Consensus Evidence-based Guidelines for Insulin Therapy in Patients with Type 1 Diabetes Mellitus as per Indian Clinical Practice

Alok Kanungo*, Ashok Jhingan**, Rakesh Kumar Sahay***, A Muruganathan****, Ashok Kumar Das*****

Abstract

Type 1 diabetes mellitus (T1DM) is a chronic disease characterised by auto-immune destruction of insulin producing beta cells of the pancreas. Most cases of T1DM are diagnosed during childhood and adolescence, and it remains the predominant form of the disease in this population. Early identification and treatment of T1DM is important in reducing complications of this form of disease. Because individuals with T1DM lack endogenous insulin production, the current consensus guideline recommends administration of rapid-acting and long-acting analogues for all patients with T1DM to achieve glycaemic goals and reduce insulin-induced side effects like weight gain and hypoglycaemia. It also emphasises that effective use of insulin requires an understanding of various insulin treatment and regimens, sick-day management regarding insulin use, and ability to manage insulin-induced hypoglycaemia to achieve the individualised treatment goals established between the patient, family and diabetes care team. The current consensus guideline has been developed by a panel of experts based on the existing guidelines which aims to provide better clinical practice in the Indian scenario for the management of T1DM.

Introduction

Diabetes mellitus (DM) is a metabolic disease characterised by high glucose level in the blood. Type 1 diabetes mellitus (T1DM) is a form of DM that results from autoimmune destruction of insulin-producing beta cells of the pancreas. It is one of the most common metabolic diseases among children and every year the number of children developing this form of diabetes is increasing rapidly.

Prevalence of T1DM: Global

According to the International Diabetes Federation (IDF), globally 366 million people are living with DM resulting in a prevalence rate of 8.3%. Out of 366 million, 70 million people live in South East Asia (prevalence rate 8.7%) with more than 50% remaining undiagnosed. T1DM accounts for 10-12% of all diabetes cases. It is estimated that 490,000 children worldwide are living with this disorder of whom 24% and 23% come from Europe and South-East Asia region respectively. The South-East Asia region has one of the highest estimates of T1DM cases in children, with India being home to an estimated 100,000 children with T1DM. Globally the incidence of T1DM is also rising at 3% per year affecting not only children but adults. Be they children or adults, the needs of people with T1DM are different from those of the majority of people with diabetes and have to be addressed separately.

Prevalence of T1DM: India

The prevalence of T1DM in India is 10.1-10.6/100,000 population. A recent study in Karnal, Haryana reported overall prevalence of T1DM to be 10.2/100,000 population with a higher prevalence in urban population than rural, and men (11.56/100,000) being more susceptible than women (8.6/100,000). In the 5 to 16 years age group, the prevalence was 22.22/100,000, while in the 0-5 years age group, prevalence was 3.82/100,000. An epidemiological study conducted in a South Indian population for a period of four years, indicated that the prevalence of T1DM in India is increasing.

Burden of T1DM

T1DM places a heavy burden on the affected individual, their family, the healthcare system, and the society. The increasing burden of T1DM is accounted by missed diagnoses or inadequate insulin supply. The costs involved in the care and management of T1DM is estimated around $14.9 billion (8.6%) that includes direct medical costs of $10.5 billion and indirect costs (as measured by loss of productivity) of $4.4 billion. The high costs of treatment among all socioeconomic patient groups will result in a serious economic burden on patients and society as well. Evidence suggest that people with T1DM and those treated with insulin show six to seven-fold higher direct cost than nondiabetic people. Moreover, reduced life expectancy among people with T1DM can have significant negative impact on the quality of life (QoL) of the patient.

Importance of glycaemic control in management of T1DM

Optimisation of glycaemic control at an early stage of the disease is a fundamental aspect of care in the management of T1DM. The association between tight glycaemic control and reduced risk of microvascular complications in patients with T1DM was demonstrated in the Diabetes Control and Complications Trial (DCCT). As assessed over 7 years in DCCT trial, intensive insulin therapy designed to maintain normal blood glucose levels greatly reduced the development and progression of retinopathy, microalbuminuria, proteinuria, neuropathy, cardiovascular events and overall mortality.

