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Use of Biphasic Insulin Aspart 30 in Type 2 Diabetes Treatment: Expert Panel Recommendations

Tip 2 Diyabet Tedavisinde Bifazik İnsülin Aspart 30 Kullanımı: Uzman Paneli Görüşleri

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Abstract

The goals of Type 2 diabetes treatment are to eliminate the hyperglycemia resulting from insulin insufficiency and/or insulin resistance, delay beta cell damage/depletion, and prevent other metabolic co-morbidities and complications. In the current treatment algorithms, lifestyle changes (medical nutrition therapy, physical exercise) and oral anti-diabetics are followed by insulin therapy, which is considered a replacement therapy for Type 2 diabetes. Pre-mixed insulin preparations, which are an option for patients with poor blood glucose level control under oral anti-diabetics treatment, have been developed to meet both basal and prandial insulin needs by simulating the physiological changes in insulin levels. The consensus on the necessity of individualizing insulin therapy requires physicians to have a detailed knowledge of the various uses of insulin. Therefore, this comprehensive consensus statement has been prepared by a panel of expert endocrinologists from different regions of Turkey to help physicians use biphasic insulin aspart 30 in suitable patients at the right time. In this statement, expert panel opinions on (a) Recommendations for the appropriate initiation, titration, and intensification of insulin treatment, and (b) The treatment algorithms in initiation, titration, and intensification of biphasic insulin aspart 30 treatment and special conditions specific to changing treatment regimen are presented.

Keywords: Biphasic insulin aspart 30; insulin intensification; premixed insulin; insulin analog

Özet

Tip 2 diyabet (T2D) tedavisinde amaç, insülinin yetersiz salgısı ve/veya insülin direnci sonucu oluşan hiperglisemiyi ortadan kaldırmak, beta hücre harabiyetini/tükenişini yavaşlatmak, eşlik eden diğer metabolik sorunları düzeltmek ve komplikasyonları önlemektir. Güncel tedavi algoritmalarında yaşam tarzı değişikliği (tıbbi beslenme tedavisi, egzersiz) ve oral antidiyabetikler ile tedavi seçeneklerini izleyen aşamada yer alan insülin, T2D için bir yerine koyma tedavisi olarak değerlendirilmektedir. Hazır karışım insülinler, oral antidiyabetikler ile kan glukoz düzeyleri kontrol altına alınamayan hastaların tedavisinde yer alması önerilen tedavi seçeneklerinden olup, hem bazal hem de prandiyal insülin ihtiyacını fizyolojiye yakın biçimde karşılamak amacıyla geliştirilmişlerdir. İnsülin tedavisinin kişiye özel olması gerektiği konusundaki konsensüs, hekimlerin değişik insülinlerin kullanımları ile ilgili daha ayrıntılı bilgiye sahip olmalarını gerektirmektedir. Bu nedenle, ülkemiz koşullarında bifazik insülin aspart 30'un doğru hastada, doğru zamanda ve doğru biçimde kullanılmasını kolaylaştırmak ve hekimlere yardımcı olmak için Türkiye'nin farklı bölgelerinde görev yapmakta olan deneyimli endokrinologlardan oluşan bir uzman paneli tarafından, bu kapsamlı uzlaşı metni hazırlanmıştır. Bu uzlaşı metninde, uzman paneli görüşleri; a) İnsülin tedavisine uygun başlangıç, titrasyon ve yoğunlaştırma algoritma önerileri ve b) Bifazik insülin aspart 30 tedavisine özgü başlangıç, titrasyon ve yoğunlaştırma tedavi algoritmaları ve tedavi geçişlerine dair özel durumlara ilişkin öneriler temelinde sunulmaktadır.

Anahtar kelimeler: Bifazik insülin aspart 30; insülin yoğunlaştırması; premiks insülin; analog insülin

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Introduction

This comprehensive consensus statement, which is an update of the previously published statement in 2011 (1), has been prepared by a panel of expert endocrinologists from different regions of Turkey to help physicians use Biphasic Insulin Aspart 30 (BIAsp 30) appropriately. In this statement, the opinions of an expert panel on (a) recommendations for the appropriate initiation, titration, and intensification of insulin treatment (making a decision on appropriate initial insulin regimen, glycemic targets, and intensification criteria) among patients with Type 2 diabetes (T2D) based on the importance of timely insulinization and targeting postprandial blood glucose increments, and (b) the initiation, titration and intensification of BIAsp 30 treatment (switching from basal insulin to BIAsp 30, switching from BIAsp 30 twice a day (BID) to thrice a day (TID)) algorithms based on the role of premixed insulin preparations in T2D treatment, and special conditions requiring treatment regimen change (initiation of a single dose of BIAsp 30 per day (OD), switching from BIAsp 30 TID to basal-bolus therapy and switching from basal-bolus therapy to BIAsp 30 therapy) are presented.

