Consensus on “Basal insulin in the management of Type 2 Diabetes: Which, When and How?”

Samit Ghosal1, Binayak Sinha2, Anirban Majumder3, Ashok Kumar Das4, Awadshesh Kumar Singh5, Biswajit Ghoshdastidar6, Debasish Maji7, Ghanshyam Goyal8, Jagti Jyoti Mukherjee9, Kalyan Kumar Gangopadhyay10, Mathew John11, Sanjay Chatterjee12, Shalini Jaggi13, Subir Ray14, Sujoy Majumdar15, Surendra Kumar Sharma16 (IDEA-2016 Expert Group)

Abstract

Introduction: Type 2 diabetes mellitus (T2DM) has attained epidemic proportions and continues to increase despite the availability of a number of oral antidiabetic medications and major advances made in insulin delivery since its discovery nearly a hundred years ago. One, amongst many other reasons responsible for the inability to achieve adequate glycaemic control in a substantial proportion of T2DM patients is the delayed initiation and inappropriate intensification of insulin treatment. Appropriate initiation and intensification of insulin is critical for the successful achievement of tight glycaemic control.

Objective: To provide simple and easily implementable guidelines to primary care physicians on basal insulin initiation and intensification, along with use of basal insulin in special situations (hepatic failure, renal failure and gestational diabetes mellitus).

Methods: Each consensus statement on basal insulin initiation, intensification and use of basal insulin in special situations was evaluated for dosing and titration based on established guidelines, data from approved pack inserts, prescribing information or summary of product characteristics for each insulin type, and published scientific literature. These evaluations were then factored into the national context based not only on the clinical experience of the expert committee representatives but also based on the common therapeutic practices followed in India to successfully achieve optimal glucose control.

Results: Recommendations on initiation and intensification of basal insulin, and its use in special situations, have been developed. The key recommendations are to initiate basal insulin when 2 or 3 oral antidiabetic medications fail to achieve target glycaemic control, or in symptomatic patients with glycated haemoglobin value greater than 9%. Depending upon patient characteristics, any of the four available basal insulins [Neutral protamine Hagedorn (NPH), Glargine (IGlar), Detemir (IDet), Degludec (IDeg)] can be used. However, IDeg has a longer duration of action, comparatively lesser hypoglycaemia (both overall and nocturnal) and more flexibility in administration timing compared to IGlar) and IDet. Inability to maintain glycaemic control should lead to prompt intensification of basal insulin treatment by adding mealtime insulin, consisting of one to three injections of either rapid-acting insulin analog or regular insulin; depending upon patient characteristics, intensification can also be achieved by transition from basal insulin to twice daily premixed insulin analogs/premixed human insulin/insulin co-formulations. IDeg/IDet can be used in all grades of renal and hepatic impairment; and IDet has been approved for use in gestational diabetes mellitus.
Conclusion: We hope that these consensus based recommendations shall be a useful reference tool for healthcare practitioners and help them in initiating and intensifying insulin therapy in T2DM patients in order to achieve optimal glycaemic control.

Introduction

Diabetes mellitus is a major health issue of the 21st century. As per the International Diabetes Federation (IDF) Atlas (7th edition), the second largest population of people with diabetes reside in India, and the number of diabetic patients aged between 20 and 79 years in India is estimated to increase from 69.2 million in 2015 to 123.5 million by 2040.1 Diabetes accounts for 14.5% of global all-cause mortality among people of age group 20 and 79 years. The highest number of deaths due to diabetes occur in China, India, USA and the Russian federation. Type 2 diabetes mellitus (T2DM), a subtype of diabetes, is the fourth most common disease worldwide, and is associated with significant morbidity and mortality.2

Insulin is the oldest available treatment option for T2DM. Unlike oral antidiabetic agents (OADs), insulin has the potential to reduce elevated glycaemic values from any value to the recommended glycaemic targets. Basal and premixed insulins are the preferred insulin options in the out-patient setting. Basal insulin provides a constant ‘background’ level of insulin that plays a key role in modulating the endogenous production of glucose from the liver.3,4 It constitutes approximately 40% of the total daily insulin secretion.5 Available basal insulin preparations can be administered by primary care physicians and the specialists alike with minimal risk and fear of inducing hypoglycaemia. Administration of basal insulin is a convenient way to initiate insulin in a subject with T2DM to achieve the desired glycaemic target. Most basal insulins are dosed at bed time and titrated based on the fasting plasma glucose value (FPG). Neutral Protamine Hagedorn (NPH) was the first basal insulin introduced and was in use for a fairly long time; however, an increase in risk of nocturnal hypoglycaemia, a short duration of action (12-18 h) necessitating twice daily administration, and excess variability in its absorption and action/delayed to development of long-acting basal insulin analogs with longer duration of action, less intra-patient variability, less pronounced peak in time-action profiles and less risk of nocturnal hypoglycaemia. Both, insulin Glargine (IGlar) and insulin Detemir (IDet), are long-acting basal insulin analogs and have been preferred over NPH because of longer duration of action, lower nocturnal hypoglycaemic risk and less variability. Despite these advantages, both IGlar and IDet do not last for full 24 h necessitating twice daily dosing to achieve glycaemic control in a number of subjects; moreover, both IGlar and IDet do not mix with other insulins. Therefore, a basal insulin, with a longer duration of action, flat peakless profile, less day-to-day variability, less overall and nocturnal hypoglycaemia, and more flexibility was warranted. IDeg is an ultra-long acting basal insulin analog with a flat peakless profile, least variability, once-daily dosing in all the patients, flexible timing of administration, lower nocturnal hypoglycaemia, mean elimination half-life of ~25 hours and the ability to mix with other insulins. The findings of published scientific literature comparing different basal insulins are summarized in Table 1. Real world data of IDeg in Sweden, United Kingdom, Japan and India is associated with reduced HbA1c level, insulin dosage and hypoglycaemia (Table 2).

