Chapter 51

Indian National Consensus Group: National Guidelines on Initiation and Intensification of Insulin Therapy with Premixed Insulin Analogs

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ABSTRACT

Currently, physicians across the world are striving to practice medicine based on evidence. Evidence-based medicine refers to the incorporation of the most recent clinical research physicians' experience and patients' wishes and needs into clinical practice. The treating physician is often confronted with the dilemma of which insulin to use and currently the use of a patient-centered approach for attaining the glycemic goals is being widely recommended. In 2009, the Indian National Consensus Group (INCG) published the "Premix Insulin: Initiation and Continuation Guidelines for Management of Diabetes in Primary Care" with the aim of providing primary care physicians (PCPs) a simplified regimen based on the patients' and physicians' needs and expectations. This guideline recommended the use of premix insulin regimen for its convenience, safety and efficacy. This was probably one of the first guidelines on insulin therapy in India, which provided a simple guide for initiation and intensification of insulin therapy. Subsequently, the improving management practices and clinical outcomes in type 2 diabetes (IMPACT) study were planned with the objective of validating this guideline and providing insights for further improvement and revision. The purpose of this paper is to contextualize the existing Indian insulin guidelines (IIGs) through evidence-based recommendations for appropriate management and its use in Indian scenario. We propose a systematic approach intended to assist PCPs in developing strategies that can effectively assist in providing optimal glycemic control in type 2 diabetes. Recommendations based on comparative effectiveness and safety of premixed insulin analogs over other regimens have been developed besides focusing on the role of high-ratio premixes, diabetes management in special populations and during periods of fasting. A systemic literature review was conducted covering peer-reviewed studies and publications in the field of management of diabetes with premixed insulin analog based therapies. Although each recommendation has been designed and graded by the weight it should have in clinical practice and by the degree of support from literature, logic and clinical judgment and decisions of individual physicians remain critical for successful implementation of any guideline. It is also worthwhile to note that evidence-based medicine keeps evolving every day and so will guidelines. It is recommended that this guideline may be used for optimizing premixed insulin analog therapy. However, individualization of therapy based on patients' preferences, needs and attitude remain most critical while treating diabetes.

BACKGROUND

Preventing the onset or delaying the progression of late complications of diabetes by achieving and maintaining optimal glycemic control is central to successful diabetes management.[1] Therapeutic strategies to reduce glycemic burden are plentiful; they act by improving insulin secretion/action or reducing intestinal carbohydrate absorption or mimicking the native glucagon-like peptide-1 (GLP-1) and acting on the incretin system.[2] Although these drugs show antihyperglycemic efficacy either as monotherapy or in combination, their utility is often limited owing to their frequent side effects, contraindications and the loss of efficacy over time, particularly in patients with severe β-cell dysfunction. This invariably leads to a situation where insulin treatment becomes mandatory, as it is the ultimate drug of choice when effective, long-term glycemic control is needed.

A wide variety of regimens for using insulin are available, including continuous subcutaneous insulin infusion (CSSI), basal bolus, split-mixed, premixed, basal alone and prandial alone therapy. However, these regimens are often restricted in their capacity to match physiologic conditions owing to the complexity of normal insulin secretion pattern and various pharmacokinetic factors. While basal-bolus regimen is the most ideal treatment strategy for people with diabetes,[3] it needs inconvenient multiple daily injections coupled with an increased cost prompting patients and physicians to delay initiation or optimization of insulin therapy despite the current burden of poor glycemic control.[4] Besides, multiple injections are often seen as an invasion of patients' privacy in some cultures in India and a social constraint.

Premixed insulin preparations, which were made available decades ago, are a simple and convenient regimen that provide, within the same injection, physiological glycemic control. Thus, it has an advantage of providing coverage for postprandial plasma glucose (PPG) in addition to fasting plasma glucose (FPG) with the same insulin resulting in effective glycemic control.[5]

It is interesting to note that both patients and physicians and have expressed a preference for an insulin that requires fewer injections while providing optimal glycemic control. Premixed human insulins have been the cornerstone of managing type 2 diabetes in India and are perhaps one of the most widely prescribed drugs. The recently reported results of A_1cheive®, the largest global observational study in diabetes, reinforce the fact that premixed insulin is the initial insulin of choice in 75% of South Asian patients with type 2 diabetes.[6]

Premixed insulin may be used in all the stages of disease progression and provides an option for easy intensification from

once to twice, and sometimes even to thrice daily dosing to achieve control with lower risk of hypoglycemia.[7] It has been recommended as a treatment strategy in several clinical practice guidelines (CPG), viz. American Association of Clinical Endocrinology (AACE), International Diabetes Federation and INCG.[8-10]

In 2009, the INCG had published the IIGs, which have been well accepted by many of the practitioners of diabetes in India. Besides, the role of using premixed human insulin in treating diabetes in India has been well accepted and appreciated by the authors. Premixed human insulins will continue to be an important modality for treating patients with diabetes. However, in a diverse country like India, patients' needs, attitudes and profiles differ. It is important to note that the current guidelines are an important and complementary addition to the existing IIGs.

Indian National Consensus Group and Premixed Insulin Guidelines

A large proportion of people with diabetes in India are treated by PCPs who perceive initiation and continuation of insulin therapy as being complex and time consuming and are often reluctant about using insulin in the treatment of diabetes.[10] With an aim to provide PCPs a simple algorithm for initiation and titration of insulin therapy, the INCG, comprising of 27 diabetes experts, formulated a guideline on the use of premixed insulin therapy in treatment of people with diabetes, which was published in **Journal of the Association of Physicians of India** (JAPI) in 2009. This was the first guideline on insulin therapy in India, suitable for the existing local needs based on the clinical experience of 250 diabetologists and physicians across the country. The INCG considered premix insulin as a reasonable option effective in all the stages of the disease with the unique advantage of being simple, safe, easy to initiate and continue, and a more physiologically similar option for treating type 2 diabetes mellitus (T2DM) **(Flow chart 1)**. The guidelines also identified differences between premixed human insulins and premixed insulin analogs, suggesting the latter may have certain benefits over the former **(Table 1)**.[10]