Existing guidelines

Several diabetes organisations around the world including the American Association of Clinical Endocrinologist (AACE), American Diabetes Association (ADA), the Canadian Diabetes Association (CDA), International Diabetes Federation/International Society for Paediatric and Adolescent Diabetes (IDF/ISPAD), Indian Society for Paediatric and Adolescent
Endocrinology (ISPAE), Australasian Paediatric Endocrine Group (APEG) and National Institute for Health and Clinical Excellence (NICE) have formulated evidence-based guidelines for the management of T1DM.\textsuperscript{11-17}

**Rationale for the need of India specific guidelines**

Several guidelines including ADA, IDF, AACE, NICE, CDA, ISPAE, and APEG have been published for the management of T1DM. These organisations provide guidelines for management of patients with T1DM in their respective regions. However, due to confounding biases and non-applicability of these guidelines in the Indian scenario, they cannot be widely used in Indian clinical practice. The current consensus guideline aims to provide specific recommendations based on published data for proper management of T1DM in India.

**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, cross sectional studies, systematic reviews and key cited articles related to T1DM 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 with the AACE protocol for standardised production of clinical practice guidelines.\textsuperscript{11} Recommendations are organised 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.

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

**Management of T1DM**

**Criteria for diagnosis of T1DM**

The diagnosis of T1DM is based on measurements of blood glucose for age groups < 30 years and the presence and absence of clinical symptoms including increased thirst and urine volume, recurrent infections, unexplained weight loss, weakness, pain, presence of ketones in urine or blood, severe abdominal pain, and diabetic ketonuria/ketoacidosis. C-peptide levels and antibody profiles may be done subsequently to confirm the diagnosis of T1DM.\textsuperscript{18,19} The current recommendations for diagnosis are in line with already published guidelines i.e. AACE, ADA, and CDA.\textsuperscript{11-13}

**Recommendations**

- In individuals < 30 years, the following criteria are recommended for diagnosis of T1DM: (Grade A; EL 4)\textsuperscript{11,13,15}
  - Symptoms of diabetes plus casual plasma glucose concentration ≥ 11.1 mmol/L (200 mg/dL) or
  - Fasting plasma glucose (FPG) ≥ 7.0 mmol/L (126 mg/dL) or
  - 2-hour postprandial glucose (PPG) ≥ 11.1 mmol/L (200 mg/dL) and
  - Symptoms of ketonuria/ketoacidosis
- Use of glycated haemoglobin (HbA1c) test is not recommended for the diagnosis of diabetes in childhood (Grade A; EL 2).\textsuperscript{12,13,17,20,21}
- Use of oral glucose tolerance test (OGTT) is not recommended for the diagnosis of diabetes in childhood (Grade A; EL 4).\textsuperscript{20}

**Criteria for screening of T1DM**

An individual’s risk of developing T1DM can be screened by presence of glutamic acid decarboxylase autoantibodies (GADA), pancreatic islet autoantibodies (PIA), insulinoma-associated (IA-2) autoantibodies, and zinc transporter autoantibodies (ZnT8).\textsuperscript{22,23} Screening can also be done by considering family history of siblings with T1DM with attention to age of onset and sex, genetic markers, and C-peptide assay.\textsuperscript{24} ADA guideline recommends considering referral of relatives of those with T1DM for antibody testing for risk assessment for T1DM.\textsuperscript{12} The current recommendations are in line with the ADA guidelines.

**Recommendations**

- In first degree relatives of T1DM patients, screening for the presence of pancreatic beta-cell antibodies and an OGTT is recommended (Grade A; EL 1).\textsuperscript{13,24,25}
- Also it is recommended (Grade B; EL 4)\textsuperscript{12,17}
  - to measure thyroid stimulating hormone annually
  - to consider screening children with T1DM for coeliac disease and other autoimmune disorders
  - to monitor growth and pubertal development

**Glycaemic targets**

For selecting glycaemic goals, the difficulty in achieving an optimal HbA1c must be balanced against the disadvantages of targeting a higher (although more achievable) goal that may not promote optimal long-term health outcomes. In addition, benefits of improved glycaemic control in children must be balanced with careful consideration of the child’s unique vulnerability to hypoglycaemia. To address these unique needs, ADA has recommended age-specific HbA1c targets for children [0-6 years, 6-12 years (pre-pubertal), and 13 years (or pubertal)] to adulthood.\textsuperscript{12} The current recommendations are in line with the ADA guidelines.

