EXPERT RECEOMMENDATIONS

# Expert Group Recommendations on Detection and Management of Hypoglycemia in Routine Clinical Practice in Insulin Treated Patients with Diabetes

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## Abstract

Hypoglycemia is a key barrier to optimum glycemic control in insulin treated diabetes patients. A national level expert group meeting was held at the 11th national insulin summit to analyze published data from clinical studies and guidelines to evolve consensus recommendations on identification and management of hypoglycemia in insulin-treated diabetes patients. This consensus statement emphasizes consideration of suggestive symptoms or blood glucose levels ≤70 mg/dl and ability to self-treat in identification and classification of hypoglycemia. Patient questionnaire administration at each patient visit will enable accurate reporting of hypoglycemia. Patients with strict glycemic control, high glycemic variability, history of severe hypoglycemia, impaired hypoglycemia awareness, long duration of disease or insulin therapy could be at an increased risk of hypoglycemia. Prevention of hypoglycemia should include monitoring and goal setting, patient education, dietary intervention, exercise counseling and medication adjustment. Basal insulin analogues (vs. NPH), rapid-acting insulin analogues (vs. RHI) and premix insulin analogues (vs. BHI) are more appropriate options with superiority of insulin degludec to insulin glargine U100 and IDegAsp to BIAsp 30 to reduce the risk of hypoglycemia. This consensus statement provides practical guidance for physicians in effectively managing and minimizing the risk of hypoglycemia in insulin treated diabetes patients.


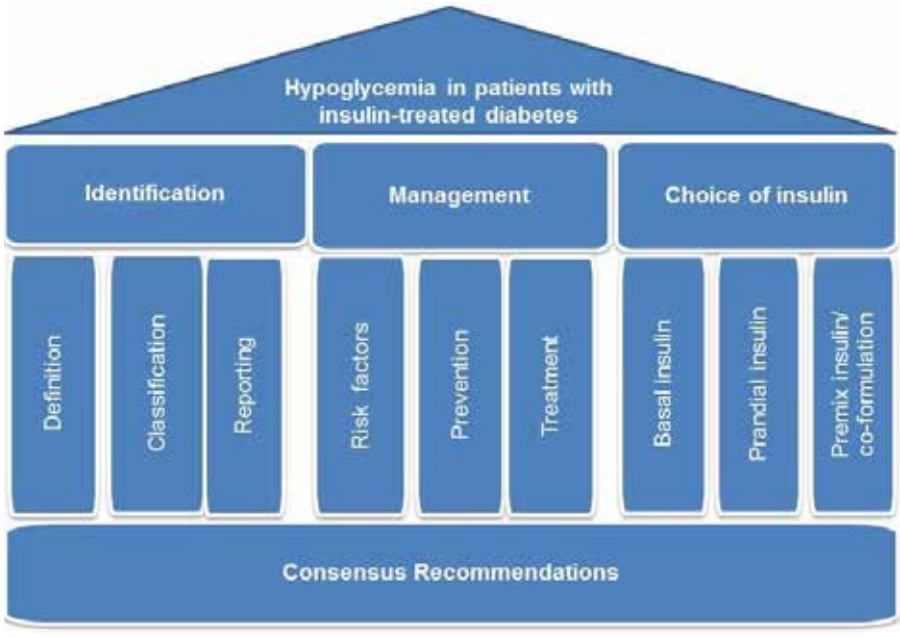


**Fig. 1: Framework for consensus recommendations**

## Introduction

Hypoglycemia in patients with insulin-treated diabetes has been considered as one of the key limiting factors in achievement of optimum glycemic control to prevent micro- and macro-vascular complications.[1-3]

Recent diabetes treatment guidelines highlight the need for personalized glycated hemoglobin (HbA1c) targets to balance control of hyperglycemia with the potential risks of hypoglycemia.[4,5] The American Diabetes Association (ADA) 2018 guidelines proposed patient-centered glycemic goals with selection of HbA1c targets more flexible (<8.0%) or tighter (6.5%) than the conventional target (<7%), depending on the presence or absence of accompanying risk of hypoglycemia, respectively.[6]

The Hypoglycemia Assessment Tool (HAT) study assessed self-reported hypoglycemia and associated predictive factors in a global population of 27585 adult patients with insulin-treated T1D (n= 8022) or T2D (n= 19563) worldwide, in a 6-month retrospective and a 4-week prospective time period. During the prospective period, the rate (events/ patient-year) of overall hypoglycemia was 73.3 in T1D vs. 19.3 in T2D. The rate of nocturnal hypoglycemia was 11.3 in T1D vs. 3.7 in T2D. The rate of severe hypoglycemia was 4.9 in T1D vs. 2.5 in T2D. South-east Asia and Latin America reported the highest rates of

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**Table 1: Definition of hypoglycemia: Available guidelines**

| Definition of hypoglycemia | | |
|---|---|---|
| **Guideline** | **Glucose value** | **Interpretation/ action** |
| The Endocrine Society 2009 Clinical Practice Guideline | Approximately 55 mg/dl | Symptoms of hypoglycemia develop in healthy individuals, |
| | SMBG is rapidly falling or is no >70 mg/dl | Consider the possibility of hypoglycemia in patients with diabetes |
| American Diabetes Association and the Endocrine Society 2013 Report | SMBG or CGM ≤ 70 mg/dl | Patients at risk for hypoglycemia should be alert to the possibility of developing hypoglycemia. People with diabetes need not always self-treat at an estimated glucose concentration of ≤ 70 mg/dL |
| Canadian Diabetes Association 2013 | < 72 mg/dl | + symptoms responding to carbohydrate administration: patient is considered to be in hypoglycemia |
| American Diabetes Association 2017 | ≤70 mg/dl | Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy |
| | ≤54 mg/dl | Sufficiently low to indicate serious, clinically important hypoglycaemia |