In spite of advancements in insulin regimens, there are both patient- and physician-related barriers that hinders the use of insulin in the management of diabetes.27,28 These barriers can be addressed by educating, counselling and supporting the patients, and enhancing the soft and hard skills of the physicians by training them about initiation and intensification of insulin regimens. In a survey of 600 physicians across 6 countries, 50% of the physicians stated that they did not have any experience with available insulins, 40% stated that due to lack of simple guidelines for insulin titration/ intensification they were not able to adequately prescribe insulin to the patients.29 Hence, simple, evidence based, and practical guidelines on insulin initiation and intensification are required to overcome insulin-related barriers among physicians. There is a lack of unified, simple and easily implementable recommendations and guidelines on the use of basal insulin in Indian T2DM patients. To address this concern, a group of experts from all across India held a consensus meeting in Kolkata, India on 08 July 2016. The idea of the consensus meeting on the use of basal insulin in current clinical practice was initiated by Integrated
Table 1: Summary of published comparisons of different basal insulins

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<tr>
<th>Study Design (Ref)</th>
<th>Objectives</th>
<th>Results</th>
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<tr>
<td>Long Acting Insulin Analogues vs. NPH</td>
<td>Hypoglycaemia outcome from meta-analysis of randomized trials</td>
<td>IGlар in comparison to NPH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Statistically significant reduction in nocturnal hypoglycaemia</td>
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<td></td>
<td></td>
<td>• Reduction in HbA1c and FBS</td>
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<tr>
<td>Meta-analysis of post-FDA approval studies</td>
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<tr>
<td>Open-label, randomized, controlled trial</td>
<td>To investigate the efficacy and safety of glimepiride combined with either morning or bedtime IGlар or bedtime NPH in patients with T2DM in terms of HbA1c, blood glucose levels, body weight</td>
<td>IGlар in comparison to NPH</td>
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<tr>
<td></td>
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<td>• Statistically significant improvement in HbA1C with morning dose than with NPH insulin (0.40% [CI, 0.23% to 0.58%]; p=0.001) or bedtime IGlар (0.28% [CI, 0.11% to 0.46%]; p=0.008)</td>
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<td>• Statistically significant less frequent nocturnal hypoglycaemia with morning (17%) and bedtime doses (23%) than with bedtime NPH insulin (38%) (p&lt;0.001).</td>
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<tr>
<td>An investigator-initiated open, parallel-group clinical trial involving seven centres</td>
<td>To compare changes in HbA1c and diurnal glucose profiles and symptomatic hypoglycaemia with the use of IGlар+Met against NPH+Met at 12 and 36 weeks in patients with T2DM</td>
<td>IGlар in comparison to NPH</td>
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<tr>
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<td>• Statistically significant lower hypoglycaemia during the first 12 weeks in the IGlар+Met group (4.1+/-0.8 episodes/patient-year) than in the NPH+Met group (9.0+/-2.3 episodes/patient-year, p&lt;0.05), but not significantly different thereafter</td>
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<td></td>
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<td>• Statistically significant lower glucose levels before dinner (8.6 ±0.3 mmol/L vs. 10.1 ±0.3 mmol/L, p=0.002)</td>
</tr>
<tr>
<td>A meta-analysis of controlled trials (24-48 weeks long except one 52-week study)</td>
