additional OADs, a single daily dose of basal insulin should be added to the OAD regimen.

They also state that basal insulin analogues are to be preferred over neutral protamine Hagedorn (NPH) insulin as a single basal dose provides a relatively flat serum insulin concentration for up to 24 hours with significantly less hypoglycemia.

IDF (International Diabetes Federation) 2012 recommends both basal and premix insulins for start. The JAPI Consensus 2014 recommends both premixed insulin and basal insulin as start insulin in patients with T2DM. They recommend the decision on the start insulin must be based on the glycaemic profile. When FPG is high they recommend initiating insulin therapy with basal insulin and recommend initiation with premix insulin for patients with both higher FPG and PPG. INCG 2013 (Indian National Consensus Group) recommends premix insulin as start insulin.

Published scientific evidence: Initiation with Basal insulins

Number of clinical trials has been published supporting initiation of insulin therapy with basal insulins. In the Hermansen and colleagues
glargine (up to four times). Is considerably lower than insulin. Moreover, its day-to-day variability is more than 25 hours (twice as long as that for insulin glargine) and duration of action beyond 42 hours. Insulin degludec is a new basal insulin analogue with a unique mode of protraction with 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. Moreover, its day-to-day variability is considerably lower than insulin glargine (up to four times).

A pre-specified meta-analysis of the phase 3a clinical trials insulin degludec was associated with significantly lower rates of confirmed overall and nocturnal confirmed hypoglycaemia vs Insulin glargine. A recently presented paper at ADA 2014 further reiterated the benefits of degludec over glargine even when the definition and timings of hypoglycaemia were modified.

Currently Insulin Glargine, Insulin Detemir and Insulin Degludec are available basal insulin analogues in India.

NIS Recommendations: Insulin initiation with basal insulins

In T2DM patients poorly controlled on oral drug therapy,

- Addition of basal analogue insulin (insulin Glargine, Insulin Detemir, Insulin Degludec) over basal human insulin (NPH) is recommended to achieve guideline-recommended HbA1c with reduced hypoglycaemia and lesser weight gain.
- Addition of insulin Degludec is preferred over Glargine to achieve similar glycaemic control with lower risk of overall and nocturnal hypoglycaemia with lower glycaemic variability and flexibility in the time of administration.

Insulin Therapy Situation 2: Insulin Initiation with Premix Insulins

Current place in Guidelines/Recommendations: Initiation with premix insulins

AACE consensus recommend basal insulin as start insulin, but also recommend that some patients could be benefited from premix insulins as a simpler regimen. IDF 2012 recommend insulin as the third-line therapy when glucose control targets are no longer being achieved with two oral agents. They also recommend premix insulin as start insulin. INCG 2013 recommend start with premix insulin and further intensification and optimization to twice and thrice daily premix insulins.

JAPI Consensus 2014 recommended initiation of insulin with premix insulin in patients with altered FPG and PPG.

Published scientific evidence: Insulin initiation with Premix Insulins

Premix insulins are an important treatment option in the management of type 2 diabetes. Asian subjects with type 2 diabetes have a tendency to develop insulin resistance at lower BMI levels as compared to Caucasians, with beta-cell dysfunction. This is characterized by early deterioration of first and second phase insulin secretion, which is believed to play a major role in the pathophysiology of type 2 diabetes in Asians. The above characteristics could contribute to the more favourable overall glycaemic control with premix insulins in the Asian subgroup of patients. It is also worthwhile to note that due to high carbohydrate intake the post prandial glycaemic excursions are higher among Indian population as compared to the other countries.

Number clinical trials published on the role of premix insulin for initiation have been considered for the development of the consensus recommendations on the initiation of insulin with premix insulins. The 26-week Once Mix trial is a multinational, randomised, parallel-group study in patients with type 2 diabetes comparing BIAsp 30 OD with insulin glargine OD, both with metformin plus glimepiride. At the end of study, HbA1c was 7.1% for BIAsp 30 and 7.3% for insulin glargine, with an estimated reduction from baseline of −1.41% with BIAsp 30 and −1.25% with insulin glargine (BIAsp 30 – insulin glargine = −0.16%; 95% CI: −0.30;−0.02; p=0.029). Plasma glucose levels were significantly lower with BIAsp 30 post-dinner and at bedtime. No difference was observed in hypoglycaemia events between both the groups with regards to Asian population.