TABLE 1 | Advantages of premix insulin analog over premix human insulin[10]

Parameter	Premixed human insulin	Premixed insulin analog
Postprandial glucose control	+	+++
Fasting glucose control	++	++
HbA_{1c} control	+	++
Less hypoglycemia	+	++
Meal-time flexibility	+	+++
Weight gain	+	++

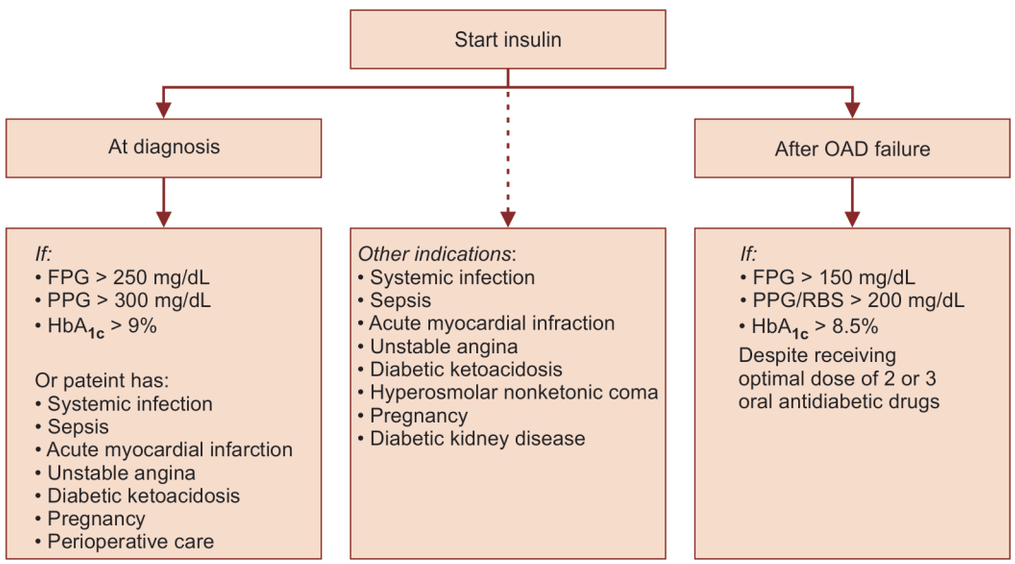
Validation of the INCG Guidelines: The "IMPACT" Study

A need to validate the effectiveness and impact of the IIGs in real-life clinical practice was felt by INCG. Hence, a 26-week prospective, randomized, open-label, comparative and multicenter study "IMPACT" was conducted. It is a first prospective study on validation of a diabetes guideline in the world and one of the largest studies in diabetes involving more than 20,653 patients and 1,133 study sites. The primary objective of the study was to evaluate effectiveness of IIG compared to routine clinical practice (RCP) in patients with T2DM. Efficacy was evaluated from the proportion of patients reaching the target hemoglobin A_{1c} (HbA_{1c}) level of less than 7% and analyzing the mean change in HbA_{1c} from baseline to the end of the study, while safety was determined by incidence of adverse drug reactions including hypoglycemia (major, minor and nocturnal events) in patients during the study period. The secondary objective of the study was to evaluate the physician's perceptions on the use of IIG versus RCP for management of T2DM.[11]

Key Results and Learning from the IMPACT

The study demonstrated that IIG make insulin initiation and intensification easy, simple and convenient to implement in clinical

Flow chart 1: Initiating insulin therapy in diabetes



Source: Adapted from the INCG Guidelines 2009[10]
Abbreviations: OAD, Oral antidiabetes drug; FPG, Fasting plasma glucose; HbA_{1c}, Glycosylated hemoglobin; PPG, Postprandial plasma glucose; RBS, Random blood sugar

practice and result in better reductions in HbA_{1c} over a period of time when compared to the RCP group [2.01 (1.201) vs 1.90 (1.179), p = 0.0115], enabling more patients to achieve the American Diabetes Association's (ADA) prescribed targets of HbA_{1c} less than 7% (32.4% vs 27.3%). Primary care physicians in India have perceived the IIG to be easy algorithm to initiate and titrate insulin therapy.[11]

Thus, the objective of this paper is to contextualize the existing IIG through evidence-based recommendations for its use in Indian scenario. We propose a systematic approach to treatment, which includes aspects such as choosing optimal insulin combinations, timely initiation, intensification and switching to insulin therapy using premixed insulin analogs, apart from the role of high mixes and insulin delivery devices in diabetes management.

METHODOLOGY

The current guideline has been developed in accordance to the AACE protocol for standardized production of CPG **(Table 2)**.[8] Recommendations are organized by topic and are assigned evidence level (EL) ratings on the basis of the quality of supporting evidence all of which have also been rated for strength **(Table 3)**.[8] The format of this CPG is based on specific and relevant clinical questions.

A thorough literature search pertaining to each of these classes of recommendations presented has been framed in terms of clinical questions, pertinent to the Indian context of diabetes. Recommendations are based on importance and evidence (Grades A, B and C) or expert opinion when there is a lack of conclusive clinical evidence (Grade D). There are four intuitive levels of evidence: 1 = "Strong", 2 = "Intermediate", 3 = "Weak" and 4 = "No Evidence" and they have been positioned on the basis of available evidence to be used for grading recommendations.

Thus, the current recommendations are a result of a process, which incorporates the patient and physician concerns of a complex clinical scenario with the objective of evidence-based rigor of different studies. Where appropriate, multiple recommendations are provided, so that the reader has management options. This document represents only a guideline. Individual patient circumstances and presentations differ, and the ultimate clinical management is based on what is in the best interest of the individual patient, involving patient input and reasonable clinical judgment by the treating clinicians. A model for incision of insulin therapy in existing algorithm for diabetes management has been proposed in **Flow chart 2** by the INCG.