<td>To assess IGlар versus OD or BID NPH in patients with T2DM in terms of risk for hypoglycaemia</td>
<td>IGlар in comparison to NPH</td>
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<tr>
<td></td>
<td></td>
<td>Statistically significant reduction of hypoglycaemia risk in terms of overall symptomatic (11%; p=0.0006) and nocturnal (26%; p=0.0001) hypoglycaemia</td>
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<td>Statistically significant reduced risk of severe hypoglycaemia and severe nocturnal hypoglycaemia by 46% (p=0.0442) and 59% (p=0.0231), respectively</td>
</tr>
<tr>
<td>Randomised, open label, parallel, 24 week multicentre trial</td>
<td>To compare associated hypoglycaemia risks of insulin glargine and NPH insulin added to oral therapy of T2DM to achieve 7% HbA1c</td>
<td>IGlар in comparison to NPH</td>
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<td></td>
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<td>• Has less within-subject variability between 7 sequential fasting measurements over the course of treatment</td>
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<td>• Statistically significant lower rates (events per patient year) of hypoglycaemia with IGlар versus NPH (13.9 vs. 17.7, p&lt;0.02)</td>
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<td></td>
<td></td>
<td>• Statistically significant lower rates (events per patient year) of nocturnal hypoglycaemia with IGlар versus NPH (4.0 vs. 6.9, p&lt;0.001)</td>
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<tr>
<td></td>
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<td>• Has higher proportion of patients attaining HbA1c targets without an episode of nocturnal hypoglycaemia (33.2% vs. 26.7%, p&lt;0.05)</td>
</tr>
<tr>
<td>IDet vs. NPH</td>
<td>Hypoglycaemia outcome from meta-analysis of randomized trials</td>
<td>IDet in comparison to NPH</td>
</tr>
<tr>
<td>Meta-analysis of post-FDA approval studies</td>
<td></td>
<td>• Statistically significant reduction in overall and nocturnal hypoglycaemia (number of episodes per patient year of exposure)</td>
</tr>
<tr>
<td>26-week randomized, controlled trial</td>
<td>To analyse weight gain in OD-IDet or NPH in already overweight T2DM patients requiring intensified insulin therapy</td>
<td>IDet in comparison to NPH</td>
</tr>
<tr>
<td></td>
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<td>• Statistically significant lesser weight gain (difference: 1.5 kg, p&lt;0.0001)</td>
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<td></td>
<td>• Statistically significant lesser BMI increase (difference: 0.6 kg/m², p&lt;0.0001)</td>
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<tr>
<td></td>
<td></td>
<td>• Statistically significant lower incidence of hypoglycaemia [relative risks 0.62 (all events) and 0.43 (nocturnal); p&lt;0.0001 for both]</td>
</tr>
<tr>
<td>20-week, multicentre, randomized, open-label, 3-arm, parallel-group trial</td>
<td>To compare the effectiveness and tolerability of IDet versus NPH administered OD with ≥1 OAD in poorly controlled T2DM patients</td>
<td>IDet in comparison to NPH</td>
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<tr>
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<td>• Even in IDet had 24 h and nocturnal hypoglycaemia statistically significant reduced by 53% (p=0.019) and 65% (p=0.031), respectively compared with evening NPH. Nocturnal hypoglycaemia was statistically significant reduced further by 87% with morning IDet compared with evening NPH (p&lt;0.001)</td>
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<td>• Statistically significant less weight gain with evening IDet vs. NPH (0.7 kg vs. 1.6 kg, p=0.005 for evening IDet vs NPH</td>
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### Table 1: Summary of published comparisons of different basal insulins