**Table 2: Classification of hypoglycemia: Available guidelines**

| Classification of hypoglycemia | |
|---|---|
| **American Diabetes Association Workgroup on Hypoglycemia – 2005 report** | |
| **Category** | **Criteria** |
| Severe | Symptoms requiring active assistance of another person to treat. Is independent of blood glucose |
| Documented symptomatic | Symptoms with a measured low plasma glucose, self-treated |
| Asymptomatic | No typical symptoms but, a measured low plasma glucose |
| Probable symptomatic | Symptoms typical of hypoglycemia, not accompanied by a plasma glucose determination |
| Pseudo/ Relative | Typical symptoms of hypoglycemia with a measured PG concentration >70 mg/dl |
| Canadian Diabetes Association 2013: Hypoglycemia Clinical Practice Guidelines | |
| Category | Criteria |
| Severe | Individual requires assistance of another person. Unconsciousness may occur. PG <50 mg/dl |
| Moderate | Autonomic and neuroglycopenic symptoms are present. The individual is able to self-treat |
| Mild | Autonomic symptoms are present. The individual is able to self-treat |

| American Diabetes Association Standards of Medical Care in Diabetes 2017 | | |
|---|---|---|
| **Level** | **Glycaemic criteria** | **Description** |
| Glucose alert value (Level 1) | ≤70 mg/dL | Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy |
| Clinically significant hypoglycemia (Level 2) | <54 mg/dL | Sufficiently low to indicate serious, clinically important hypoglycemia |
| Severe hypoglycemia (Level 3) | No specific glucose threshold | Hypoglycemia associated with severe cognitive impairment requiring external assistance for recovery |

severe hypoglycemia in patients with insulin treated T2D.[7]

However, there is no existing comprehensive consensus on identification and management of hypoglycemia in routine clinical practice, particularly in terms of most appropriate insulin type and regimen, which can act as a practical national guidance for primary care physicians and specialists managing diabetes in India.

## Methods

An expert panel of physicians, diabetologists and endocrinologists met at the 11th national insulin summit in September 2017, Hyderabad, India to discuss and develop these consensus guidelines. The panel critically analyzed published data from clinical trials, real world evidence and guidelines regarding hypoglycemia in insulin-treated patients with diabetes and agreed on a series of recommendations supported by scientific evidence and experts' clinical opinion on the below topics (Figure 1).

## Identification of Hypoglycemia: Definition, Classification and Reporting

### Definition of hypoglycemia

*Published scientific evidence:*

As per the Whipple's triad, hypoglycemia is defined by the presence of decreased plasma glucose (PG) concentration, symptoms of hypoglycemia and rapid symptom relief after restoration of normoglycemia.[8]

Acute hypoglycemia induces a glucose counterregulatory mechanism comprised of a series of hormonal, neurophysiological, symptomatic and cognitive changes that occur at different blood glucose (BG) levels. BG levels <70 mg/dl initiate suppression of endogenous insulin secretion and production of counter regulatory hormones (glucagon, adrenaline, cortisol) to restore the circulating glucose levels by stimulating hepatic glucose production and limiting glucose utilization in peripheral tissues. Further decline in BG <60 mg/dl stimulates secretion of neurohormones with onset of autonomic and neurogenic warning symptoms (sweating, paresthesia, hunger, palpitation, trembling, anxiety). If BG levels drop further, <54 mg/dl, cognitive dysfunction and confusion with neuroglycopenic symptoms occur and there will be severe neuroglycopenia with drowsiness and coma with BG <27 mg/dl.[9-11]

*Current place in guidelines/ recommendations:*

Table 1 summarizes the definitions of hypoglycemia as recommended by The Endocrine Society (ES) 2009,[12] ADA and the ES 2013[13] and Canadian Diabetes Association (CDA) 2013.[14]

| Expert group recommendation 1: Definition of hypoglycemia |
|---|
| 1. Blood glucose value of ≤ 70 mg/dl with or without symptoms and demonstrating response to corrective measures. |
| 2. Re-evaluate Treatment and Patient Education |

### Classification of hypoglycemia

*Current place in guidelines/ recommendations*

Table 2 summarizes the classification of hypoglycemia from the ADA and the ES 2013,[13] CDA 2013[14] and ADA and the European Association for the Study of Diabetes 2017 guidelines.[15,16]

| Expert group recommendation 2: Classification of hypoglycemia | | |
|---|---|---|
| **Clinical feature** | **Ability to self-treat** | **Classification** |
| Symptoms suggestive of hypoglycemia ± Low blood glucose | Present | Mild hypoglycemia |
| Symptoms suggestive of hypoglycemia ± Low blood glucose | Absent | Severe hypoglycemia |
| Documentation to be encouraged in both minor and severe hypoglycemia | | |

### Reporting of hypoglycemia

*Published scientific evidence*

In a study in patients with T1D (n=40) and T2D (n=30), continuous glucose monitoring (CGM) data showed that unrecognized hypoglycemic episodes were common, often occur at night (73.5%) and frequently go unrecognized by patients (62.5% in T1D and 46.6% in T2D). Global HAT study also revealed that hypoglycemia episodes often go unrecognized or unrecorded by patients.[6] Hypoglycemia unawareness is considered to predispose the patient to a vicious cycle of repeated and more serious future hypoglycemia.[17] A visual vignette of an adult lady with 9 years of T1D showed that a serious episode of hypoglycemia occurred possibly due to blunted glucagon response, autonomic failure and defective counterregulatory hormone response.[18] According to ADA and the ES 2013 Report, clinicians and educators must assess the risk of hypoglycemia at every visit with patients receiving insulin therapy.[13,14]

*Current place in guidelines/ recommendations*

Patient hypoglycemia questionnaire from the ADA and the ES 2013,[13] Stanford hypoglycemia questionnaire[19] and Hypoglycemic Health Association of Australia questionnaire[20] are summarized in Table 3.

## Management of Hypoglycemia in Routine Clinical Practice: Risk Factors, Prevention and Treatment

### Risk factors

*Published scientific evidence:*

A retrospective cross-sectional analysis in 1,055 patients with T2D revealed a prevalence of hypoglycemic symptoms in 30% of patients on insulin. The study also showed that prevalence

**Table 3: Patient questionnaire on reporting of hypoglycemia: Available guidelines**

**The ADA and The Endocrine Society 2013 questionnaire**

| No. | Question |
|---|---|
| 1 | To what extent can you tell by your symptoms that your blood glucose is LOW?<br>____ Never ____ Rarely ____ Sometimes ____ Often ____ Always |
| 2 | In a typical week, how many times will your blood glucose go below 70 mg/dL _____ a week? |
| 3 | When your blood glucose goes below 70 mg/dL, what is the usual reason for this? |
| 4 | How many times have you had a severe hypoglycemic episode (where you needed someone's help and were unable to treat yourself)?<br>Since the last visit ____ times; In the last year ____ times |
| 5 | How many times have you had a moderate hypoglycemic episode (where you could not think clearly, properly control your body, had to stop what you were doing, but you were still able to treat yourself)?<br>Since the last visit ____ times; In the last year _____ times |
| 6 | How often do you carry a snack or glucose tablets (or gel) with you to treat low blood glucose?<br>Never ___ Rarely ___ Sometimes___ Often___ Almost always___ |
| 7 | How LOW does your blood glucose need to go before you think you should treat it?<br>Less than ____mg/dL |
| 8 | What and how much food or drink do you usually treat low blood glucose with? |
| 9 | Do you check your blood glucose before driving?<br>Yes, always___ Yes, sometimes ___ No___ |
| 10 | How LOW does your blood glucose need to go before you think you should not drive? ____mg/dL |
| 11 | How many times have you had your blood glucose below 70 mg/dL while driving?<br>Since the last visit ____ times; In the last year _____ times |
| 12 | If you take insulin, do you have a glucagon emergency kit? Yes___/ No ___ |
| 13 | Does a spouse, relative, or other person close to you know how to administer glucagon? Yes___/ No ___ |