**Recommendations**

- In individuals with T1DM, age-specific glycaemic goals with different targets for different time periods (preprandial, bedtime and overnight) are recommended. The targets are listed in Table 1 (Grade B; EL 4).\textsuperscript{12}
Education

Diabetes education is the cornerstone of care for children with TIDM to achieve a successful health-related outcome. Proper diabetes education for a child and family of a child with TIDM requires educators with a set of skills including good communication, compassion, sensitivity, humour, and in-depth knowledge of childhood diabetes.

Systematic reviews of educational and psychosocial interventions in diabetes care for children demonstrated small to medium beneficial effects on glycaemic control and greater effect on psychological outcomes. AACE, ISPAE, NICE, and ADA recommend that education should be provided by a team of certified professionals, including a physician, nurse, dietician, and mental health professional who are dedicated to communicating basic diabetes management skills within a context that addresses the need for lifelong treatment with insulin, sick day management, and treatment of hypoglycaemia.

Proper diabetes education for a child and family of a child with T1DM requires educators with a set of skills including good communication, compassion, sensitivity, humour, and in-depth knowledge of childhood diabetes. Systematic reviews of educational and psychosocial interventions in diabetes care for children demonstrated small to medium beneficial effects on glycaemic control and greater effect on psychological outcomes. AACE, ISPAE, NICE, and ADA recommend that education should be provided by a team of certified professionals, including a physician, nurse, dietician, and mental health professional who are dedicated to communicating basic diabetes management skills within a context that addresses the need for lifelong treatment with insulin, sick day management, and treatment of hypoglycaemia.

### Table 1: Glycaemic targets and plasma blood glucose for T1DM by age group

<table>
<thead>
<tr>
<th>Values (age in years)</th>
<th>Plasma blood glucose range (mg/dL)</th>
<th>HBAlc (%)</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toddlers and preschoolers (0-6)</td>
<td>100-180</td>
<td>110-200</td>
<td>7.5 to 8.5</td>
</tr>
<tr>
<td>Adolescent and young adults (13-19)</td>
<td>90-180</td>
<td>100-180</td>
<td>&lt;8</td>
</tr>
<tr>
<td>Adolescents and young adults (13-19)</td>
<td>90-130</td>
<td>90-150</td>
<td>&lt;7.5%</td>
</tr>
</tbody>
</table>

* a lower goal < 7% is reasonable if it can be achieved without excessive hypoglycaemia.

Key concepts in setting glycaemic goals:
- Ideally, capillary blood glucose measurements should be done 4 times a day
- In resource-limited settings capillary blood glucose measurements should be done at least once/twice weekly, based on physician’s discretion
- 3 a.m. capillary blood glucose monitoring should be done to assess nocturnal hypoglycaemia

Abbreviations: T1DM: Type 1 diabetes mellitus; HbA1c: Glycated haemoglobin

### Table 2: Insulin therapy regimens for children and adolescents with T1DM.

<table>
<thead>
<tr>
<th>Common insulin regimens</th>
<th>Pre-breakfast</th>
<th>Pre-lunch</th>
<th>Pre-dinner</th>
<th>Bedtime</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal-bolus regimen (using analogues)</td>
<td>Rapid-acting insulin</td>
<td>Rapid-acting insulin</td>
<td>Rapid-acting insulin</td>
<td>Glargine or detemir</td>
<td>Preferred regime</td>
</tr>
<tr>
<td>Basal-bolus regimen (using human insulins)</td>
<td>Regular</td>
<td>Regular</td>
<td>Regular</td>
<td>NPH</td>
<td>Preferred if analogues use is not possible</td>
</tr>
<tr>
<td>Split-mix regimen (2 injections a day)</td>
<td>Regular or rapid-acting analogue plus NPH</td>
<td>Regular or rapid-acting analogue plus NPH</td>
<td>-</td>
<td>-</td>
<td>With resource limitation and when there is a concern to reduce number of injections</td>
</tr>
<tr>
<td>Split-mix regimen (3 injections a day)</td>
<td>Regular or rapid-acting analogue plus NPH</td>
<td>Regular or rapid-acting analog</td>
<td>NPH</td>
<td>-</td>
<td>With above concerns and when nocturnal hypoglycaemia is an issue</td>
</tr>
<tr>
<td>Premix insulins (conventional/analogues)</td>
<td>Premix</td>
<td>Premix</td>
<td>-</td>
<td>-</td>
<td>Concern of number of injections</td>
</tr>
</tbody>
</table>