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>A parallel-group, multicentre randomised trial. Over 24 weeks</td>
<td>To assess efficacy and tolerability of IDet or NPH insulin added to oral therapy for T2DM in a treat-to-target titration protocol</td>
<td>IDet in comparison to NPH</td>
</tr>
<tr>
<td>26-week, multinational, open-label, parallel group, randomized trial</td>
<td>To compare efficacy and safety of IDet with NPH in combination with mealtime IAsp in T2DM</td>
<td>IDet in comparison to NPH</td>
</tr>
<tr>
<td>IDet/IGlar vs. NPH</td>
<td>Comparison of IDet or IGlar with NPH insulin in T2DM patients in terms of HbA1c, BMI, symptomatic, severe and nocturnal hypoglycaemia</td>
<td>IDet/IGlar vs. NPH</td>
</tr>
<tr>
<td>Inter-comparison of Long Acting Insulin Analogues</td>
<td>To compare IDet with IGlar when administered as an add-on to glucose lowering drugs in insulin naïve patients with T2DM</td>
<td>IDet vs. IGlar</td>
</tr>
<tr>
<td>IDet vs. IGlar</td>
<td>To compare the changes in various glycemic parameters in insulin-naive T2DM patients who were initiated on IGlar or IDet in real world setting</td>
<td>IDet vs. IGlar</td>
</tr>
<tr>
<td>52-week multinational, randomised, open-label, parallel-group, non-inferiority trial</td>
<td>To compare efficacy and safety in insulin-naive patients with T2DM inadequately controlled with OADs when treated with IDet vs. IGlar</td>
<td>IDet vs. IGlar</td>
</tr>
<tr>
<td>IDet vs. IGlar</td>
<td>To compare long term glycemic control in patients with advanced T2DM patients on basal – bolus therapy</td>
<td>IDet vs. IGlar</td>
</tr>
<tr>
<td>Two-year, randomized, treat-to-target trial (BEGIN Once Long)</td>
<td>To compare the efficacy and safety of insulin degludec given in Variable once-daily dosing intervals compared with insulin glargine and insulin degludec dosed at the same time daily</td>
<td>IDet vs. IGlar</td>
</tr>
<tr>
<td>78 Week, randomized, Treat to target trial (BB – T2)</td>
<td>To compare the efficacy of IDet vs IGlar in the rates of severe or blood glucose (BG)-confirmed symptomatic hypoglycaemia during the maintenance period (after 16 weeks of treatment)</td>
<td>IDet vs. IGlar</td>
</tr>
<tr>
<td>2×32-week randomized, double-blind, crossover, multicentre, treat-to-target phase 3b clinical trial</td>
<td>To confirm superiority of IDet compared with IGlar in the rates of severe or blood glucose (BG)-confirmed symptomatic hypoglycaemia during the maintenance period (after 16 weeks of treatment), IDet vs IGlar</td>
<td>IDet vs. IGlar</td>
</tr>
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</table>
| Inter-comparison of Long Acting Insulin Analogues and NPH IGlar vs. NPH and IDet Systematic review and meta-analysis of 28 randomized clinical trials from major medical databases up to Dec 201223 | To compare efficacy and safety outcomes of IGlar with NPH and IDet, added to OADs or/ and in combination with bolus insulin. | IGlar in comparison to NPH and IDet  
- IGlar+OAD use was associated with higher probability of reaching target HbA1c level without hypoglycemia as compared to NPH+OAD (RR=1.32 [1.09, 1.59]) and similar effect as IDet+OAD (RR=1.07 [0.87, 1.33])  
- IGlar+OAD demonstrated statistically significant lower risk of symptomatic hypoglycemia as compared to NPH+OAD (RR=0.89 [0.83, 0.96]) but not with IDet + OAD (RR=0.99 [0.90, 1.08])  
- In basal-bolus regimens:  
  - IGlar demonstrated similar proportion of T2DM patients achieving target HbA1c as compared to NPH (RR=1.14 [0.91, 1.44]) but higher than IDet (RR=1.38 [1.11, 1.72])  
  - Risk of severe hypoglycemia was lower in IGlar than in NPH (RR=0.77 [0.63, 0.94]), with no differences in comparison with IDet (RR=1.10 [0.54, 2.25])  
  - IGlar + OAD has comparable safety profile to NPH, with less frequent adverse events leading to treatment discontinuation than IDet + OAD (RR=0.40 [0.24, 0.69]) |

Table 2: Post approval studies of Insulin Degludec

<table>
<thead>
<tr>
<th>Properties</th>
<th>Sweden24</th>
<th>UK25</th>
<th>Japan26</th>
<th>India27</th>
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</thead>
<tbody>
<tr>
<td>Reduction in HbA1C (%)</td>
<td>0.30</td>
<td>0.70</td>
<td>0.60</td>
<td>0.36</td>
</tr>
<tr>
<td>Reduction in insulin dosage (%)</td>
<td>14</td>
<td>-</td>
<td>10-20</td>
<td>27</td>
</tr>
<tr>
<td>Reduction in overall hypoglycaemia (%)</td>
<td>22</td>
<td>90</td>
<td>-</td>
<td>70</td>
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</table>

Diabetes and Endocrine Academy (IDEA), and was supported by Novo Nordisk India. The objectives of the meeting were to:  
- Evaluate the published evidence on use of basal insulins in T2DM patients  
- Examine the existing evidence for dosing and titration from currently available treatment guidelines, such as the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD), IDF, American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE), National Institute for Health and Care Excellence (NICE) and Canadian Diabetes Association (CDA)  
- Evolve consensus/unified statement of recommendations for initiation of basal insulin, intensification of insulin treatment, and the use of insulin in special situations based on published guidelines, evidence and clinical experience, which are simple and easily implementable

Methods

During the consensus meeting on basal insulin in the management of diabetes, the expert group committee deliberated and finally proposed recommendations by consensus for initiation of insulin with a basal insulin, intensification of insulin treatment with a basal insulin and additional rapid or short acting insulin, and the use of basal insulin in special situations, including hepatic failure, renal failure and gestational diabetes mellitus.

The consensus was proposed based on established guidelines from globally recognised professional bodies as well as those published within India), prescribing information or summary of product characteristics for each insulin type, and published scientific literature. These evaluations were then factored into the national context based not only on the clinical experience of the expert committee representatives’ but also on the common therapeutic practices followed in India. The evaluations were debated and discussed within the expert group committee. The final proposed consensus-based recommendations were proposed and collectively recorded for each insulin regimen without any bias, and as much as possible in an unambiguous language.