In the INITIATE study BIAsp 30 BID was compared with bedtime insulin glargine, both with metformin, and with or without pioglitazone. At 28 weeks, the mean HbA1c value in the BIAsp 30 group was significantly lower than in the insulin glargine group (6.91±1.17 vs. 7.41±1.24%, respectively; p=0.0026). In addition, more BIAsp 30-treated patients than insulin glargine-treated patients reached target HbA1c values of ≤6.5% and <7.0%.

The members of the consensus group have also evaluated the available evidence for the insulin co-formulation IDegAsp. The members have agreed to include the recommendations on IDegAsp under the section of premix insulins.

Co-formulation of long-acting insulin analogues with rapid acting insulin analogues was not possible in the past due to the physicochemical incompatibilities. IDegAsp is a new soluble co-formulation of basal insulin Degludec and prandial insulin aspart. It is different from the existing premix insulins, with a basal component much flatter with duration of action beyond 24 hours. Both basal and prandial insulins exist separately, both in formulation as well as subcutaneous tissue, providing distinct and separate action.

The efficacy and safety of IDegAsp administered once daily with the largest meal (on discretion of each subject) was compared with insulin glargine (IGlar) OD in insulin-naïve patients with T2DM.
in Japan. IDegAsp administered with the largest meal demonstrated a superior reduction in HbA1c from baseline compared with IGLar (1.4% vs. 1.2%). While the two treatment groups achieved similar FPG (Flasting Plasma Glucose) control, treatment with IDegAsp was superior to IGLar in terms of reducing the prandial PG (Plasma Glucose) increment at the evening meal with a treatment difference of 57 mg/dL (p < 0.001).

Currently Human Premix 30/70, Biphasic insulin Aspart 30/70 and Insulin Lispro mix 25/75 are the premix insulins available in India. Insulin co-formulation IDegAsp are also available in India

### NIS Recommendations: Insulin initiation with premix insulins

- Both premixed insulin and basal insulin can be considered as start insulin in patients with T2DM
- When FPG is elevated consider initiating insulin therapy with basal insulin. When both FPG and PPG are high, consider initiating insulin therapy with premixed insulin/insulin Co-formulation
- For patients who have high FPG and high PPG, once daily IDegAsp can be considered for initiation over basal insulin for superior glycemic control and higher chances of reaching glycemic target without hypoglycemia
- Since, PPG response to a meal is more pronounced in ethnic Asian communities, premixed insulin that improves PPG should be the preferred method of insulin initiation in this population.

### Insulin Therapy Situation 3: Insulin Initiation At Diagnosis

#### Current place in Guidelines/Recommendations: Insulin initiation at diagnosis

AACE and clinical practice guidelines by Canadian diabetes association recommend initiation of insulin at the time of diagnosis for those patients with symptoms of hyperglycaemia. On similar lines, JAPI Consensus 2014 also recommend short term intensive insulin therapy for 2 to 3 weeks in patients with high body mass index and lower FPG. The same was also recommended by INCG 2013.10,11

#### Published scientific evidence: Insulin initiation at diagnosis

Studies have demonstrated that 2–3 weeks of intensive insulin therapy can induce a so-called glycaemic remission where, patients are able to maintain normal glucose levels with no further antidiabetic medication. This drug-free glycaemic remission can last up to 2 years in many patients as per published literature.23

In 2013, Kramer and colleagues conducted a meta-analysis of the seven studies which further confirmed that post-intensive insulin there was significant improvement in beta cell function.23

#### Published scientific evidence: Insulin intensification with premix insulins

In a study conducted by Garber, a total of 100 patients with HbA1c ranging from 7.5 to 10%, (failing oral agent therapy with or without basal insulin) discontinued their prior basal insulin and were initiated on once daily BIAsp 30. After 16 weeks, those who did not reach A1C target <6.5, were added additional injection of BIAsp 30. After another 16 weeks of follow up, those patients who still did not achieve A1c of less than 6.5 %, third dose of BIAsp was added in lunch.

Addition of once-daily BIAsp 30 before dinner enabled 41% to achieve ADA targets (HbA1c <7%), with twice and thrice daily injections of BIAsp 30, 70% and 77% of subjects were able to achieve an A1c target less than 7%.24

The members of the consensus group have also reviewed the evidences for intensification with insulin co-formulation IDegAsp and agreed to include these under the section of premix insulins.