Ideal versus minimal as we move down the table. Abbreviations: RAI: Insulin aspart, lispro, glulisine; NPH, neutral protamine Hagedorn.
hypoglycaemia and number of injections, split-mix regimen or premixed regimen is recommended.\textsuperscript{15}

**Recommendations**

- In individuals with T1DM, insulin regimens with different targets for pre-breakfast, pre-lunch, pre-dinner, and bedtime have been recommended (Table 2).
- In individuals with T1DM, use of rapid-acting insulin is recommended pre-breakfast, pre-lunch, and pre-dinner, while insulin glargine or detemir is recommended at bedtime (Grade A; EL 1).\textsuperscript{15, 39}
- In case of unavailability of insulin analogues, use of regular insulin is recommended pre-breakfast, pre-lunch, and pre-dinner, while neutral protamine Hagedorn (NPH) is recommended at bedtime (Grade B; EL 2).\textsuperscript{40}
- In case of resource limitation when there is a concern to reduce number of injections, split-mix regimen (two injections/day) is recommended pre-breakfast, and pre-dinner (Grade B; EL 2).\textsuperscript{41, 42}
- In case of resource limitation when there is a concern for nocturnal hypoglycaemia, split-mix regimen (two injections/day) is recommended pre-breakfast, and pre-dinner (Grade B; EL 4).\textsuperscript{15}
- When there is a concern of number of injections, premix insulin preparations (conventional/analogues) are recommended pre-breakfast, and pre-dinner (Grade B; EL 3).\textsuperscript{43}

**Basal-bolus insulin**

Basal-bolus insulin therapy mimics healthy pancreas by delivering insulin constantly as a basal and when needed as a bolus component.\textsuperscript{44} Basal insulin is administered constantly to keep the blood glucose from fluctuating due to the normal release of glucose from the liver whereas; bolus insulin mimics the burst secretions of the pancreas in response to increases in blood glucose.\textsuperscript{45} In a basal-bolus therapy in T1DM, the doses of individual insulin regimens are divided based on target FPG and HbA1c. In general, basal dose includes 25\% to 30\% of the total dose in toddlers and 40\% to 50\% in older children given at bedtime while rest of the dose is divided in to three pre-meals doses given as bolus insulin which limits post-prandial hyperglycaemia.\textsuperscript{46}

**Good glycaemic control**

Randomised trials comparing the efficacy of insulin analogues with human insulin have demonstrated better glycaemic control with low risk of hypoglycaemia.\textsuperscript{47-49} Evidence suggest that use of insulin detemir/insulin aspart provide better glycaemic control compared to NPH insulin/regular human insulin (RHI) (HbA1c: 7.88\% vs. 8.11\%; mean difference: - 0.22\%; P < 0.001).\textsuperscript{49} Moreover, insulin detemir is associated with fewer episodes of hypoglycaemia compared to NPH insulin (60\% vs. 77\%; P = 0.049).\textsuperscript{49} The ISPAE guideline recommends the use of RHI plus insulin glargine or insulin detemir; and rapid-acting analogue plus insulin glargine or insulin detemir as basal-bolus therapy.\textsuperscript{15}

Among rapid acting analogues, insulin aspart is approved in children above 2 years of age, insulin lispro above 3 years of age and insulin glulisine above 4 years of age.\textsuperscript{50} Among long acting analogues, both insulin detemir and glargine are approved above 2 years of age.\textsuperscript{50} The Canadian guideline recommended the use of rapid-acting insulin analogues in combination with adequate basal insulin, over RHI to improve HbA1c while minimising the occurrence of hypoglycaemia.\textsuperscript{15} ISPAD guideline recommends insulin glargine/detemir to improve HbA1c and reduce risk of hypoglycaemia.\textsuperscript{14} Our current recommendation is in line with CDA and ISPAD guidelines which recommend use of basal-bolus regimen using insulin analogues for better glycaemic control.