Type 2 diabetes worldwide and in Turkey

The number of diabetic patients is rapidly increasing worldwide. By 2015, 415 million individuals had been diagnosed with diabetes. It is estimated that the number of patients with T2D will reach 592 million by 2035 and 642 million by 2040, affecting one out of every 10 adults (2, 3). Diabetes is responsible for 14.5% of all-cause deaths globally among the 20-79 age group, and 2015 data show approximately five million deaths due to diabetes or associated causes (2, 4).

The Turkish Diabetes Prevalence Study (TURDEP-I) conducted in 1997-1998 cited the prevalence of T2D in Turkey among those ≥20 years of age as 7.2% (5). The Turkish Diabetes Hypertension Obesity and Endocrine Disease Prevalence Study (TURDEP-II), which was conducted 12 years later, showed that the prevalence of T2D has increased to 16.5% (with 7.5% new diagnoses) in the total population, and when standardized by age, to 13.7%, with an increase in T2D prevalence by 90% compared to TURDEP-I (6). According to the Health Statistics Yearbook-2015 published by the General Directorate of Health Research of the Ministry of Health of Turkey in 2016, the prevalence of diabetes in individuals aged ≥15 years in the last 12 months has been 11.1% in females, 6.8% in males, and 9% in the total population (7). Based on these figures, the total number of diabetics in Turkey has reached eight million.

Diabetes-related complications are the main cause of premature deaths among the diabetics (2), and plasma glucose levels above optimal values play a significant role in increasing the risk of cardiovascular disease (8).

Importance of timely insulinization

Observational studies worldwide indicate that insulin therapy is considered as an option for patients with an average A1C levels above 9% following around 10-years of T2D history (9). This is important as it demonstrates the need to initiate insulin therapy in a population where diabetes-related complications are already prevalent (10). The effect of insulin therapy on glycemic control is based on the maintenance of beta-cell mass/function and the enhancement of insulin sensitivity by preventing glucotoxicity. Independent of glycemic control, insulin also has anti-inflammatory and antioxidant functions, in addition to its inhibitory effects on endothelial dysfunction. Timely initiation of insulin therapy is therefore important not only for glycemic control but also for other proven benefits. Early achievement of glycemic control in patients with T2D with insulin therapy provides long-term protection, regardless of subsequent treatment and glycemic control levels, through a form of 'metabolic memory' in target organs. Therefore, early insulin therapy cannot only help prevent the effects of a prolonged glycemic load but also control disease progression (10). Appropriate treatments and necessary intensification are delayed in patients receiving oral antidiabetic drug (OAD) treatment due to clinical inactivity, poor treatment compliance, and side effects (10). Accordingly, patients are often exposed to a prolonged glycemic load, and insulin treatment is initiated only after complications appear (10).

The Vascular Risk Study on 2,226 diabetic patients from Turkey revealed suboptimal treatment in a considerable proportion of diabetic patients subjected to diet-exercise (14.9%), OAD (single: 46.7%, multiple: 20%), and insulin treatment (18.4%) (11). In addition, 30% of patients with A1C values >8% were reported to be under OAD monotherapy and 32.6% were under insulin therapy, despite the presence of poor metabolic control (11). Based on the SOLVE study data, insulin treatment was started considerably late in Turkey, given the average duration of diabetes (8.1 ±5.6 years) and the duration of OAD use (7.6 ±6.6 years). It was determined that as a result of this delay, 30% of the patients had microvascular and 21.3% had macrovascular complications, and 9.2% had myocardial infarction history prior to insulin treatment (9).

In terms of an A1C lowering effect, insulin treatment (1.5-2.5%) is considered to be more effective than OADs (0.5-2.0%) (12-14). As per the recommendations of the Turkish Society of Endocrinology and Metabolism 2017 Guideline for Diagnosis, Treatment and Monitoring of Diabetes Mellitus and its Complications (15), new treatment regimens (the most effective being insulin) should be introduced rapidly in cases where glycemic targets cannot be achieved or maintained with the use of OADs as the first or second line treatment.