TABLE 2 | Evidence rating according to AACE protocol 2010[8]

Evidence level*	Semantic descriptor (reference methodology)
1	Meta-analysis of randomized controlled trials
1	Randomized controlled trials
2	Meta-analysis of nonrandomized prospective or case-controlled trials, systemic literature review
2	Nonrandomized controlled trial
2	Prospective cohort study
2	Retrospective case-control study
3	Cross-sectional study
3	Surveillance study (registries, surveys, epidemiologic study, retrospective chart review, mathematical modeling of database)
3	Consecutive case series
3	Single case reports, observational study, Pilot study
4	No evidence (theory, opinion, consensus, review or preclinical study)

* 1 = strong evidence; 2 = intermediate evidence; 3 = weak evidence and 4 = no evidence

Abbreviation: AACE, American Association of Clinical Endocrinologists

TABLE 3 | Recommendation grading according to the AACE protocol 2010[8]

Grade	Strength of recommendation
A	Strong
B	Intermediate
C	Weak
D	Not evidence-based

Abbreviation: AACE, American Association of Clinical Endocrinologists

INTEGRAL ETHNOPHARMACY AND INSULIN THERAPY

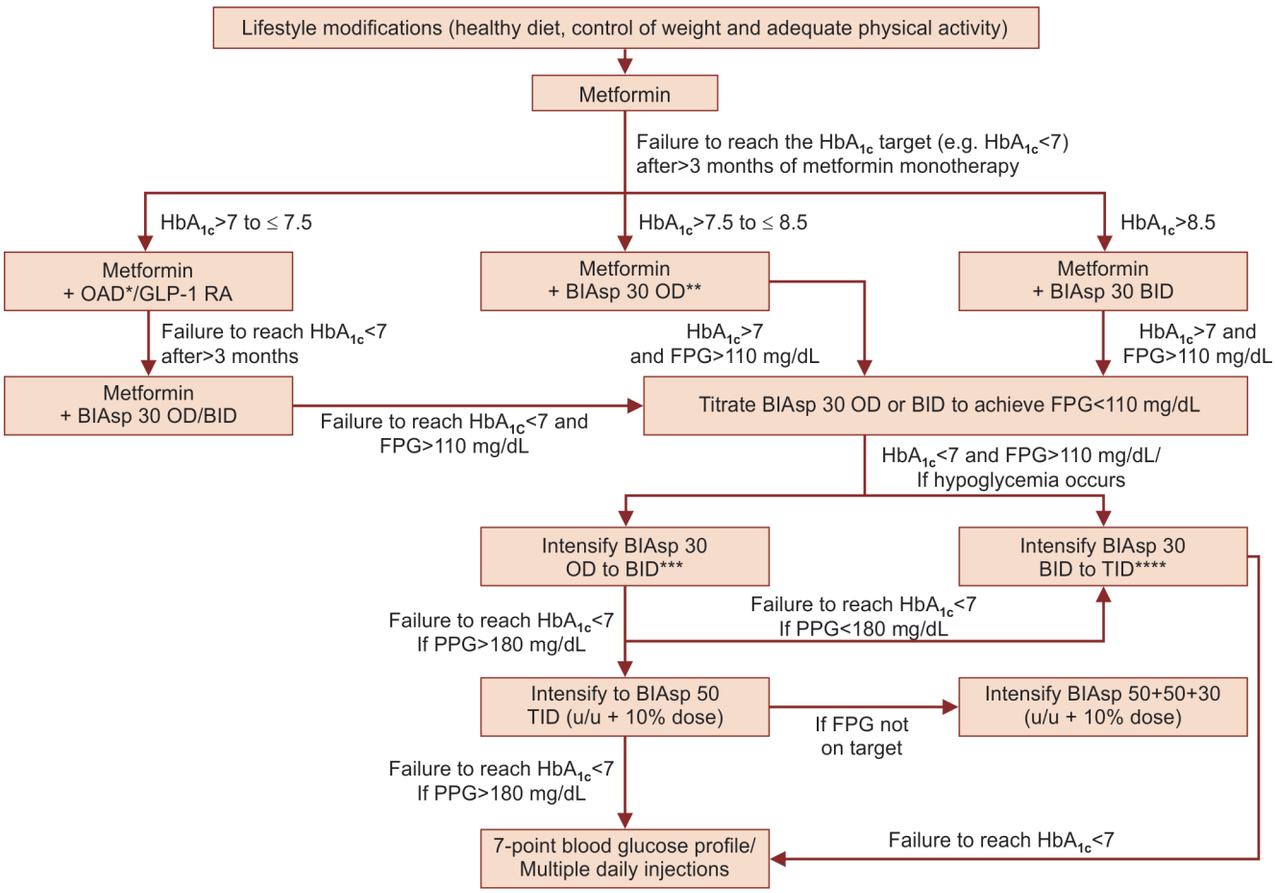
The degree of success of antidiabetic therapy depends on number of variables that could include the type of medication and dosing algorithm, possible cultural and physiological variables that differ by race or ethnicity, and the extent of healthcare professional involvement. Racial, cultural and ethnic disparities are known phenomena for differences in dietary patterns, glucose metabolism, insulin resistance that are responsible for variations in glucose control.[12] Data from several studies indicate that high intake of fats, saturated fats, carbohydrates and trans fatty acids in South Asians is associated with hyperinsulinemia, postprandial hyperglycemia and hypertriacylglycerolemia among adults and fasting hyperinsulinemia in children and young individuals.[13] Studies have also shown that young South-east Asians had the highest postprandial glycemia in response to a realistic carbo-hydrate load compared to matched Caucasians (135 mg/dL vs 111.6 mg/dL) even in patients with low body mass index (BMI).[14] Furthermore, it was found that South Asians are at increased risk for insulin resistance and dyslipidemia irrespective of BMI, which may account for hyperinsulinemia and increased prevalence of diabetes and cardiovascular diseases (CVDs) compared with other ethnic groups.[15]