**Recommendations**

- An intensive insulin regimen (insulin aspart/insulin detemir) is recommended over RHI/NPH insulin for improved glycaemic control, reduced risks of nocturnal hypoglycaemia and less weight gain (Grade A; EL 1).\textsuperscript{48}
- Insulin detemir may be recommended over NPH for effective glycaemic control, more predictable FBG, and reduced risk of hypoglycaemia (Grade A; EL 1).\textsuperscript{48}

**Reduced weight gain**

Weight gain accompanying insulin treatment is considered an inevitable side effect.\textsuperscript{50} A consistent difference in terms of weight change was found in a number of Phase III studies of insulin detemir in T1DM.\textsuperscript{52-54} Studies evaluating the safety of insulin detemir either alone or in combination with rapid-acting insulin over other insulin regimens (NPH) have demonstrated modest increase or no change in weight.\textsuperscript{50} Moreover, gain in body weight was significantly lower after 6 months with insulin detemir than with NPH (– 0.54 kg difference; P = 0.024).\textsuperscript{53} Evidence suggests, that twice daily injection of insulin detemir (morning and dinner time) produced greater change in mean body weight compared to that given during morning and bed time (Difference: (IDet morn+bed)-1.3 kg, P < 0.001, (IDet morn+din)-1.3 kg, P < 0.001).\textsuperscript{54}

In the absence of guidelines on weight change in these patients, recommendations were framed from the cited articles.

**Recommendations**

- Insulin detemir is recommended over NPH insulin to minimise weight gain in individuals with T1DM (Grade A; EL 1).\textsuperscript{49, 52-54}

**Reduced nocturnal hypoglycaemia**

Insulin-induced nocturnal hypoglycaemia is a significant problem for children and adults. CDA recommends insulin degludec or insulin glargine as an alternative to NPH to reduce the risk of daytime and nocturnal hypoglycaemia.\textsuperscript{15} Reduced nocturnal hypoglycaemia was seen in T1DM patients using long-acting insulin. Randomised controlled trials which compared the use of insulin detemir versus NPH insulin in T1DM patients showed 26\% reduction in the risk of nocturnal hypoglycaemia (14.71 vs. 17.09, P = 0.005).\textsuperscript{53, 55} Switching patients from basal-bolus regimen to insulin detemir demonstrated reduction in episodes of total and nocturnal hypoglycaemia (P < 0.001 for all).\textsuperscript{53} Reduced nocturnal hypoglycaemia was also reported in trials comparing insulin degludec versus insulin glargine in patients with T1DM (25\% lower with insulin degludec than with insulin glargine at P = 0.01).\textsuperscript{56-59} The current consensus is in line with CDA guidelines.

**Recommendations**

- In T1DM patients with HbA1c ≤ 12\%, a basal-bolus therapy with once daily RHI and insulin detemir at bed time may be recommended over RHI and NPH insulin/insulin glargine for lower FPG level, less day-to-day variability, less fluctuation from blood glucose levels, and reduced risk of nocturnal hypoglycaemia (Grade A; EL 1).\textsuperscript{35, 58, 60}
- In T1DM patients with HbA1c ≤ 10\%, despite similar glycaemic control, long-term basal therapy with once daily insulin degludec ± mealtime insulin aspart may be recommended over insulin glargine for reduced risk of
Flexible dosing
Option to dose flexibly is important because such option would allow individuals with T1DM to achieve a better QoL without compromising glucose control or safety. Randomised controlled trials comparing day-to-day variability in the glucose-lowering effect and options for more flexible dosing demonstrated four-times lower day-to-day glycaemic variability and fewer episodes of hypoglycaemia with insulin degludec than insulin glargine. In the absence of guidelines on flexible dosing in patients with T1DM, recommendations were framed from the cited articles.

Recommendation
- Insulin degludec may be recommended over insulin glargine for reduced nocturnal confirmed hypoglycaemia and as an option for more flexible dosing (Grade A; EL 1).
- At steady-state condition, insulin degludec may be recommended over insulin glargine for more predictable glucose-lowering effect with low pharmacodynamics variability and better flexibility (Grade A; EL 1).