The global and national guidelines, and widely accepted and evaluated consensus statements that were evaluated by the expert group include: ADA Standard of Medical Care 2016 (ADA 2016), consensus statement by AACE/ACE on the comprehensive T2DM management algorithm 2016 Executive Summary (ACE/ACE Consensus statement 2016), Global guideline for T2DM IDF (IDF 2012), NICE-UK: Clinical Guidelines on
Type 2 diabetes (NICE UK, 2009) and Canadian Diabetes Association guidelines (CDA, 2013).30-34

Consensus 1: Insulin Initiation with Basal Insulins (Which, When and How)

Current place in guidelines

Most guidelines (ADA/EASD, IDF, AACE/ACE, NICE and CDA) recommend initiation with basal insulin early in the natural history of diabetes.28-32 The ADA and CDA guidelines recommend initiating either intermediate acting (IA) or long acting (LA) basal insulin. IDF recommends using either LA or IA basal insulins for insulin initiation. NICE recommends LA or IA insulins for basal insulin initiation.30-34

ADA 2016 guidelines for management of diabetes mellitus recommends that one could initiate basal insulin if HbA1c target is not achieved after three months of Metformin treatment. Basal insulin should be initiated at a dose of 10 U/day or 0.1-0.2 U/kg/day, and further adjusted by 10-15% or 2-4 U once or twice weekly to reach fasting blood glucose (FBG) target. In case of hypoglycaemia, it recommends determining and addressing the cause of hypoglycaemia, followed by a dose reduction by 4 U or 10-20% of the applied dose.30

The NICE guidelines are a little more conservative in approach, and recommends insulin along with Metformin and Sulfonylurea in patients with T2DM where HBA1c value is ≥7.5%.31

IDF 2012 recommends initiation of basal insulin after failure of 2 OADs to maintain target HbA1c value (Metformin/Sulfonylurea/glucosidase inhibitor/DPP-4 inhibitor/thiazolidinedione).32

AACE/ACE consensus statement 2016 recommends the use of single daily dose of basal insulin, as a part of dual/triple therapy, when glycated haemoglobin (HbA1c) value is ≥7.5%. In these subjects, basal insulin is given along with Metformin and another OHA (dual therapy). If the target HbA1c goal is not achieved in 3 months, then the patients are given triple therapy where basal insulin is given along with Metformin and two other OHAs. If the target goal is still not achieved in 3 months, then ‘add or intensify insulin’ algorithm is followed where LA basal insulin is given at a total daily dose (TDD) of 0.1-0.2U/kg when HbA1c < 8% or at TDD of 0.20.3 U/kg when HbA1c > 8%. The dose may be titrated every 2-3 days to reach the glycaemic goal. In a fixed regimen, the guideline recommends to increase the TDD by 2 U whereas in an adjustable regimen the insulin doses can be adjusted by adding 20% of TDD, 10% of TDD, and 1 U for corresponding mean FBG > 180 mg/dL, 140 to 180 mg/dL, and 110139 mg/dL, respectively. In case of hypoglycaemia, TDD can be reduced by 10-20% and 20-40% for FBG values < 70 mg/dL and < 40 mg/dL, respectively. They recommend use of basal insulin analogues over NPH as it provides insulin concentration for a prolonged period of time and to either discontinue or reduce sulfonylurea after the start of basal insulin.31

CDA 2013 suggests the starting dose of 10U OD at bedtime with titration of 1 U/day until target of FPG 72-126 mg/dL is reached.34

Published scientific literature

Basal insulin should be initiated when glycaemic targets are not achieved with Metformin alone or together with other OAD(s). The approved pack inserts recommend the starting dose of basal insulin as 10 U or 0.2-0.3 U/kg/day. Most basal insulins should be dosed at bedtime and titrated based on mean FPG levels.35

Various studies have shown a significant higher reduction in FPG, lesser incidence of total and nocturnal hypoglycaemia, lesser dose requirement and higher flexibility with the use of IDeg when compared to other basal insulin analogues and NPH insulin; this is due to its flat and stable glucose-lowering effects with a half-life of > 25 h and duration of action > 42h.5,18,19,36

IDEACON Expert Group Recommendation

Expert Group Recommendation 1: Basal Insulin for Insulin Initiation: Which, When and How?