**Stanford hypoglycemia questionnaire**

In the past week, did you ever have:

1. Morning headaches ..... ☐ No ☐ Yes ☐ Don't know
2. Nightmares..... ☐ No ☐ Yes ☐ Don't know
3. Night sweats..... ☐ No ☐ Yes ☐ Don't know
4. Lightheadedness ..... ☐ No ☐ Yes ☐ Don't know
5. Shakiness or weakness ..... ☐ No ☐ Yes ☐ Don't know
6. Intense hunger..... ☐ No ☐ Yes ☐ Don't know
7. Times when you passed out, fainted, or lost consciousness, even for a short time?..... ☐ No ☐ Yes ☐ Don't know

**Scoring**

Score items as follows: No="0", Yes="1", Don't know=blank. Score is the sum of the seven items, with higher score indicating more hypoglycemia symptoms.

**Hypoglycemic Health Association of Australia questionnaire**

| Questionnaire | Never | Rarely | Occasionally | Usually |
|---|---|---|---|---|
| 1 I get tired or exhausted. | | | | |
| 2 I forget things easily. | | | | |
| 3 I feel sleepy during the day. | | | | |
| 4 I get down or depressed. | | | | |
| 5 I get down over nothing. | | | | |
| 6 I have trouble concentrating. | | | | |
| 7 I get nervous or shaky. | | | | |
| 8 I easily get angry. | | | | |
| 9 I eat or crave sweets, or once used to. | | | | |
| 10 I am awaken during the night. | | | | |
| TOTAL: | | | | |

**SCORING**

Total the number of ticks in each column for RARELY, OCCASIONALLY, and USUALLY and then calculate as follows:-

RARELY (Total) x 1 = _____

OCCASIONALLY: (Total) x 2 = _____

USUALLY: (Total) x 3 = _____

Add together for TOTAL SCORE _____

If your TOTAL SCORE IS:

<8: Hypoglycemic disease is unlikely; 8-15: Hypoglycemic disease is possible; >15: Hypoglycemic disease is present.

| Expert group recommendation 3: Hypoglycemia reporting questionnaire | |
|---|---|
| 1 | Can you predict Hypoglycemia?<br>• Yes<br>• No<br>• Not Always |
| 2 | Was Hypoglycemia confirmed by SMBG? If yes, what is your blood glucose level for Hypoglycemia?<br>_____ |
| 3 | How many times per week do you get Hypoglycemia?<br>• Confirmed:<br>• Unconfirmed: |
| 4 | Are there identifiable causes for hypoglycemia? Such as delayed food intake, fasting, treatment overdose, etc.<br>• Yes (Specify)<br>• No<br>• Not Always |
| 5 | How do you treat Hypoglycemia?<br>• Food<br>• Table Sugar<br>• Glucose<br>• Any other |
| 6 | Do you check Blood sugar before driving, exercise? If yes, mention a particular level below which you will not engage in that activity.<br>_____ |

of hypoglycemia was higher in patients with insulin therapy, younger age, lower A1C at follow-up, and hypoglycemia at baseline visit.[21]

The UK Hypoglycemia Study in 383 patients with diabetes revealed that during early (<2 years) insulin use in T2D compared to T1D (<5 years), the frequency of mild hypoglycemia [(4 episodes vs. 36 episodes per patient-year (PPY), respectively] and severe hypoglycemia (0.2 episodes vs. 1.1 episodes PPY, respectively) were lower in T2D. However, the frequency of both mild and severe hypoglycemia were similar between early insulin use for <2 years and sulfonylurea use in T2D.[22]

*Intensive glycemic control*

The association of severe hypoglycemia with intensive glycemic control have been reported in several large clinical trials including the UKPDS (n=5,102; 1.8 events vs. 0.7 events per 100 patient years for insulin vs. dietary restriction) [23], ADVANCE study (n=11,140; 0.7 events vs. 0.4 event per 100 patient years for insulin vs. standard therapy)[24] and ACCORD study (n=10,251; 3.0 events vs. 1.0 event per 100 patient years for intensive therapy vs. standard therapy)[25] among patients with T2D; as well as in the Stockholm Diabetes Intervention Study [(SDIS) n=97; 2.5-fold increase with intensified conventional treatment vs. regular treatment][26] and the Diabetes Control and Complications Trial [(DCCT) n=1441, 2 to 3-fold increase vs. conventional therapy][27] among patients with T1D.

**Table 4: Risk factors for hypoglycemia: Available guidelines**

| The Endocrine Society 2009 Clinical Practice Guideline | |
|---|---|
| **Conventional factors** | **Due to compromised counter-regulation** |
| • Insulin or insulin secretagogue (Excessive/ ill-timed)<br>• Decreased exogenous glucose delivery (missed meals)<br>• Increased glucose utilization (Exercise)<br>• Decreased endogenous glucose production (Post-alcohol ingestion)<br>• Increased insulin sensitivity (weight loss, an increase in regular exercise, improved glycemic control, middle of the night)<br>• Decreased insulin clearance (Renal failure) | • Absolute endogenous insulin deficiency (Loss of α cell response to hypoglycemia as a result of absent β cell signaling in type 1 diabetes)<br>• H/O of severe hypoglycemia, Hypoglycemia unawareness, Recent antecedent hypoglycemia, Prior exercise and sleep (Hypoglycemia associated autonomic failure)<br>• Aggressive glycemic therapy (Lower HbA1C levels, lower glycemic goals) |
| **Canadian Diabetes Association 2013: Hypoglycemia Clinical Practice Guidelines** | |
| • Prior episode of severe hypoglycemia<br>• Current low A1C (<6.0%)<br>• Hypoglycemia unawareness<br>• Long duration of insulin therapy<br>• Autonomic neuropathy<br>• Low economic status<br>• Food insecurity | |
| **India Hypoglycemia Study Group (2012): Uncommon risk factors for hypoglycemia** | |
| Uncommon risk factors : General anesthesia or sedation, critical illnesses, endocrine deficiencies, sudden reduction of corticosteroid dose, concomitant medications which includes high dose aspirin, sulfonamides, warfarin, fibrates, warfarin, aspirin, allopurinol, NSAIDs and ACE inhibitors | |

*Current place in guidelines/ recommendations*

Table 4 summarizes the risk factors for hypoglycemia according to available guidelines.