The "metabolically obese" phenotype (i.e. normal body weight with increased abdominal adiposity), increased risk of gestational diabetes combined with exposure to poor nutrition in Asian population may contribute to increased diabetes and its complications in Asia.[16] As evident from initiation of insulin to reach A_{1c} target (INITIATE) plus trial, diabetes self-management with premixed insulin analog, biphasic insulin aspart 30 (BIAsp 30) with an easily followed self-titration algorithm has shown to produce better glycemic control with low hypoglycemia rates irrespective of race and ethnic backgrounds.[17] In another study by Strojek et al. involving both Asians and Caucasians, the subgroup analyzes suggest that treatment with BIAsp 30 might be favorable compared to insulin glargine in Asians particularly with respect to nocturnal hypoglycemia.[18,19]

Recommendations

- Since, PPG response to a meal is more pronounced in ethnic Asian communities, premixed insulin analogs that improve PPG should be the preferred method of insulin initiation in this population[12,14,18,19] **(Grade A, EL 1)**.
- Initiating insulin with, or switching to, insulin analog therapies is recommended for greater treatment satisfaction and increased health related quality of life irrespective of race, ethnicity and gender[20,21] **(Grade A, EL 1)**.
- In insulin-naïve (Asian) patients with T2DM inadequately controlled with oral antidiabetes drugs (OADs), combination of once or twice daily premixed insulin analogs, with metformin and/or glimepiride should be recommended over basal insulins

Flow chart 2: Insulin therapy algorithm: a proposed model for inclusion of insulin therapy in existing algorithm for diabetes management



*OAD can be a sulfonylurea/ TZD/ DPP-4i or any other drug as per the clinician's judgment
**Start with OD 10-12 units (0.1-0.2 U/kg body wt.)
- In the morning: if the pre-dimmer blood glucose is high
- In the evening: if the pre-breakfast blood glucose is high
- Split the dose when dose is > 30 units

***Intensification from OD to BID
- Split the OD dose into equal breakfast and dinner doses (50:50)

****Intensification from OD to BID
- Add 2-6 U or 10% of total daily BIAsp 30 dose before lunch
- Down-titration of morning dose (-2 to 4U) may be needed after adding the lunch dose

In both cases, continue metformin and administer BIAsp 30 just before meals

Abbreviations: BIAsp, Biphasic insulin aspart; BhAlc, Glycosylated haemoglobin; OAD, Oral antidiabetic drug; GLP-1 RA, Glucagon like peptide receptor agonist; TZD, Thiazolidinedione; DPP4-i, Dipeptidyl peptidase inhibitor; PPG, Postprandial glucose; FPG, Fasting plasma; OD, Once daily; TID, Thrice daily; u/u + 10% dose, unit/unit plus 10% of total dose (added at lunch).

BIAsp is the most widely prescribed premixed insulin analogue in India and consequently has been chosen as an example to describe the initiation and intensification of insulin therapy using premixed insulin analogs.

with metformin and/or glimepiride combination for greater reduction in HbA_{1c}, PPG levels and lower risk of nocturnal hypoglycemia[18,19,22,23] **(Grade A, EL 1)**.

- Initiation of twice daily premixed insulin analogs using self-titration dose algorithm in insulin-naïve patients irrespective of race and ethnicity is recommended for better glycemic control and lower rates of hypoglycemia (compared to premixed human insulins)[17] **(Grade A, EL 1)**.

GLYCEMIC PARAMETERS

Glycated Hemoglobin (HbA_{1c})

Evidence from several studies indicate that use of premixed insulin analogs showed significant reductions in HbA_{1c} and better glycemic control in insulin-naïve patients with inadequately controlled type 1 diabetes mellitus (T1DM) or T2DM.[24] Additionally, patients treated with premixed insulin analogs were also more likely to reach a target HbA_{1c} of 6.5% or lower compared to those treated with basal insulin.[25]

Recommendations

- Addition of premixed insulin analog to optimized OAD regimen in patients with T2DM uncontrolled on OADs should be considered for effective reduction in HbA_{1c}[24-26] **(Grade A, EL 1)**.
- Addition and progressive intensification of premixed insulin analogs OD to TID over second oral agent to metformin is recommended for achieving better glycemic control, particularly where HbA_{1c} more than or equal to 9%[27,28] **(Grade A, EL 1)**.

Fasting Plasma Glucose

The overall hyperglycemia in T2DM can be depicted as the sum of both fasting and postprandial hyperglycemia; however, the relative contribution of FPG to HbA_{1c} may predominate as the disease worsens.[29] Several trials evaluating the efficacy of premixed insulin analogs in T2DM patients have reported similar reduction in FPG when compared to long-acting insulin analogs,[22,23] or intermediate-acting human insulin preparations.[30,31] However, premixed analogs were found to be more effective than long-acting insulin analogs in lowering pre-dinner glucose levels ($p < 0.05$).[22]

Recommendations

- Premixed insulin analogs are recommended for T2DM over insulin glargine or insulin detemir for better glycemic control and similar FPG reduction in older individuals with higher BMI and bedtime plasma glucose[22,32,33] **(Grade A, EL 1)**.
- Type 2 diabetes mellitus patients on premixed human insulin should be considered switching to premixed insulin analogs for improved pre-dinner and pre-lunch glucose levels respectively[34] **(Grade A, EL 2)**.