Consensus1.1: Basal insulin for insulin initiation: Which insulin?
- NPH insulin can be given once or twice daily (most patients will require twice daily administration)
- Basal insulin analogues are preferred because of lesser nocturnal hypoglycaemia
- Both IGlar and IDet (sometimes in twice daily doses) are effective
- IDet is weight neutral
- IDeg has a longer duration of action, lesser incidence of overall and nocturnal hypoglycaemia, flexibility in administration timing compared to IGlar/IDet

Consensus1.2: Basal insulin for insulin initiation: When?
- Basal insulin can be considered when Metformin fails to achieve target glycaemic control
- Basal insulin is recommended when 2 or 3 OAD agents fail to achieve target glycaemic control
- Basal insulin can be recommended at diagnosis in patients with HbA1c > 9% with symptoms

Consensus1.3: Basal insulin for insulin initiation: How?
- It is recommended to start basal insulin (IDeg/IGlar/IDet) at a dose of 10 U once daily subcutaneously at bedtime OR 0.1-0.2 U/kg/day subcutaneously
- Consensus 1.4: Basal insulin titration
  - The recommended target for titration of basal insulin dose is the FPG value, which should be 80-130 mg/dL
Current place in guidelines

ADA 2016 recommends intensification of insulin treatment with one rapid-acting bolus insulin injection before the largest meal together with continued use of basal insulin or switching from basal insulin to twice-daily premixed (or biphasic) insulin analogs (70/30 Aspart mix, 75/25 or 50/50 Lispro mix) to cover post prandial glucose (PPG) excursions when FBG target is reached. The bolus insulin dose can be initiated at 4 U or 0.1 U/kg or 10% of basal dose. If HbA1c is < 8%, basal dose should be decreased by the same amount. The dosing of twice daily (BID) premix insulin should be as per the previous basal insulin dose where the premix insulin doses needs to be calculated by splitting the total current basal dose either as 2:1 (2/3 of the dose in the morning [AM] and 1/3 of the dose in the evening [PM]) or 1:1 (½ of the dose in the morning and ½ of the dose in the evening). Both bolus and premix doses may be titrated by 1-2 U or 10-15% once or twice weekly until self-measured plasma glucose (SMBG) target is reached. In case of hypoglycaemia, the corresponding insulin doses can be decreased by 2-4 U or 10-20%.

The AACE consensus statement 2016 treatment algorithm recommends intensifying treatment by combining basal insulin with mealtime bolus insulin when glycaemia is uncontrolled on basal insulin alone. Rapid-acting analogs (Aspart, Lispro or Glulisine) are preferred over regular insulin because they have a more rapid onset and offset of action and are associated with less hypoglycaemia. The simplest approach is to cover the largest meal with a prandial injection of a rapid-acting insulin analog (initiate with 10% of basal dose or 5U) before the largest meal (i.e. Basal Plus 1). If glycaemic goal is not reached, then treatment can be progressively intensified by adding bolus injections before 2 (i.e. Basal Plus 2) or 3 meals (Basal Plus 3). Another way to intensify insulin treatment is to switch to a full basal-bolus program, which provides greater flexibility for patients with variable meal times and carbohydrate content. In this program, the TDD of insulin (0.3-0.5 U/kg) is distributed as basal insulin alone to correct excessive PPG necessitating intensification of insulin treatment. In a 52-week, phase 3, randomised, open-label, treat-to-target non-inferiority trial, IDeg was compared with IGlar in a basal bolus treatment regimen with IAsp in patients with T2DM of age ≥18 years and HbA1c of 7-10%. Patients were randomised in a 3:1 ratio to receive IDeg or IGlar. The target FPG was 3.9 to < 5 mmol/L. After 52 weeks, IDeg was associated with less hypoglycaemia with the use of IDeg compared to IGlar. The rates of severe hypoglycaemia and adverse events were comparable.
Table 3: Recommendations as per approved pack inserts in patients with renal, hepatic failure and gestational diabetes mellitus

<table>
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<th>Insulin</th>
<th>Recommendations in prescribing information</th>
<th>Results from PK/PD and clinical studies</th>
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<tbody>
<tr>
<td>Renal/Hepatic failure diseases</td>
<td></td>
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<tr>
<td>NPH</td>
<td>In patients with renal/hepatic impairment, No PK/PD study reported glucose monitoring should be intensified and the human insulin dose adjusted on an individual basis.</td>
<td></td>
</tr>
<tr>
<td>IGlар</td>
<td>In patients with renal/hepatic impairment, No PK/PD study reported insulin requirements may be diminished due to reduced insulin metabolism.</td>
<td></td>
</tr>
<tr>
<td>IDет</td>
<td>In patients with renal/hepatic impairment, No change in PK or PD glucose monitoring should be intensified and the Levemir dose adjusted on an individual basis.</td>
<td></td>
</tr>
<tr>
<td>IДег</td>
<td>Insulin degludec can be used in renal/hepatic impaired patients. Glucose-monitoring is to be intensified and the insulin dose adjusted on an individual basis.</td>
<td></td>
</tr>
</tbody>
</table>

| Gestational diabetes mellitus |
| NPH | There are no restrictions on treatment of diabetes with NPH insulin during pregnancy, as NPH insulin does not pass the placental barrier. |
| IGlар | Use of lantus may be considered during pregnancy if clinically indicated (I think we need to add a rider as for IDет) |
| IDет | Treatment with IDет can be considered during pregnancy, but any potential benefit must be weighed against a possibly increased risk of an adverse pregnancy outcome. |
| IДег | There is no clinical experience with use of IDег in pregnant women. |