Premixed insulin analogues
Premixed insulin analogues seek to mimic physiologic endogenous insulin secretion. Premixed insulin combines rapid-acting insulin with NPH basal insulin analogues available in different ratios where percentage of rapid-acting/regular to intermediate-acting varies with the formulation. It provides an option for intensification from once to twice to thrice daily dosing to achieve glycaemic control with lower risk of hypoglycaemia and may be used in all stages of disease progression. Indian National Consensus Group (INCG) guidelines recommend the use of premix insulin to achieve glycaemic control in children and adolescents with T1DM and type 2 diabetes mellitus. Evidence suggests that compared to RH1, patients treated with biphasic insulin aspart-30 achieved long-term glycaemic control without increased risk of hypoglycaemia. Glycaemic targets set by AACE, ADA, CDA, IDF, NICE, and INCG also include post-prandial glucose goals. Growing evidence suggests that reducing PPG is important for achieving glycaemic goals.

In a randomised trial, biphasic insulin aspart-30 reduced the postprandial serum glucose area under curve by 23% compared with RHI 30 (t = 0) (P < 0.0001) and by 9% compared with RH1 30 (t = -30) (P = 0.013). Similarly, other studies also reported improved HbA1c and reduced hypoglycaemic episodes with no differences in weight change by the use of biphasic insulin aspart-30 than RHI 30. The current consensus is in line with INCG guidelines.

Recommendations
- Biphasic insulin aspart-30 is recommended over RHI to improve long-term HbA1c, minimise glycaemic variability and risk of hypoglycaemia (Grade A; EL 1).
- In adults with T1DM, biphasic insulin aspart-30 may be recommended over premixed human insulin 30 to achieve PPG targets without weight gain (Grade A; EL 1).

Avoiding hypoglycaemia with insulin
Hypoglycaemia is a major problem for individuals trying to achieve glycaemic targets. Hypoglycaemia can be severe and result in confusion, coma or seizure, anxiety, headache, requiring the assistance of other individuals. Evidence from several studies has indicated that the risk of hypoglycaemia is high among patients treated with insulin. In the DCCT trial, 35% of patients in the conventional treatment group and 65% in the intensive treatment group experienced at least 1 episode of severe hypoglycaemia. Given the risks, avoidance of insulin-related hypoglycaemia is important for establishing glycaemic goals in individuals with T1DM. Canadian guideline recommended that all individuals with T1DM should be educated about the complications of insulin-induced therapy. The current consensus is in line with Canadian guidelines.

Recommendations
- All individuals with T1DM should be counselled about the risk and prevention of insulin-induced hypoglycaemia, and risk factors for severe hypoglycaemia should be identified and addressed (Grade B; EL 2).
- In individuals with hypoglycaemia unawareness, the following strategies may be used to reduce the risk of hypoglycaemia and to attempt to regain hypoglycaemia awareness:
  - Continuous glucose monitoring preferably or SMBG, including periodic assessment during sleeping hours (Grade B; EL 1).
  - Less stringent glycaemic targets for up to 3 months (Grade B; EL 2).
  - A psycho-educational intervention programme (Grade B; EL 1).

Choice of insulin regimen: Multiple daily injections versus continuous subcutaneous insulin infusion
Continuous subcutaneous insulin infusion (CSII) therapy or insulin pump therapy is an alternative means of delivering insulin to patients with T1DM. CSII makes use of an external pump that delivers insulin continuously from a refillable storage reservoir by means of a subcutaneously placed cannula. The pump can be programmed to deliver a basal rate of insulin throughout the day, with higher infusion rates triggered by the push of a button at meal times. This may be a bolus or over a period of time, and it can also deliver different basal rates of insulin at different times of the day and night. The choice of pump in very young children should take into account the ability to deliver a very low basal rate.

Compared with traditional delivery of insulin preparations by MDIs, delivery of insulin via CSII reduces the frequency and number of injection allowing for greater flexibility and accurate dosing. AACE, ADA, ISPAE, APEG, NICE, and Scottish Intercollegiate Guidelines Network (SIGN) guidelines recommend the use of CSII in T1DM patients who are unable to achieve optimal glycaemic control with MDI. On the other hand, CDA guideline advocates the use of insulin aspart or insulin lispro over RHI in patients using CSII for improving glycaemic control and reducing hypoglycaemia.

Beneficial use of insulin pump therapy over MDI in terms of improved glycaemic control, improved QoL, and reduced risks of hypoglycaemia have been reported in children’s with T1DM. Currently in India, insulin pumps are usually not reimbursable or covered by insurance, and the patient needs to buy the pump and also the consumables, both of which are currently expensive.