Postprandial Plasma Glucose

It is well-known that PPG control may play a crucial role in achieving near normal glycemic control especially in the low range of HbA_{1c} values.[29] Evident from several studies indicate that even in patients with good overall glycemic control, elevated PPG levels are a substantial contributor to daytime hyperglycemia. Premixed insulin analogs offer the advantage of combining in a single injection before a meal both the rapid-acting insulin, which is needed to control PPG and the basal insulin, which covers the inter-meal period.[35] Several studies have shown that premixed insulin analogs are superior over other insulin regimens in decreasing PPG with an added advantage of lower risk of hypoglycemia.[24]

Premixed insulin analogs have been found to be more effective than long-acting insulin analogs alone[22-24] and premixed human insulin[30] in lowering PPG. Mean difference of change in PPG level with premixed insulin analogs was found to be: –27.9 mg/dL, –19.2 mg/dL and –37.4 mg/dL against long-acting insulin analogs, premixed human insulin and noninsulin antidiabetic agents respectively.[24] Furthermore, premixed analogs were found to be more effective in lowering breakfast and dinner PPG than intermediate-acting insulin preparations.[31]

Recommendations

- Initiation or switching to twice daily premixed insulin analogs should be considered in patients with T1DM and T2DM, poorly controlled on premixed human insulin or normal pressure hydrocephalus (NPH) for improved PPG control without increased risk of hypoglycemia[31,36,37] **(Grade A, EL 1)**.
- Initiation of insulin regimen with premixed insulin analogs rather than basal insulin may be considered as an appropriate choice to target HbA_{1c}, in older individuals and those with higher bedtime plasma glucose[32] **(Grade A, EL 1)**.
- Given the evidence that PPG control may be more important when HbA_{1c} levels are low, premixed insulin analog would be most appropriate choice for patients requiring insulin[24] **(Grade A, EL 1)**.

Hypoglycemia

The fear of developing hypoglycemia remains a substantial barrier to the initiation and optimal use of insulin therapy. Data from several studies indicate that incidence of hypoglycemia, particularly major and nocturnal hypoglycemia was significantly lower with premixed insulin analogs when compared to premixed human insulin.[30,37-39] A recent meta-analysis indicated that analogs were associated with a significantly lower rate of nocturnal and major hypoglycemia compared to premixed human insulin in T2DM patients.[38]

Recommendation

Premixed insulin analogs are recommended over premixed human insulin as they have comparatively lower rates of nocturnal and major hypoglycemia[38] **(Grade A, EL 1)**.

Glycemic Variability

Meeting the glycemic goals while minimizing glucose variability and hypoglycemia is of much importance while considering insulin therapy. An emerging body of evidence supports the view that glycemic variability is an HbA_{1c} independent risk factor, and has deleterious effects than sustained hyperglycemia in the development of diabetic complications. Data from several observational studies have shown that PPG is a substantial contributor to daytime hyperglycemia even in those patients with T2DM who have good overall glycemic control.[29] As patients get closer to their target HbA_{1c} levels, an elevation in PPG has a much greater impact on HbA_{1c} compared with FPG.[29] In a study by Ohta et al. T2DM patients on treatment with twice daily premixed analogs were found to improve the 48-hour average glucose level and mean amplitude of glucose excursion compared with the same dosage of premixed human insulin.[40] Furthermore, the premixed insulin analog (BIAsp 30 in this case) was not associated with hypoglycemia or deterioration of glycemic control before meals and at night. Evidence from the multiple studies clearly indicate that regimens such as premixed insulin analogs may be considered a suitable therapeutic option to prevent glycemic variability among patients with diabetes who are at greater risk of diabetic complication despite well-controlled HbA_{1c}.[24,31,36,40]

Recommendations

- Patients with T2DM experiencing rapid glucose excursions irrespective of controlled HbA_{1c} should be considered for twice daily premixed insulin analog therapy for effective reduction in glycemic variability aimed through PPG control[36] **(Grade A, EL 1)**.
- Twice daily BIAsp 30 may be considered over premixed human insulin for favorable 48-hour glucose profile with reduced mean amplitude of glucose excursion, PPG and standard deviation (SD) of glucose excursion, without additional hypoglycemia or deterioration of glycemic control[40] **(Grade A, EL 2)**.

Glycemic Durability

After initiation of insulin therapy, if patients with T2DM are unable to achieve HbA_{1c} level less than 7.0%, insulin intensification may be indicated. However, it should be noted that an ideal therapy is one which will be able to provide sustained glycemic control over longer duration. Thus, a better understanding of factors influencing the ability of specific regimens to achieve and maintain glycemic control is needed. Although several studies have compared the safety and efficacy of starter insulin regimens in T2DM, evidence regarding the length of time a patient is able to maintain glycemic control with a specific starter insulin regimen is lacking.[24] Evident from durability of basal versus lispro mix 75/25 insulin efficacy (DURABLE) trial, which compared the safety, efficacy and durability of twice daily premixed insulin analog to once daily insulin glargine resulted in better glycemic control with higher percentage of patients reaching HbA_{1c} targets compared to the basal insulin. Furthermore, patients with lower baseline HbA_{1c} were more likely to achieve longer

glycemic durability for over 2 years with premixed insulin analogs than with basal insulins, supporting the concept of earlier insulin initiation.[41,42]

Recommendation

Early initiation of insulin therapy with premixed insulin analogs BID or TID is recommended in T2DM patients for better and longer glycemic durability and lower incidence of nocturnal hypoglycemia[41,42] **(Grade A, EL 1)**.

NONGLYCEMIC PARAMETERS

Flexibility and Lifestyle

Premixed insulin analogs offer several advantages over other insulin regimens in terms of convenience, meal time flexibility and less monitoring.[7,24,30] Furthermore, they offer the patient a greater degree of flexibility in terms of injection timing, allowing individual adjustment for meal size and timing without significantly affecting efficacy warranting greater patient satisfaction and improved treatment adherence. This may be particularly useful for the elderly, in circumstances where meal size and/or timing are uncertain.[43] Moreover, availability of these formulations as portable insulin pens in fixed-mixed combinations allows rapid selection of the correct dose minimizing the errors that can occur when patients self-mix insulin combinations. By enabling more discrete injection, they minimize potential embarrassment associated with public injection, giving individuals more lifestyle flexibility.

Recommendations

- For enhanced meal time flexibility and convenience, premixed insulin analog should be considered over other insulin regimens (including premixed human insulin) as treatment option for insulin-naïve patients with T2DM[43] **(Grade A, EL 1)**.
- Premixed insulin analogs may be considered a suitable option for elderly T2DM patients with irregular meal size and/or timing for better glycemic control and lower incidence of day time hypoglycemia[43,44] **(Grade A, EL 1)**.