IAsp=insulin Aspart; IDег=insulin Degludec; IDет=insulin Detemir; IGlар=insulin Glargin; NPH=Neutral Protamine Hagedorn

between both insulin therapies. In a one-year randomized study, BID premixed insulin was compared to basal insulin with either basal plus one prandial insulin or basal-bolus up to 3 prandial injections. The results indicated that basal insulin plus a single prandial injection was as effective in improving glycaemic control as premixed insulin while basal-bolus up to 3 prandial injections was only slightly more effective than premixed insulin. In a 26-week, randomized, open-label, treat-to-target trial, T2DM patients who were inadequately controlled with OD or BID pre- or self-mixed insulin with/without OADs were randomized 1:1 to receive BID injections of IDегAsp (combination of IDег with rapid acting insulin in a single injection) or Biphasic IАsp 30. The FPG target was 4.0–5.0 mmol/L. IDегAsp was found to be superior in lowering HbA1c and FPG levels, overall, nocturnal and severe hypoglycaemia and had lower mean daily insulin dose than BIАsp 30. In another 26-week, open-label, treat-to-target phase III trial, the efficacy and safety of IDегAsp was compared with IDег and IАsp (in separate injections) in T2DM patients previously treated with basal insulin. Both IDегAsp and basal bolus regimens effectively improved glycaemic control. Although, there was no statistical significant difference in the proportion of patients achieving HbA1c < 7% between the treatment groups, there was a significant lower total daily insulin dose and numerical lower rates of confirmed hypoglycaemia and nocturnal confirmed hypoglycaemic episodes in IDегAsp group compared to IDег+IАsp group. In 2016, Christansen et al. presented a combined analyses of two Phase 3a trials where the incidence of hypoglycaemia was compared in T2DM patients treated BID with IDегAsp or BIАsp 30. Over a period of 26 weeks, there was a statistically significant improvement in overall and nocturnal hypoglycaemic episodes in patients treated with IDегAsp than BIАsp 30. In a post-hoc analyses, the combination of IDег with Liraglutide (IDегLira) was compared to IDег and Liraglutide alone in T2DM patients, regardless of the stage of diabetes progression (baseline HbA1c as ≤7.5-9%). HbA1c reductions were significantly greater with IDегLira than IDег or Liraglutide alone, indicating its high efficacy for patients with early or advanced T2DM.

IDEACON Expert Group

Recommendation

Expert Group Recommendation 2: Insulin intensification

Consensus 2.1: Insulin intensification. When?
- When basal insulin has been titrated to achieve an acceptable FBG value, but A1C still remains above target

Consensus 2.2: Basal insulin intensification. How?
- Add mealtime insulin, consisting of one to three injections of rapid-acting insulin analog (Aspart, Lispro or Glulisine) or regular insulin
- Transition from basal insulin to twice-daily premixed insulin analogs or premixed human insulin or insulin co-formulation.
- Add glucagon-like peptide-1 (GLP-1) analogue to preexisting basal insulin
Basal insulins in Special Situations (Renal Failure, Hepatic Failure and Gestational Diabetes Mellitus): Which, when and How?

Recommendations as per pack inserts

Table 3 summarizes the recommendations for use of basal insulin as per pack inserts in patients with renal failure, hepatic failure and gestational diabetes mellitus (GDM).

Current place in guidelines

In patients with gestational diabetes mellitus

All guidelines, including ACOG, IDF, NICE and DIPSI recommend rapid-acting insulins (IAsp) to be safe and effective in achieving targeted PPG values during pregnancy since they do not cross the placenta. IDF guideline recommends initiation of insulin, if FPG is ≥90 mg/dL or PPG ≥140 mg/dL in 1-hour or ≥120 mg/dL in 2-hours after 2 weeks of medical nutrition therapy and exercise. The usual recommendation is to use NPH or IDet as a basal insulin (IDF 2015).39 Rapid acting insulin analogues (IAsp) have been found to be safe and effective in achieving the targeted post prandial glucose value during pregnancy.43

Published scientific evidence

In patients with gestational diabetes mellitus

One open-label, randomised controlled clinical trial has been conducted in pregnant women with type 1 diabetes with no safety issues.44 In patients with hepatic impairment