## Prevention of hypoglycemia

*Published scientific evidence:*

*Patient education*

Use of DAFNE (Dose Adjustment For Normal Eating) structured 5-day education program focusing on flexible insulin therapy according to carbohydrate intake and home BG monitoring data in adults with T1D was associated with decline in severe hypoglycemia rate (from 1.7 episodes at baseline to 0.6 episodes per person per year after the education). Periodic patient programs to educate on the importance of self-monitoring of blood glucose, symptoms of hypoglycemia and methods of prevention and immediate treatment of an episode of hypoglycemia were stressed.[28]

| Expert group recommendation 4: Risk factors for hypoglycemia | |
|---|---|
| **Medical factors** | **Lifestyle factors** |
| 1. Strict glycemic control<br>2. High glycemic variability<br>3. Previous history of severe hypoglycemia<br>4. Impaired awareness of hypoglycemia<br>5. Inadequate treatment of previous hypoglycemia<br>6. Long duration of type 1 diabetes<br>7. Long duration of insulin therapy in type 2 diabetes<br>8. Lipohypertrophy at injection sites<br>9. Hepatic or renal dysfunction<br>10. Illness: Terminal illness, Addison's disease & hypothyroidism due to loss of counter-regulatory hormone function<br>11. Concomitant use of insulin secretagouges<br>12. Concomitant non-ADMs: HCQs, Aspirin, sulfonamides, warfarin, fibrates, allopurinol, NSAIDs, ACEI, quinolones, quinine, etc. | 1. Increased exercise (relative to usual)<br>2. Irregular lifestyle<br>3. Increasing age<br>4. Alcohol intake<br>5. Inadequate blood glucose monitoring<br>6. Weight loss<br>7. Fasting<br>8. Lack of care givers |

*CGM*

Real-time CGM not only helps keep a track of glucose levels but also alerts the user of a possible episode of hypoglycemia by the display of direction and rate of change of glucose levels.[13]

Data from a randomized, open-label, crossover IN CONTROL trial in patients with T1D and impaired hypoglycemia awareness revealed that CGM vs. SMBG was associated with lower number of severe hypoglycemic events (14 vs. 34 events), higher amount of time spent in normoglycemia (65.0 vs. 55.4%) and reductions in time spent

**Table 5: Prevention of hypoglycemia: Available guidelines**

| The Endocrine Society 2009 Clinical Practice Guideline | |
|---|---|
| **Acknowledge:**<br>• Consider the issue of hypoglycemia in each patient visit<br>• Elicit patient concerns about hypoglycemia<br>• Critical review of SMBG record | **Application of principles of intensive glycemic therapy to prevent hypoglycemia**<br>• Patient education and empowerment<br>• Frequent SMBG and CGM in certain instances<br>• Flexible and appropriate insulin regimen<br>• Individualized glycemic goals<br>• Ongoing professional guidance and support |

| American Diabetes Association and the Endocrine Society 2013 report |
|---|
| 1. Glucose monitoring and goal setting |
| 2. Clinical surveillance |
| 3. Patient education |
| 4. Dietary intervention |
| 5. Exercise counselling |
| 6. Medication adjustment & individualized targets |

| Expert group recommendation 5: Prevention of hypoglycemia (Multi-faceted approach) | | | | |
|---|---|---|---|---|
| **Monitoring & goal setting** | **Patient education** | **Dietary intervention** | **Exercise counseling** | **Medication adjustment** |
| SMBG before meals, at bedtime, and during suggestive symptoms | Training to recognize and respond promptly to symptoms of hypoglycemia | Adequate caloric intake | To follow regular exercise pattern | Adjust insulin regimen: Basal/ Premix/ Basal-bolus |
| Individualize SMBG frequency based on treatment | Negative effects of hypoglycemia unawareness | Inter-prandial and bedtime snacks | SMBG before, during, and after exercise | Use insulin analogues to reduce the risk of hypoglycemia |
| Individualize glucose targets. | Caretaker education | All-time access to table sugar/ glucose/ glucose tablets | Pre-exercise caloric intake if BG<140 mg/dL | Consider CSII if appropriate |
| Caretaker/ spouse to be trained. Consider CGM if needed | Carry diabetes ID card with sugar tablets | | Consumption of additional calories during/ after exercise if BG< 140 mg/dL | |

**Table 6: Treatment of hypoglycemia: Available guidelines**

| The Endocrine Society 2009 Clinical Practice Guidelines | |
|---|---|
| **Mild-to-moderate symptomatic hypoglycemia** | **Patient is unwilling or unable to take carbohydrate orally** |
| • Ingestion of glucose tablets or carbohydrate containing juice, soft drinks, milk, candy, other snacks or a meal<br>• Recommended dose of glucose: 20g<br>• Expected time for improvement: 15-20 min<br>• Ingestion of a more substantial snack/meal after BG is raised<br>• Serial monitoring of BG after self-treatment | • Glucagon 1mg (SC or IM injection.)<br>• Hospital management of hypoglycemia in case of no improvement<br>• Standard IV glucose dose of 25 g<br>• Food intake as soon as the patient is able to safely ingest orally<br>• Consider octreotide in SU-induced hypoglycemia |

| Canadian Diabetes Association 2013: Hypoglycemia Clinical Practice Guidelines | | | |
|---|---|---|---|
| **Mild-to-moderate symptomatic hypoglycemia** | **Severe hypoglycemia in a conscious person** | **Severe hypoglycemia in an unconscious person** | **Post-hypoglycemic episode** |
| • 15g carbohydrate ingestion (glucose/ sucrose tabs, orange juice, glucose gels)<br>• Retest BG in 15 minutes<br>• Re-treat (15 g carbohydrate) if BG < 70 mg/dl | • 20g carbohydrate ingestion (Glucose tabs or equivalent)<br>• Retest BG in 15 minutes<br>• Re-treat (15 g carbohydrate) if BG < 70 mg/dl | • Glucagon 1mg (SC or IM injection)<br>• Call for emergency services<br>• Discuss the episode with diabetes health care system<br>• With IV access: 10-25 g of glucose (20-50 cc of D50W) over 1-3min | • Usual meal or snack that is due at that time of the day to prevent repeated hypoglycemia<br>• If a meal is >1 hour away, a snack (15 g carbohydrate and a protein source) should be consumed |

in hypoglycemia (BG <70 mg/dl) (6.8 vs 11.4%).[29]