The current consensus is in line with AACE, ADA, ISPAE, APEG, NICE, and SIGN guidelines.

Recommendations
- CSII may be recommended over MDI for better glycaemic control, improved quality of life, reduced insulin dose and risk of hypoglycaemia (Grade A; EL 1).
Table 3: Comparison of recommendations from current consensus guidelines and existing guidelines

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Glycaemic targets, HbA1c%</th>
<th>AACE</th>
<th>ADA</th>
<th>ISPAD</th>
<th>NICE</th>
<th>CDA</th>
<th>ISPAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: &lt; 6 years</td>
<td>&lt; 8.5</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 8.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age: 6-12 years</td>
<td>&lt; 8</td>
<td>&lt; 6.5</td>
<td>&lt; 8</td>
<td>6.2-7.5</td>
<td>≤ 6.5-7.5</td>
<td></td>
<td>&lt; 8.0</td>
</tr>
<tr>
<td>Age: 13-19 y</td>
<td>&lt; 7.5</td>
<td>&lt; 7.5</td>
<td>&lt; 7.5</td>
<td>≤ 7.0</td>
<td>≤ 7.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FPG, mmol/L</td>
<td>≥ 7.0</td>
<td>6.1</td>
<td>3.9-7.2</td>
<td>5.1-6.5</td>
<td>4.0-8.0</td>
<td></td>
<td>4.0-7.0</td>
</tr>
<tr>
<td>PPG, mmol/L</td>
<td>≥ 11.1</td>
<td>&lt; 7.7</td>
<td>&lt; 10.0</td>
<td>7.6-9.0</td>
<td>&lt; 10.0</td>
<td></td>
<td>5-10.0</td>
</tr>
<tr>
<td>Criteria for screening for T1DM</td>
<td>First degree relative has T1DM</td>
<td>Family history of T1DM</td>
<td>Relatives of those with T1DM</td>
<td>-</td>
<td>First- and second-degree relatives of those with T1DM</td>
<td>Regular screening for long-term complications</td>
<td></td>
</tr>
<tr>
<td>Screening of non-glycaemic parameters</td>
<td>Thyroid disease; coeliac disease; monitoring growth and pubertal development</td>
<td>PIA-2/GAD autoantibodies; profiling immunity and genetic markers</td>
<td>Same as ISPAD; vitamin B12 deficiency</td>
<td>Thyroid disease; coeliac disease</td>
<td>Thyroid disease; coeliac disease</td>
<td>Rest same as AACE</td>
<td>Same as ISPAD</td>
</tr>
<tr>
<td>Diabetes education</td>
<td>Education to patients and family for insulin therapy and injection techniques; caution against the use of alternative therapies; sick day management; hypoglycaemia</td>
<td>Education on diabetes self-management at the time of diagnosis to patients</td>
<td>Education to child and family about diabetes self-management by health care providers</td>
<td>Diabetes education for insulin use, risk of hypoglycaemia and self-management of diabetes</td>
<td>Education for children and adolescents for insulin therapy, self-monitoring of blood glucose, hypoglycaemia</td>
<td>Education for insulin treatment; monitoring and care by a nurse, pharmacist or dietician</td>
<td>Education for diabetes self-management; insulin pump treatment by a diabetic educator and a dietician</td>
</tr>
<tr>
<td>Insulin therapy</td>
<td>Insulin glargine/detemir/NPH at bedtime and regular insulin/rapid-acting analogue/regular human insulin/regular plus NPH at pre-breakfast/pre-lunch/pre-dinner to reduce glycaemic control and improve health related QoL</td>
<td>MDI of basal insulin and prandial insulin; insulin analogues if hypoglycaemia is a problem</td>
<td>Same as AACE</td>
<td>Rapid-acting analogues immediately before meals; insulin glargine/detemir: most commonly given twice daily</td>
<td>NPH at bedtime; rapid-acting insulin analogues are given at mealtimes or NPH insulin; long-acting insulin analogues is administered when nocturnal hypoglycaemia is a problem on NPH</td>
<td>Rapid-acting bolus insulin analogues, in combination with adequate basal insulin to minimise the occurrence of hypoglycaemia; long-acting insulin analogues (detemir, glargine) to reduce nocturnal hypoglycaemia</td>
<td>Insulin glargine/detemir/NPH at bedtime and regular insulin/rapid-acting analogue/regular human insulin/regular plus NPH at pre-breakfast/pre-lunch/pre-dinner</td>
</tr>
<tr>
<td>CSII</td>
<td>CSII over MDI for better glycaemic control, improved QoL, less insulin dose; greater convenience, no hypoglycaemia</td>
<td>CSII for better glycaemic control and reduce risk of hypoglycaemia</td>
<td>CSII for achieving near-normal levels of blood glucose</td>
<td>Same as AACE</td>
<td>Recommends CSII when MDI fails and those receiving the treatment have the commitment and competence to use the therapy</td>
<td>Rapid-acting insulin analogues (aspart or lispro) for intensive diabetes management</td>
<td>Insulin pumps to pump regular insulin or rapid-acting analogue for providing good glycaemic control with low hypoglycaemia and better QoL</td>
</tr>
</tbody>
</table>