A clinical trial was conducted to examine the effect of hepatic impairment on pharmacokinetics of IDet. A total of 24 subjects, including 6 healthy subjects and 18 subjects with hepatic impairment (6 subjects in each Child Pugh groups A, B, and C) participated in the study. There was a statistical significant difference in AUC_{0-∞} between healthy and severe hepatic impaired patients. The clearance increased with increasing degree of hepatic impairment. No statistically significant difference in C_{max}, t_{1/2} or MRT was found between the groups. Hence, hepatic impairment was not associated with clinically important changes in IDet pharmacokinetic parameters and the patients should use typical starting doses of IDet with subsequent dose adjustment according to their individual therapeutic response.45 In patients with renal impairment

There is a high frequency of renal impairment in diabetic patients and hence they have an increased risk of hypoglycaemia.46 Few studies have reported that insulin analogues, IDet, IDeg, IAsp maintain their pharmacokinetic profile in patients with renal failure. A clinical trial was conducted to examine the effect of renal impairment on pharmacokinetics of IDet. A total of 28 subjects, including 6 healthy subjects and 16 subjects with renal impairment (6 subjects each with mild and moderate renal impairment and 4 subjects with severe renal impairment) participated in the study. IDet did not show any significant alterations in any pharmacokinetic parameters (C_{max}, t_{1/2} or MRT) with renal impairment and the patients should use typical starting doses of IDet with subsequent dose adjustment according to their individual therapeutic response.45 In a study, the pharmacokinetic properties of IDeg was assessed in 30 subjects; 6 subjects each with normal renal function, mild, moderate or severe renal impairment or with end stage renal disease undergoing haemodialysis. There were no statistically significant differences in absorption or clearance of IDeg in renal impaired subjects compared with normal renal function; indicating that pharmacokinetic properties of IDeg are preserved in patients with renal impairment and specific dose adjustments may not be required for subjects with renal impairment.47 In a multicentre, prospective, randomized trial, the efficacy of OD IGlar (0.5 U/kg/day) and TID insulin glulisine (IGlu; 0.25 U/kg/day) was compared in a total of 107 T2DM patients with glomerular filtration rate < 45 mL/min. There was no statistical significant difference in the mean blood glucose levels on day 1 to day 6 between the treatment groups; indicating that both treatment groups can achieve equivalent control of hyperglycaemia in T2DM patients.48

Recommendation 3: Use of Basal insulin in patients with renal failure, hepatic failure and gestational diabetes mellitus.

Expert Group Recommendation 3: Basal insulin in special situations

Consensus 3.1: Basal insulin in special situations (Renal failure)

- Insulin requirements may be diminished due to reduced insulin metabolism.
- No PK/PD studies have been reported for NPH and IGlar; PK/PD studies for IDeg and IDet indicate no change in PK/PD
- IDeg/IDet can be used in all grades of renal impairment
- Glucose-monitoring should be intensified and the insulin dose adjusted on an individual basis
Conclusion

Achieving appropriate glycaemic targets in patients with T2DM is important to delay long-term complications associated with this disease. Among other factors, timely initiation and appropriate intensification of insulin is a key factor in achieving optimal glycaemic control. The majority of T2DM patients in India are managed in primary care settings. Thus, simple, concise and easily implementable consensus-based recommendations will help the primary care physicians to initiate and intensify basal insulin therapy for effective T2DM management. The doses of basal insulin need to be adjusted on an individual basis in certain special situations; hence the expert committee has also provided consensus-based recommendations in these special situations. The recommendations put forth are based on the existing established guidelines and published literature.

The recommendations presented in this paper include the following: Basal insulin is recommended when 2 or 3 OAD agents fail to achieve target glycaemic control and in patients with HbA1c > 9% with symptoms

- Basal insulin analogues are preferred because of lesser nocturnal hypoglycaemia and meal time flexibility
- Basal insulins (IDeg/IGlar/IDet) should be initiated at a dose of 10 U OD subcutaneously at bedtime or as 0.1-0.2 U/kg/day subcutaneously
- IDeg/IDet can be used in all grades of renal and hepatic impairment
- IDet can be considered useful in GDM

Intensification of insulin treatment should be done by adding mealtime insulin, consisting of one to three injections of rapid-acting insulin analog (Aspart, Lispro or Glulisine) or regular insulin to basal insulin or transition from basal insulin to BID premixed insulin analogs/preserved human insulin/insulin co-formulations or addition of GLP-1 analogues to existing basal insulin

The strength of the current consensus recommendations is that it has been developed with due considerations to national context based on experience and common therapy practices in India while drawing on recommendations from globally acceptable guidelines and relevant clinically published evidence. The final proposed consensus-based recommendations were collectively recorded for each insulin regimen in easily implementable steps.

The weakness of this consensus statement is that it does not provide guidance regarding allowance or discontinuation of OADs and insulin secretagogues along with various insulin regimens.

We hope that these consensus recommendations 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 T2DM in India.

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