*Individualized glycemic targets*

The accumulated data from T2D cardiovascular trials suggest that not everyone benefits from aggressive glycemic control, and that it is important to individualize treatment targets.[4,24,25,30]

*HAAF: Restoration of autonomic symptoms of hypoglycemia*

Modifications in dietary intake and insulin regimen are needed to prevent frequent and recurrent hypoglycemia. Regular clinic visits and counselling with a health care professional will help to make necessary changes to the above.[31-33] With this approach, by 2 weeks, restoration of autonomic symptoms of hypoglycemia is considered to occur. However, complete reversal of hypoglycemia unawareness could take up to 3 months.[31-37]

*Current place in guidelines/ recommendations:*

Table 5 summarizes the methods for prevention of hypoglycemia according to available guidelines.

**Treatment of hypoglycemia**

*Published scientific evidence:*

A modelled study of clinical hypoglycemia in patients with insulin dependent diabetes mellitus was conducted to evaluate the rise in PG concentrations after treatment with oral glucose or subcutaneous glucagon. The study showed that 10 g oral glucose, 20 g oral glucose and 1.0 mg SC glucagon produced prompt but transient increments in PG concentrations from hypoglycemic levels compared to placebo.[38]

*Current place in guidelines/ recommendations*

Table 6 summarizes the treatment of hypoglycemia according to available guidelines.

## Choice of Insulin to Minimize Hypoglycemia Risk

Initiation and intensification of insulin therapy need to be balanced against the increase in the risk of hypoglycemia attributable to more intensive glucose-lowering treatment regimens.[39]

**Choice of basal insulin**

*Published scientific evidence:*

*Basal insulin analogues vs. NPH insulin*

In a multicenter, randomized, open-label, 3-arm, parallel-group trial in 504 patients with T2D across Europe and the United States, once-daily insulin detemir vs. NPH insulin was reported to reduce the risk of 24-hour and nocturnal hypoglycemia by 53% and 65%, respectively.[40] Similarly, in an open-label, parallel, 24-week multicenter treat-to-target trial in 756 patients with T2D, once-daily glargine

**Expert group recommendation 6: Treatment of hypoglycemia**

| If the patient is conscious | If the patient is unconscious |
|---|---|
| 1. Treat immediately with 15–20 g fast-acting carbohydrate:<br>a. Small glass of sugary drink<br>b. ≥3 glucose tablets<br>c. Sweets<br>d. Small carton of pure fruit juice<br>2. Retest BG after 15–20 minutes and re-treat if needed<br>3. 15–20 g of carbohydrate containing snacks after BG correction | 1. IV infusion of 50-100 ml of 25% Dextrose in a healthcare setting under medical supervision<br>2. Give glucagon injection SC 1mg |

Note: If the hypoglycemia was due to SU or long-acting insulin therapy, the risk of hypoglycemia may persist for up to 24–36 hours following the last dose, especially if there is concurrent renal impairment

U100 was reported to reduce the risk of overall confirmed and nocturnal confirmed hypoglycemia by 29% and 44% versus NPH, respectively.[41] A review on available basal insulins indicated that higher variability and higher risk of hypoglycemia were the limitations of treatment with NPH. Insulin glargine U100 could reduce the risk of nocturnal hypoglycemia compared to NPH due to its lower variability. The basal insulin treatment was further improvised with the introduction of insulin detemir demonstarting a much lesser variability and lower risk of nocturnal hypoglycemia compared to insulin glargine U100 along with the added advantage of lesser weight gain.[42]

*Comparison of basal insulin analogues*

Meta-analysis of 5 phase IIIA RCTs showed that among insulin-naive T2DM subjects, insulin degludec had a significantly lower risk of overall confirmed hypoglycemia by 17%, nocturnal confirmed hypoglycemia by 36% and severe hypoglycemia by 86% vs. insulin glargine U100.[43]

The SWITCH 2 trial in 721 adults with T2D and at least 1 hypoglycemia risk factor revealed that during the maintenance period, insulin degludec was associated with lower rates of overall symptomatic hypoglycemia by 30%, symptomatic nocturnal hypoglycemia by 42% and severe hypoglycemia by 46% compared to insulin glargine U100.[44]

The DEVOTE trial, a long-term, randomized, double-blinded and event-driven trial in more than 7,500 people with T2D, demonstrated superiority of insulin degludec to insulin glargine U100 in terms of lesser hypoglycemia risk with reduction in severe hypoglycemia by 40% and nocturnal hypoglycemia by 53%.[45]

A retrospective Indian real world comparative data in T2D revealed that the patient reported hypoglycemic episodes were lesser with degludec vs glargine U100 (12 versus 40 episodes, respectively).[46]

Evidence from a pharmacological study shows that degludec U200 has a lower day-to-day variability in glucose lowering effect by ~4 times and within day variability by 37% compared to glargine U300 which might help achieve a better glycemic control with a reduced risk of hypoglycemia with degludec vs glargine U300.[47] Another pharmacological study showed a lower within day variability with glargine U300 vs degludec U100 with a treatment ratio of 0.80 ($P$ = 0.047). However, the limitation of the study was that it did not measure the difference in day-to-day variability and measured only the absolute within day variability without taking into account the significantly lower potency of glargine U300 compared to degludec.[48]

*Current place in guidelines/ recommendations:*

The ES 2009 Clinical Practice Guideline and ADA and the ES 2013 report recommends the use of long-acting basal insulin analogues (glargine, detemir) to minimize the risk of nocturnal hypoglycemia.[12,13]

## Choice of prandial insulin

*Published scientific evidence:*

*Insulin aspart vs. regular human insulin (RHI)*

A multinational, double-blind, randomized, crossover trial with 155 T1D patients showed a 72% reduction in major nocturnal hypoglycemia with insulin aspart vs RHI.[49]

*Insulin lispro vs RHI*

In a crossover, open-label study in 463 adolescents with T1D, insulin lispro resulted in lower rates for overall hypoglycemia and nocturnal hypoglycemia as compared with RHI.[50]

**Expert group recommendation 7: Choice of basal insulin to minimize hypoglycemia risk**

1. Basal insulin analogues are associated with a lesser risk of hypoglycemia compared to NPH
2. New generation ultra-long acting insulin degludec has a significantly lower day-to-day variability compared to insulin glargine U100. Insulin degludec U200 (bioequivalent to degludec U100) also has demonstrated a lower day-to-day variability compared to insulin glargine U300.
3. Insulin degludec has a lesser risk of hypoglycemia compared to insulin glargine U100 in both patients without and with high risk for severe hypoglycemia based on available evidence.