Body Weight

Besides hypoglycemia, fear of weight gain is another major limitation for early initiation of insulin therapy in patients with T2DM. Numerous studies have documented that in spite of improvements in glycemic control with insulin and/or oral hypoglycemic agents (OHAs), they are frequently associated with undesirable increase in bodyweight. Studies have shown that treatment with analogs in T2DM patients was associated with relatively lesser weight gain over premixed human insulin or rapid acting insulin analogs;[30,37] while it showed no significant difference in the body weight in patients when compared to combination of rapid and long-acting insulin analogs.[44]

Recommendation

Obese T2DM patients inadequately controlled on premixed human insulin may be considered switching to premixed insulin analogs to minimize further weight gain and provide better glycemic control[45] **(Grade A, EL 2)**.

Quality of Life

Uncontrolled T2DM has a negative impact on the quality of life (QoL). Successful management of diabetes constitutes effective glycemic control along with, maintaining or improving QoL. Some of the factors contributing to poor QoL include lifestyle change, complex treatment regimens, multiple and self-injection, and sometimes fear of hypoglycemia and weight gain along with adverse perceptions of diabetes therapies. Data from several studies clearly demonstrate that beginning or switching to BIAsp 30 was associated with significant improvements in the glycemic control and health-related QoL (HRQoL) in people with poor glycemic control in RCP across diverse geographical regions.[21,46]

Recommendation

Initiating insulin therapy with or switching to premixed insulin analog therapy should be considered in patients with T2DM for enhanced QoL in terms of mobility, self-care, usual daily activities, pain/discomfort and anxiety/depression[21,46] **(Grade A, EL 1).**

INDICATIONS IN SPECIAL POPULATIONS

Hypersensitivity and Hypoglycemia

Premixed insulin analogs are generally well-tolerated in patients with T2DM. Data from clinical studies indicate no adverse events in patients treated with premixed insulin analogs except for hypoglycemic episodes and weight gain. Premixed insulin analogs should not be used in patients who are suspected to be allergic to either insulin aspart or insulin lispro or any of the excipients contained in the formulation. These formulations can be used in reduced doses in cases of hypoglycemia based on the clinical judgment of the treating physician.

Pregnancy and Lactation

Gestational diabetes mellitus (GDM) is associated with an increased rate of adverse outcomes for both mother and fetus. Women with GDM may be prescribed either soluble human insulin or fast-acting insulin analogs when uncontrolled on medical nutrition therapy. Data from studies indicate no significant difference between premixed insulin analogs and premixed human insulin in terms of glycemic control or difference in neonatal birth weight. However, mean total dose of insulin was found to be lower with BIAsp 30 suggesting that a lower dose is required to achieve a comparable level of glycemic control.[47] Furthermore, pregnant women found analogs to be convenient due to flexible dosing and more importantly it was found to be safe during pregnancy.[48] Although there are no restrictions on treatment with premixed insulin analog during breastfeeding, it is advised for adjustment of dose based on need of the patient. The United States Food and Drug Administration (US-FDA) classify BIAsp 30 as pregnancy category B, reflecting the fact that they are safe in pregnant woman at clinically relevant doses.

Recommendations

- Intensified blood glucose control and monitoring of pregnant women with diabetes are recommended throughout pregnancy and when contemplating pregnancy. The dose of premixed insulin needs to be adjusted during pregnancy and lactating mothers on an individual basis **(Grade A, EL 4)**.
- Premixed insulin analogs may be considered over premixed human insulin in pregnant women for better glycemic control with lower doses of insulin and greater flexibility in the meal time insulin dosing without disturbing their routine life pattern[47,48] **(Grade A, EL 2)**.

Type 1 Diabetes Mellitus and Children

Data from a study comparing the efficacy of premixed insulin analogs and premixed human insulin in 167 adolescent patients with T1DM indicate similar glycemic control and similar incidence of hypoglycemic episodes between the two groups.[49] In another study, premixed analogs given TID resulted in significant reduction in HbA_{1c} compared to human insulin in patients with T1DM (BIAsp

30 vs human insulin: 8.6% vs 8.3%; p < 0.013).[50] However, treatment with premixed insulin analogs resulted in a more favorable degree of PPG control than premixed human insulin.

Recommendation

In adolescent patients with type 1 diabetes, premixed insulin analogs should be considered over human insulin for favorable degree of PPG control and significant lowering of HbA_{1c}[49,50] **(Grade A, EL 1)**.

Cardiac, Renal and Hepatic Failure

Given that premixed insulin analogs reduce PPG more effectively than premixed human insulins and basal insulin analogs it could be hypothesized that they may help to reduce the long-term risk of cardiovascular (CV) complications. Also, there is paucity of data to determine the effects of premixed insulin analogs on long-term outcomes, such as mortality, CVD, kidney disease, neuropathy, retinopathy and long-term weight change, compared with other antidiabetic medications.

Recommendations

- A regular blood glucose monitoring and dose adjustments are recommended in T2DM patients with reduced kidney or liver function when they are treated with premixed insulin analog, BIAsp 30 **(Grade A, EL 4)**.
- Patients with T2DM on combination therapy of premixed insulin analogs and OADs should be carefully monitored for signs and symptoms of heart failure, weight gain and edema, and a prompt clinical action is recommended if any deterioration in cardiac symptoms occurs **(Grade A, EL 4)**.

GUIDANCE FOR THERAPY IN TYPE 2 DIABETES MELLITUS

Initiation of Insulin Therapy

Recommendations

- In patients with T2DM poorly controlled on OADs, initiating insulin therapy with premixed insulin analogs should be considered over basal insulin analogs or premixed human insulin, especially in patients with HbA_{1c} more than 8.5%, for effective glycemic control[18,19,22,23,25,33,41,42] **(Grade A, EL 1)**.
- The initiation of premixed insulin analog is recommended in insulin-naïve patients aged more than 65 years with T2DM poorly controlled by OADs and dietary counseling interventions for improved glycemic control and significant reduction in FPG[33] **(Grade A, EL 2)**.