Insulin co-formulation IDegAsp has also been studied extensively in insulin experienced patients with type 2 diabetes. IDegAsp was non-inferior to BIAsp 30 in reducing the HbA1c levels in insulin-experienced patients. The fasting glucose levels were reduced from baseline to a significantly greater extent with IDegAsp than with BIAsp 30. The rates of severe hypoglycaemia were lower (by 84%; p = 0.0061) for IDegAsp. Similarly, differences in rates of overall and nocturnal confirmed hypoglycaemia were more pronounced during the maintenance period favouring IDegASp over BIAsp.25

Similarly IDegAsp twice daily has demonstrated comparable A1C reduction with lower dose and lesser weight gain vs basal bolus therapy.26

### Insulin Therapy Situation 4: Insulin Intensification with Premix Insulins

The ability to start insulin therapy with premix insulins does provide the possibility of a step-wise approach to intensify therapy to twice and even thrice daily in patients to achieve target HbA1c levels.

#### Current place in Guidelines/Recommendations: Insulin intensification with premix insulins

The ADA 2015 and ADA/EASD consensus recommend transitioning from basal insulin to twice-daily premix (or biphasic) insulin analog (70/30 aspart mix, 75/25 lispro mix).5

INCG 2013 recommend start with premix insulin and further intensification and optimization to twice and thrice daily premix insulins. The same has also been recommended in the JAPI 2014. Both INCG-2013 and JAPI recommend use of premix analogues over human premix insulins for lower risk of hypoglycaemia, superior postprandial glucose control and meal time flexibility.10,11
NIS Recommendations: Insulin intensification with premix insulins

- When intensifying premix insulin therapy from OD to BID, split the OD dose into equal breakfast and dinner doses (50:50) and titrate further.
- When intensifying premix insulin therapy from BID to TID, consider adding 2–6 U or 10% of total daily premixed insulin dose before lunch which may require down titration of morning dose (1-2 U).
- For patients on previous treatment with premix/basal insulin failing to achieve HbA1c target, twice daily IDegAsp can be recommended over premix insulin analogues for intensification
- For patients requiring further intensification of basal / premix insulin twice daily, IDegAsp can be considered as a reasonable option ahead of basal bolus therapy, for simplicity of regimen.

Published scientific evidence: Insulin intensification with basal bolus therapy

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.12

Insulin Degludec based basal bolus has demonstrated lower risk of overall and nocturnal hypoglycaemia in a setting of type 2 diabetes vs Glargine based basal bolus therapy.27

NIS Recommendations: Insulin intensification with Basal bolus:

- Despite comparable glycaemic control in T2DM patients, all analogue basal-bolus regimen may be considered over all human basal-bolus regimen for reduced risk of nocturnal hypoglycaemia, less weight gain and lower day-to-day within-person variation in FPG.
- Insulin Degludec shows significantly lower rates of both overall and nocturnal confirmed hypoglycaemia in T2D with comparable glycaemic control as compared with insulin glargine as part of basal bolus therapy.

Conclusion

The strength of the current consensus is that it has been developed with due considerations to national context based on personal experience and common therapy practices in India while drawing on relevant and published clinical/epidemiological evidence as well as treatment guidelines/algorithms from national and global professional associations. The consensus was aimed at providing simple and easily implementable recommendations on the use of insulin therapies in routine clinical practice.

The weakness of the consensus emanates from the lack of published and robust evidence from studies amongst local population. This may look surprising given the huge burden of type 2 diabetes in India. For the same reason, we also stopped short of adding any dose-specific recommendation agreeing that these be as in published global and national guidelines as well as in the approved labels on available products.

We recognize that clinical and epidemiological research in India is resource-intensive in terms of economy and other resources. It is encouraging that several efforts are now visible for investments in such research at a population level. Professional associations have also stepped in to contribute to such efforts by publishing national guidelines. Our effort is also a step in the same direction. We hope that these consensus recommendations on insulin therapies in diabetes will be a useful reference tool for physicians and that their impact will be validated through observational research in real life practice involving large number of physicians and in the setting of routine outpatient care of type 2 diabetes in India.

Acknowledgements

We thank the consensus group members; Sukhananda Shenoy, Arun

Table 2: List of studies for short term intensive insulin therapy.79

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<thead>
<tr>
<th>Year</th>
<th>N</th>
<th>Design</th>
<th>Regimen</th>
<th>Duration (years)</th>
<th>mean age (years)</th>
<th>BMI (kg/m²)</th>
<th>HbA1c (%)</th>
<th>Follow up years</th>
<th>Evaluation of glycaemic remission</th>
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<td>48-6 (11-6)</td>
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References


5. ORG IMS Market survey data. As of April 2015.