In preschool-age children with T1DM, CSII is recommended over MDI for higher treatment satisfaction and improved QoL (Grade A; EL 1).96

Switching from multiple injection therapy to insulin pump therapy may be recommended in patients who are adequately educated, motivated and can afford pump therapy (Grade A; EL 1).92,95

In toddlers and younger children, CSII may be recommended over MDI (Grade A; EL 1).96

Monitoring of glycaemic control: continuous glucose monitoring

Continuous glucose monitoring (CGM) provides the patient with not only a real-time notification of interstitial blood glucose values but also sounds auditory alerts for extreme changes in blood glucose values, particularly nocturnal hypoglycaemia in patients with T1DM.97 CGM, together with intensive insulin therapy is recommended for better glycaemic control in T1DM patient’s ≥ 25 years.13 The Endocrine Society recommends the use of CGM at 8 years of age for anyone with T1DM.97 ISPAE guideline recommends the use of CGM for measuring interstitial

Abbreviations: AACE: American Association of Clinical Endocrinologist; ADA: American Diabetes Association; CDA: Canadian Diabetes Association; IDF: International Diabetes Federation; ISPAE: Indian Society for Paediatric and Adolescent Endocrinology; ISPAD: International Society for Paediatric and Adolescent Diabetes; NICE: National Institute for Health and Clinical Excellence; GIA: Glutamic acid decarboxylase; PIA: Pancreatic islet antigen; CSII: Continuous subcutaneous insulin infusion; MDI: Multiple daily injections; QoL: quality of life; NPH, neutral protamine Hagedorn
fluid glucose. NICE and AACE guidelines recommend the use of CGM in children and adolescents with TIDM who have persistent problems with hypoglycaemia unawareness or repeated hypoglycaemia or hyperglycaemia. CGM has been shown to be helpful in adults with diabetes and offers potential to improve care for children with TIDM beyond what can be achieved with self-monitoring blood glucose (SMBG) alone.

With the availability of CGM devices, it is anticipated that decreased HbA1c goals may be achieved more safely, allowing further decreases in target HbA1c levels and improved outlooks for children’s with TIDM. A meta-analysis of six trials which compared the clinical effectiveness of real time CGM with SMBG in TIDM patients demonstrated overall mean difference in HbA1c of −0.30% (95% confidence interval: −0.43% to −0.17%) (−3.0, −4.3 to −1.7 mmol/mol) and reduced overall area under the curve of hypoglycaemia − 0.28 (−0.46 to −0.09), corresponding to a reduction in median exposure to hypoglycaemia of 23% for CGM compared with SMBG. The current consensus is in line with ISPAE, NICE, and AACE guidelines.

Recommendations

- CGM is recommended over SMBG for improved glycaemic control and reduced risk of hypoglycaemia (Grade A; EL 1).12,9,10

Summary

Patients with TIDM require lifelong treatment with insulin. Management of TIDM involves systematic evaluation of glycaemic status, setting of glycaemic target and providing therapeutic interventions. The advent of new rapid-acting insulin analogues like aspart and ultra-long acting insulin degludec provide better therapeutic options to achieve glycaemic goals without the risk of hypoglycaemia. The current consensus guideline was developed based on the best clinical observations for management of TIDM from exiting guidelines and protocols (Table 3). With a focus on high quality evidence it is hoped that the adoption of the current guideline in Indian medical practice will help in delivering better healthcare to patients with TIDM.

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