Intensification of Insulin Therapy

Patients requiring intensified insulin therapy can essentially be grouped into two categories: (1) those who started insulin with basal therapy and can no longer maintain glycemic control, and (2) those using premixed insulin analogs OD or BID and failing to maintain adequate glycemic control.[51] The ability to start insulin therapy with BIAsp 30 OD opens the possibility of a step-wise approach to intensify therapy to twice and even thrice daily in patients to achieve target HbA_{1c} levels.[5] As evident from PRESENT and IMPROVE™ studies, intensification with premixed analogs in T2DM patients inadequately controlled on basal insulin, has been shown to improve glycemic control with mean reduction in HbA_{1c} of 1.6% and 1.83% compared to 1.42% and 1.72% as observed with basal insulins.[52,53]

Initiation and/or intensification of insulin therapy with premixed insulin analogs in patients with T2DM is an effective treatment approach for achieving glycemic goals as illustrated by an observational "1 2 3 study" which indicated that addition and self-titration of BIAsp 30 once, twice, or three times daily enabled 41%, 70% and 77% of patients to achieve an HbA_{1c} goal of less than 7.0%, respectively.[54] It has been suggested that physicians should consider intensifying basal insulin to BIAsp 30 BID if HbA_{1c} is more than 8.0%, or if HbA_{1c} is between 7% and 8% and FPG is optimized. If a patient on BIAsp 30 OD or BID has within-target FPG but an HbA_{1c} more than 7%, a switch to BIAsp 30 BID or TOD should be considered. If their FPG is above target, the dose should be titrated to achieve FPG 4–6 mmol/L (72–108 mg/dL); however, if hypoglycemia occurs, an additional daily dose should be added rather than further dose titration.[51]

Recommendations

- In patients with T2DM failing to reach glycemic targets on basal insulin treatment, intensification with premixed insulin analogs is recommended for better glycemic control and greater treatment satisfaction without an increase in overall hypoglycemia[52,53] **(Grade A, EL 2)**.
- In patients with T2DM failing to achieve glycemic control on OADs alone, addition and sequential dose titration of BIAsp 30 from OD to TID is recommended for improved glycemic control[51,54] **(Grade A, EL 2)**.
- When intensifying BIAsp 30 from OD to BID, it is recommended to split the OD dose into equal breakfast and dinner doses (50:50) that is to be taken just before meals and titrate doses as per the algorithm given in **Table 4**[51] **(Grade A, EL 3)**.
- When intensifying BIAsp 30 from BID to TID, consider adding 2–6 U or 10% of total daily BIAsp 30 dose before lunch, which may require down titration of morning dose (–2 to 4 U)[51] **(Grade A, EL 3)**.

Switching Prior Insulin Therapy to Premixed Insulin Analogs

Data from large observational studies suggested that when patients were switched from existing insulin therapy to premixed insulin analogs for 6 months, significant reduction in HbA_{1c} with lower incidence of hypoglycemia and greater treatment satisfaction were observed. A unit-for-unit switch in patients with T2DM from premixed human insulin or basal-bolus regimen to BIAsp 30 showed a significant reduction in HbA_{1c}, FPG and PPG (p < 0.0001) with greater proportion of patients (91%) achieving target HbA_{1c} less than 7%.

Recommendation

A unit-for-unit switch from premixed human insulin to premixed insulin analog is recommended for improvements in glycemic control with reduced risk of hypoglycemia and improved patients' satisfaction[55] **(Grade A, EL 1)**.

TABLE 4 | Titration algorithm for BIAsp 30 based on PPG values[51]

PPG values		Dose change
< 4.4 mmol/L	< 80 mg/dL	–2 U
4.4–6.1 mmol/L	80–110 mg/dL	0
6.2–7.8 mmol/L	111–140 mg/dL	+2 U
7.9–10.0 mmol/L	141–180 mg/dL	+4 U
> 10.0 mmol/L	> 180 mg/dL	+6 U

Abbreviations: BIAsp 30, Biphasic insulin aspart 30; PPG, Postprandial plasma glucose

Role of High Mixes in Intensification of Insulin Therapy

Patients with T2DM on premixed insulin are commonly prescribed to "low-ratio" premixed insulin analogs with low prandial insulin content, such as BIAsp 30, comprising 30% rapid acting insulin. However, some patients continue to have high PPG levels despite twice daily regimens of low-ratio premixes requiring intensified insulin therapy, which can be provided by a third-daily injection but may sometimes result in hypoglycemia. Alternatively, a twice or thrice daily regimen of mid-ratio insulin (comprising 50% rapid-acting insulin) or high-ratio insulin (comprising 70% rapid-acting insulin) may be incorporated in the treatment regimen for patients who require more prandial insulin to reach glycemic control.[35,56] Although, the number of studies reporting the use of mid-ratio and high-ratio premix regimens are few, the available indicate that they are generally well-tolerated with less frequent incidence of nocturnal hypoglycemia than with premixed human insulin.

Recommendations

- Substituting dinner injections of low-mix regimens (BIAsp 30) of premixed insulin analogs with high-mix regimens (BIAsp 50) should be considered in patients with higher incidence of nocturnal hypoglycemia for improved glycemic control[35] **(Grade A, EL 1)**.
- Patients with T2DM and elevated FPG and PPG levels may benefit most on treatment with high-mix regimen (BIAsp 50) than with low-mix regimen (BIAsp 30), as it has equal proportions of prandial and basal insulin analog[56] **(Grade A, EL 1)**.
- Patients may be switched from other premixed insulins on a 1:1 dose substitution, depending on the needs of the individual patient and their prior regimen[56] **(Grade A, EL 1)**.