*Insulin glulisine vs RHI*

In an open-label, randomized, controlled, multicenter, parallel-group, 12-week study in 860 patients with T1D, there was a similar rate of severe hypoglycemic episodes with pre-meal RHI, pre-meal glulisine and post-meal glulisine groups (8.4%, 8.4%, and 10.1%, respectively).[51]

*Current place in guidelines/ recommendations*

According to The ES 2009 Clinical Practice Guideline and ADA and the Endocrine Society 2013 report, the use of rapid-acting insulin analogues (lispro, aspart, glulisine) can minimize the risk of nocturnal and interprandial hypoglycemia.[12,13]

**Expert group recommendation 8: Choice of prandial insulin to minimize hypoglycemia risk**

1. Prandial insulin analogues, insulin aspart, lispro and glulisine are associated with a lesser risk of inter-prandial and nocturnal hypoglycemia compared to RHI
2. The benefit of meal-time flexibility with prandial insulin analogues can improve treatment convenience and reduce the chances of RHI associated hypoglycemia due to missed meal post-dosing

## Choice of premix insulin/co-formulation

*Published scientific evidence*

Premixed insulin analogues are effective and safe agents that provide both basal and prandial coverage in relation to their biphasic pharmacokinetic properties and are therefore among the preferred treatment options.[52-54] They include biphasic human insulin (BHI) 30/70 (needs to be dosed 30 minutes before a meal), lispro 75/25 [better postprandial control with lesser hypoglycemia than BHI], lispro 50/50, aspart 70/30 (BIAsp 30; better postprandial control with lesser hypoglycemia than BHI), aspart 50/50 (better PPG control than low mix

fixed dose combination] and insulin degludec/insulin aspart (IDegAsp; superior FPG control with reduced risk of hypoglycemia than BIAsp 30). Premix insulins/co-formulation targets all three components of the glucose triad (HbA1c, FPG and PPG) and thus are useful options for initiation and intensification of insulin treatment.[52-57]

*BIAsp 30 vs BHI*

BIAsp 30 is the most prescribed analogue premix with the largest evidence base in terms of randomized controlled trials and observational data.[58] In a meta-analysis of 9 randomized, parallel, crossover trials comparing BIAsp 30 with BHI 30 in adult patients with T2D, BIAsp 30 was reported to be associated with a significantly lower rate of nocturnal (50% lesser) and major hypoglycemia (55% lesser) compared with BHI 30.[59]

*IDegAsp vs BIAsp 30*

In a 26-week, multinational, open-label, randomized trial in 394 insulin-naïve patients with T2D, twice-daily IDegAsp produced effective HbA1c reduction with superior reductions in overall confirmed (54% lesser) and nocturnal confirmed (75% lesser) hypoglycemia compared with BIAsp 30.[60] A review of evidence on all available premix insulins and insulin co-formulation also showed that IDegAsp provided non-inferior HbA1c reductions with a significantly better control of FPG at lesser mean daily insulin dose and lesser risk of overall and nocturnal hypoglycemia compared to BIAsp 30.[61]

*Current place in guidelines/ recommendations:*

The Indian national consensus on initiation and intensification of premix insulin in T2D management[62] states that:

- Premix analogues can be preferred over BHI due to a lower incidence of severe and nocturnal hypoglycemia and flexibility in administration.
- IDegAsp can be preferred over premix insulin analogues due to superior FPG control and a reduced risk of overall and nocturnal hypoglycemia compared to BIAsp 30.
- Thrice daily premix insulin analogue and twice daily IDegAsp can be a preferred alternative to basal bolus regimen due to comparable control and more convenience.

| Expert group recommendation 9: Choice of premix insulins/ co-formulation to minimize hypoglycemia risk |
|---|
| 1. Due to the reduced risk of hypoglycemia, analogue premix insulins can be preferred over biphasic human insulin. |
| 2. IDegAsp has a significantly lesser risk of hypoglycemia compared to BIAsp 30 in both insulin naïve and insulin treated patients with T2D |

## Conclusion

This expert panel based consensus statement provides practical national guidance on identification of hypoglycemia, management of hypoglycemia and choice of insulin to minimize the risk of hypoglycemia.

Accordingly,

- Suggestive symptoms or BG levels ≤ 70 mg/dl should help identify an episode of hypoglycemia
- Assessment of severity of hypoglycemia should be based on the ability to self-treat.
- The use of recommended patient questionnaire can help in accurate reporting of hypoglycemia.
- Screening for the recommended high risk factors can help take suitable measures to minimize future risk of hypoglycemia.
- Use of a multi-faceted approach consisting of monitoring and goal setting, patient education, dietary intervention, exercise counseling and medication adjustment can help prevent episodes of hypoglycemia.
- Analogue insulins could be better alternatives to human insulins with superiority of insulin degludec to insulin glargine U100 and superiority of IDegAsp to BIAsp 30 in terms to lower risk of hypoglycemia.

As hypoglycemia is a key barrier to the achievement of optimum glycemic control, we hope that these consensus recommendations will provide practical guidance to clinicians and specialists to minimize the risk of hypoglycemia in insulin treated diabetes patients.

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*Disclosures*

Awadhesh Kumar Singh, Pradeep G Talwalkar, Abhay Ahluwalia, Kirtikumar D Modi and Banshi Saboo declare that they have no conflict of interest.

*Compliance with Ethics Guidelines*

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

## References

1. Cryer PE. Hypoglycaemia: the limiting factor in the glycaemic management of type I and type II diabetes. *Diabetologia* 2002; 45:937-948.
2. Viswanathan M, Joshi SR, Bhansali A. Hypoglycemia in type 2 diabetes: Standpoint of an experts' committee (India hypoglycemia study group). *Indian J Endocrinol Metab* 2012; 16:894-8.
3. Amiel SA, Dixon T, Mann R, Jameson K. Hypoglycaemia in Type 2 diabetes. *Diabet Med* 2008; 25:245–54.
4. Inzucchi SE, Bergenstal RM, Buse JB et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2012; 35:1364–1379.
5. Chiang JL, Kirkman MS, Laffel LM, Peters AL, Type 1 Diabetes Sourcebook Authors. Type 1 diabetes through the life span: a position statement of the American Diabetes Association. *Diabetes Care* 2014; 37:2034–2054.