Role of Insulin Delivery Devices

Currently available insulin pens are either durable (penfill is replaceable, e.g. NovoPen® 4, HumaPen®) or disposable (prefilled, e.g. FlexPen®, SoloStar®, KwikPen®). They typically feature a large dose selector dial-up and dial-down facility, audible clicks when selecting the dose and a discreet appearance, which are generally viewed as being easy for patients to use and preferred over syringes and vials. The potential for dosing errors is thus reduced with these devices, with other benefits including ease of learning and greater user confidence. These user-friendly devices may facilitate both compliance and effective insulin treatment of patients with T1DM or T2DM. In addition, they offer a more accurate way to inject insulin. This can be particularly important for those patients with vision impairment or manual dexterity issues and can allow them to independently manage their disease.[5] A majority of patients have considered devices easier, more convenient and quicker to use than conventional insulin therapy (with vials and syringes); and more than 94% of patients have agreed that with pen devices it is easy to set the dose, read the dose scale, change the cartridge and convenient for everyday handling. Recently, a large real-life study in patients with diabetes evaluated treatment satisfaction with NovoPen® 4 compared with their previous device (NovoPen® 3, HumaPen®Ergo, OptiPen® Pro, others) in insulin-experienced and insulin-naïve patients. People with diabetes reported significantly greater satisfaction with their diabetes treatment after 12 weeks of using NovoPen® 4, compared with their previous insulin delivery device. Ease of use and patient preference for pen devices may lead to improved management of insulin injections in people with diabetes requiring insulin treatment.[57] Similarly, studies have shown that the new generation FlexPen® has advantages over SoloStar® and KwikPen® in terms of improved accuracy and reduced injection force.[58]

Recommendations

Type 2 diabetes mellitus (T2DM) patients with mild visual impairment and dexterity deficits, use of an insulin pen device is recommended for more accurate way of injecting insulin and avoids dosing errors that can allow them to independently manage their disease[5] **(Grade A, EL 2)**.

- Use of insulin pen device is recommended in patients on premixed insulin analogs for rapid selection of the correct dose, as it minimizes the errors that can occur when patients self-mix insulin combinations[5] **(Grade A, EL 2)**.
- Use of reusable pen (e.g. NovoPen® 4) should be considered as they present with improved features that may ultimately encourage greater compliance with prescribed treatment regimens[58] **(Grade A, EL 1)**.

Treatment Adherence

Patient adherence to treatment is the greatest predictor of success that not only determines intermediate and clinical outcomes but also quality of life. Although no direct studies evaluating patient adherence on premixed insulin analog therapy has been reported, given the higher patient satisfaction over premixed human insulins, simplified treatment regimen with fewer injections and less monitoring than a basal-bolus regimen and the fact that the premixed insulin analogs allow more flexible injection timing;[10,54] they have the potential to increase adherence-related cost reduction. American association of clinical endocrinologists (AACE) guidelines have also indicated the use of premixed insulin analogs for patients in whom adherence to treatment regimen is an issue.[8,10]

Recommendation

Use of premixed insulin analogs should be considered over premixed human insulins and more complex basal bolus regimen in management of diabetes for higher patient satisfaction, flexible meal-time dosing, and fewer daily injections coupled with lesser monitoring that would result in increased treatment adherence and reduced adherence related cost[8,10,46,54] **(Grade A, EL 2)**.

GUIDELINES FOR USE OF PREMIXED INSULIN ANALOGS DURING FASTING

In many developing countries including India, diverse sociocultural and religious factors play an important role in the clinical progression, treatment and outcome of any disease management. Specialized fasting periods, which are defined as a partial or total abstinence from food in many religions across the country, may warrant supervised treatment of chronic diseases like diabetes. Often, these cultural factors coupled with lower awareness and literacy rates contribute to poor adherence to therapy resulting in unsatisfactory glycemic control. Although diabetes management during shorter fasting periods as observed in Hindus could be managed by appropriate adjustment in dose and dosing schedule, the health effects of religious fasting, particularly during Ramadan which is observed for a period of 1 month, have been the subject of scientific inquiry for the past two decades.

Fasting during Ramadan is one of the principal rituals among Muslims during which they abstain from eating and drinking from dawn to sunset for about 30 days. Besides hypoglycemia, other risk factors include hyperglycemia, diabetic ketoacidosis, dehydration and thrombosis.[59]

Judicious use of long-acting or intermediate-acting insulin preparations in combination with short-acting insulin preparations administered before meals may be considered as treatment of choice to prevent fasting hyperglycemia in diabetic patients fasting during

Ramadan. Premixed insulin analogs offer several advantages over human insulin regimens including rapid onset of action, better PPG control, lower incidence of nocturnal hypoglycemia and greater meal time flexibility. Furthermore, they can be started once daily before evening meal and can be intensified to twice daily (morning and evening) to reach target glycemic control without significant risk of hypoglycemia.

Recommendations

- Type 2 diabetes mellitus patients on premixed insulin therapy are recommended to use the usual morning dose at the sunset and half the usual evening dose at pre-dawn meal, i.e. patients on BIAsp 30 with 30 units in morning and 20 units in the evening before Ramadan, the recommended dose will be 30 units in the evening (Iftar) and 10 units in the morning (Sahur) during Ramadan[60] **(Grade A, EL 3)**.
- Physicians should educate the patients on the availability of modern insulin analogs for diabetes care during Ramadan for better control and therapeutic outcome[60] **(Grade A, EL 4)**.

CONCLUSION

In patients with T2DM inadequately controlled with OADs, insulin is often required in order to achieve good glycemic control as the disease progresses. Premixed insulin analogs are an effective and well-tolerated treatment option for patients with T2DM particularly in Asian (and Indian) patients that and can be administered once, twice or thrice daily based on the needs of the patient. With the availability of a wide range of rapid:intermediate insulin ratios, they also allow for a more individualized treatment and therefore address the issue of regimen complexity at initiation and intensification, adaptable to patient lifestyle.

The objective of this paper is to contextualize the existing IIGs through evidence-based recommendations for appropriate management and its use in the Indian scenario. The systematic approach presented here would assist PCPs and specialists to optimize the use of premixed insulin analogs for initiation and intensification of insulin therapy in patients with T2DM who are not controlled on oral antidiabetic drugs and other regimens.

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