6. American Diabetes Association. Standards of medical care in diabetes-2018. *Diabetes Care* 2018; 41:S1-S159.
7. Khunti K, Alsifri S, Aronson R, Cigrovski Berković M, Enters-Weijnen C, Forsén T, et al. HAT Investigator Group. Rates and predictors of hypoglycaemia in 27 585 people from 24 countries with insulin-treated type 1 and type 2 diabetes: the global HAT study. *Diabetes Obes Metab* 2016; 18:907-15.
8. Gumprecht J, Nabrdalik K. Hypoglycemia in patients with insulin-treated diabetes. Polskie Archiwum Medycyny Wewnętrznej 2016; 126:870-7.
9. Reno CM, Litvin M, Clark AL, Fisher SJ. Defective counterregulation and hypoglycemia unawareness in diabetes: mechanisms and emerging treatments. *Endocrinol Metab Clin North Am* 2013; 42:15-38.
10. Frier & Fisher. In Hypoglycaemia in Clinical Diabetes 3rd ed. Frier & Fisher, eds. Chichester, UK. John Wiley and Sons, 2013; 114–144.
11. Amiel SA. R.D. Lawrence Lecture 1994. Limits of normality: the mechanisms of hypoglycaemia unawareness. *Diabet Med* 1994; 11:918-24.
12. Cryer PE, Axelrod L, Grossman AB, Heller SR, Montori VM, Seaquist ER, Service FJ; Endocrine Society. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2009; 94:709-28.
13. Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, Heller SR, Rodriguez H, Rosenzweig J, Vigersky R. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care* 2013; 36:1384-95
14. Clayton D, Woo V, Yale JF. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Hypoglycemia. *Can J Diabetes* 2013; 37:S69-71.
15. American Diabetes Association. Standards of medical care in diabetes-2017. *Diabetes Care* 2017; 40:S64-S74.
16. Glucose Concentrations of Less Than 3.0 mmol/L (54 mg/dL) Should Be Reported in Clinical Trials: A Joint Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2017; 40:155-157.
17. Watkins et al. Diabetes and its Management. Blackwell Publishing 2003 Pickup & Williams. Slide Atlas of Diabetes. Blackwell Publishing 2004.
18. Muthukrishnan J, Harikumar K, Abhyuday V, Modi K (2008) Visual Vignette. *Endocrine Practice* 2008; 14:799-799.
19. Piette J, A study of English- and Spanish-speakers with diabetes. *American Journal of Preventive Medicine* 1999; 17:138-141.
20. Hypoglycemia questionnaire. Hypoglycemic health association. Last accessed on 27 May 2018. Available from: http://www.hypoglycemia.asn.au/2012/hypoglycemia-questionnaire/.
21. Miller CD, Phillips LS, Ziemer DC, Gallina DL, Cook CB, El-Kebbi IM. Hypoglycemia in patients with type 2 diabetes mellitus. *Arch Intern Med* 2001; 161:1653–1659.
22. UK Hypoglycaemia Study Group. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. *Diabetologia* 2007; 50:1140-1147.
23. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; 352:837–53.
24. Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, et al.; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008; 358:2560-72.
25. Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, et al.; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; 358:2545-59.
26. Reichard P, Britz A, Carlsson P, Cars I, Lindblad L, Nilsson BY, et al. Metabolic control and complications over 3 years in patients with insulin dependent diabetes (IDDM): The Stockholm Diabetes Intervention Study (SDIS). *J Intern Med* 1990; 228:511-7.
27. The DCCT Research Group. Epidemiology of severe hypoglycemia in the diabetes control and complications trial. *Am J Med* 1991; 90:450-9.
28. Shriraam V, Mahadevan S, Anitharani M, Jagadeesh NS, Kurup SB, Vidya TA, et al. Knowledge of hypoglycemia and its associated factors among type 2 diabetes mellitus patients in a Tertiary Care Hospital in South India. *Indian J Endocrinol Metab* 2015; 19:378-382.
29. van Beers CA, DeVries JH, Kleijer SJ, Smits MM, Geelhoed-Duijvestijn PH, Kramer MH, et al. Continuous glucose monitoring for patients with type 1 diabetes and impaired awareness of hypoglycaemia (IN CONTROL): a randomised, open-label, crossover trial. *Lancet Diabetes Endocrinol* 2016; 4:893-902.
30. Turnbull FM, Abraira C, Anderson RJ, Byington RP, Chalmers JP, Duckworth WC, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. *Diabetologia* 2009; 52:2288–2298. Erratum 52:2470.
31. Fanelli CG, Epifano L, Rambotti AM, et al. Meticulous prevention of hypoglycemia normalizes the glycemic thresholds and magnitude of most of neuroendocrine responses to, symptoms of, and cognitive function during hypoglycemia in intensively treated patients with short-term IDDM. *Diabetes* 1993; 42:1683–1689.
32. Amiel SA, Tamborlane WV, Simonson DC, Sherwin RS. Defective glucose counterregulation after strict glycemic control of insulin-dependent diabetes mellitus. *N Engl J Med* 1987; 316:1376–1383.
33. Dagogo-Jack SE, Craft S, Cryer PE. Hypoglycemia-associated autonomic failure in insulin-dependent diabetes mellitus. Recent antecedent hypoglycemia reduces autonomic responses to, symptoms of, and defense against subsequent hypoglycemia. *J Clin Invest* 1993; 91:819–828.
34. Fanelli C, Pampanelli S, Epifano L, et al. Long-term recovery from unawareness, deficient counterregulation and lack of cognitive dysfunction during hypoglycaemia, following institution of rational, intensive insulin therapy in IDDM. *Diabetologia* 1994; 37:1265–1276
35. Cranston I, Lomas J, Maran A, Macdonald I, Amiel SA. Restoration of hypoglycemia awareness in patients with long-duration insulindependent diabetes. *Lancet* 1994; 344:283-287.
36. Dagogo-Jack S, Rattarasarn C, Cryer PE. Reversal of hypoglycemia unawareness, but not defective glucose counterregulation, in IDDM. *Diabetes* 1994; 43:1426–1434.
37. Dagogo-Jack S, Fanelli CG, Cryer PE. Durable reversal of hypoglycemia unawareness in type 1 diabetes. *Diabetes Care* 1999; 22:866–867.
38. Wiethop BV, Cryer PE. Alanine and terbutaline in treatment of hypoglycemia in IDDM. *Diabetes Care* 1993; 16:1131-1136.
39. Atkin S, Javed Z, Fulcher G. Insulin degludec and insulin aspart: novel insulins for the management of diabetes mellitus. *Ther Adv Chronic Dis* 2015; 6:375-88. Review
40. Philis-Tsimikas A, Charpentier G, Clauson P, Ravn GM, Roberts VL, Thorsteinsson B. Comparison of once-daily insulin detemir with NPH insulin added to a regimen of oral antidiabetic drugs in poorly controlled type 2 diabetes. *Clin Ther* 2006; 28:1569-81.
41. Riddle MC, RosenstockJ, GerichJ, for the Insulin Glargine 4002 Study Investigators. The treat-to-target trial: Randomized addition of.glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care* 2003; 26:3080-86.
42. Singh A K. Gangopadhyay KK. Modern basal insulin analogs: An incomplete story. *Indian J Endocrinol Metab* 2014; 18:784–793.
43. Ratner RE, Gough SC, Mathieu C, Del Prato S, Bode B, Mersebach H, et al. Hypoglycaemia risk with insulin degludec compared with insulin glargine in type 2 and type 1 diabetes: a pre-planned meta-analysis of phase 3 trials. *Diabetes Obes Metab* 2013; 15:175-84.
44. Wysham C, Bhargava A, Chaykin L, de la Rosa R, Handelsman Y, Troelsen LN, Kvist K, Norwood P. Effect of Insulin Degludec vs Insulin Glargine U100 on Hypoglycemia in Patients With Type 2 Diabetes: The SWITCH 2 Randomized Clinical Trial. *JAMA* 2017; 318:45-56.
45. Marso SP, McGuire DK, Zinman B, Poulter NR, Emerson SS, Pieber TR, et al. Efficacy and Safety of Degludec versus Glargine in Type 2 Diabetes. *N Engl J Med* 2017; 377:723-732.
46. Ghosal S, Sinha B, Gangopadhyay KK. Insulin glargine versus insulin degludec in patients failing on oral therapy in type 2 diabetes: A retrospective real world comparative data from India. *Diabetes Metab Syndr* 2016; 10:161-5.
47. Heise T, Nørskov M, Nosek L, Kaplan K, Famulla S, Haahr HL. Insulin degludec: Lower day-to-day and within-day variability in pharmacodynamic response compared with insulin glargine 300 U/mL in type 1 diabetes. *Diabetes Obes Metab* 2017; 19:1032-1039.
48. Bailey TS, Pettus J, Roussel R, Schmider W, Maroccia M, Nassr N, et al. Morning administration of 0.4U/kg/day insulin glargine 300U/mL provides less fluctuating 24-hour pharmacodynamics and more even pharmacokinetic profiles compared with insulin degludec 100U/mL in type 1 diabetes. *Diabetes Metab* 2018; 44:15-21.
49. Heller SR, Colagiuri S, Vaaler S, Wolffenbuttel BH, Koelendorf K, Friberg HH, et al. Hypoglycaemia with insulin aspart: a double-blind, randomised, crossover trial in subjects with Type 1 diabetes. *Diabet Med* 2004; 21:769-75.
50. Holcombe JH, Zalani S, Arora VK, Mast CJ. Lispro in Adolescents Study Group. Comparison of insulin lispro with regular human insulin for the treatment of type 1 diabetes in adolescents. *Clin Ther* 2002; 24:629-38.
51. Garg SK, Rosenstock J, Ways K. Optimized Basal-bolus insulin regimens in type 1 diabetes: insulin glulisine versus regular human insulin in combination with Basal insulin glargine. *Endocr Pract* 2005; 11:11-7.
52. Yavuz DG, Bilen H, Sancak S, Garip T, Hekimsoy Z, Sahin I, Yilmaz M, Aydin H, Atmaca A, Sert M, Karakaya P, Arpaci D, Oguz A, Guvener N. Impact of telephonic interviews on persistence and daily adherence to insulin treatment in insulin-naïve type 2 diabetes patients: dropout study. *Patient Prefer Adherence* 2016; 10:851-61.
53. Rizvi AA, Ligthelm RJ. The use of premixed insulin analogues in the treatment of patients with Type 2 Diabetes Mellitus: Advantages and limitations. *Insulin* 2007; 2:68-79.
54. Garber AJ, Wahlen J, Wahl T, Bressler P, Braceras R, Allen E, Jain R. Attainment of glycemic goals in type 2 diabetes with once-, twice- or thrice-daily dosing with biphasic insulin aspart 70/30 (The 1-2-3 study). *Diabetes Obes Metab* 2006; 8:58-66.
55. Liebl A. Management of postprandial glucose: Recommended targets and treatment with biphasic insulin. *Prim Care Diabetes* 2016; 10:391-7.
56. Home P, Naggar NE, Khamseh M, Gonzalez-Galvez G, Shen C, Chakkarwar P, Wenying Y. An observational non-interventional study of people with diabetes beginning or changed to insulin analog therapy in non-Western countries: the A1chieve study. *Diabetes Res Clin Pract* 2011; 94:352-63.
57. Liebl A, Prager R, BinzK, et al., PREFER Study Group, Comparison of insulin analog regimens in people with type 2diabetesmellitus in the PREFER Study: a randomized controlled trial. *Diabetes Obes Metab* 2009; 11:45–52.
58. Unnikrishnan AG, Tibaldi J, Hadley-Brown M, Krentz AJ, Ligthelm R, Damci T, Gumprecht J, Gero L, Mu Y, Raz I. Practical guidance on intensification of insulin therapy with BIAsp 30: a consensus statement. *Int J Clin Pract* 2009; 63:1571-7.
59. Davidson JA, Liebl A, Christiansen JS, Fulcher G, Ligthelm RJ, Brown P, Gylvin T, Kawamori R. Risk for nocturnal hypoglycemia with biphasic insulin aspart 30 compared with biphasic human insulin 30 in adults with type 2 diabetes mellitus: a meta-analysis. *Clin Ther* 2009; 31:1641-51.
60. Franek E, Haluzík M, Canecki Varžić S, Sargin M, Macura S, Zacho J, Christiansen JS. Twice-daily insulin degludec/insulin aspart provides superior fasting plasma glucose control and a reduced rate of hypoglycaemia compared with biphasic insulin aspart 30 in insulin-naïve adults with Type 2 diabetes. *Diabet Med* 2016; 33:497-505.
61. Singh AK. Science of premix insulin: where have we reached?. *Expert Review of Endocrinology & Metabolism* 2014; 10:65-74.
62. Mohan V, Kalra S, Kesavadev J, Singh AK, Kumar A, Unnikrishnan AG, et al. Consensus on Initiation and Intensification of Premix Insulin in Type 2 Diabetes Management. *J Assoc Physicians India* 2017; 65:59-73.