Initiation, titration, and intensification of insulin therapy

A significant number of patients with T2D require insulin after OAD therapy. Several strategies should be implemented to ensure success when insulin is initiated. For example, the patient should be guided on how to measure blood glucose and use the insulin pen, and if possible, should be encouraged to perform first injections in the clinic (16, 17). When making treatment-related decisions, patient characteristics such as age, lifestyle, education, ability to understand the side effects of insulin and to monitor blood sugar, and willingness to communicate with the healthcare professionals throughout the treatment should be considered. In addition, information on the duration of diabetes, complications, and endogenous insulin reserves should be evaluated, and co-medications and co-morbidities should be considered (Table 1).

If available, plasma C-peptide levels may aid in the decision to start insulin treatment, with values below 1 ng/mL supporting initiation of insulin therapy. After the initiation of insulin therapy, dose titration and intensification must be performed to keep the treatment consistent with the progression of the disease. Dose titration is the process of adjusting the insulin dose until the patient achieves the optimal insulin levels required to reach fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) targets. Intensification can be defined as modifying the current insulin treatment by supplementing the treatment, changing the treatment regimen, or increasing the number of injections in order to maintain glycemic control (Table 2).

Based on the positive effects of intensive treatment and tight glycemic control on mortality and morbidity among diabetic patients, the glycemic control targets for A1C were, respectively set at <7.0%, ≤ 6.5% and <6.5% by the American Diabetes Association (ADA) (18), American College of Endocrinology/American Association of Clinical Endocrinologists (ACE/AACE) (19,20), and

Table 1. Expert Panel Recommendation 1: Insulin initiation algorithm.*

	Appropriate insulin regimen	
Criteria	**Basal**	**Premixed**
How much is the postprandial plasma glucose increment?	<20 mg/dL	>55 mg/dL
Will the patient be able to undergo basal-bolus therapy when there is a need for intensification?	Yes	No
Is there carbohydrate overload for a meal or two?	No	Yes
Is the lifestyle of the patient predictable (eating habits, working hours)?	No	Yes

*Adapted from Wu T et al., Diabetes Ther. 2015 Sep;6 (3):273-87.

Table 2. Expert Panel Recommendation 2: Glycemic targets for adults with Type 2 diabetes.

Glycemic parameters	Treatment targets
A1C	<%7
Fasting plasma glucose	80–130 mg/dL
Postprandial plasma glucose*	<160 mg/dL

More or less stringent targets can be determined according to the clinical condition of the patients. Targets should be individualized based on disease duration, age, life expectancy, comorbid factors, the presence of known CVD or advanced microvascular complications, awareness of hypoglycemia, and patient preferences. To achieve glycemic goals, both fasting and postprandial plasma glucose should be targeted along with A1C.
* Postprandial plasma glucose measurements should be done after two hours following the start of the meal.

International Diabetes Federation (IDF). While the ADA recommends an A1C target of <7.0% for adult patients, more stringent (<6.5%, no short-term disease history, long life expectancy, and no CVD comorbidity) or less stringent (<8.0% severe hypoglycemia, limited life expectancy, advanced microvascular and macrovascular complications, multiple co-morbidities, long-term history of diabetes mellitus) individual targets can be set according to the patient's clinical condition (18). The glycemic targets according to the Turkish Society of Endocrinology and Metabolism 2017 Guideline for Diagnosis, Treatment, and Monitoring of Diabetes Mellitus and its Complications are ≤7% for A1C, 80-130 mg/dL for pre-meal and fasting plasma glucose, and <160 mg/dL for two-hour PPG (15).

Many international guidelines recommend premixed insulin or basal insulin treatment options following the first line of treatment, including lifestyle changes and metformin. Intensive insulin therapy, which is recommended in the third step, involves two different intensification regimens to provide postprandial glucose control. While one option is to add short-acting insulin to basal insulin (basal-bolus treatment), the other is switching to twice daily injections of premixed insulin. The 2017 consensus statement from AACE/ACE stated that insulin therapy should be closely monitored after initiation (2-3 months) and that it is necessary to intensify treatment until the target is reached (20).

Premixed insulin therapy is recommended as an option for intensifying insulin therapy in the ADA/EASD 2015 (12), AACE/ACE 2017 (20), and ADA 2017 (18) guidelines. According to IDF (21), Australian Diabetes Society and the National Health and Medical Research Council (22), Royal Australian College of General Practitioners (23), New Zealand Guidelines Group (24), and Turkish Society of Endocrinology and Metabolism 2017 Guideline for Diagnosis, Treatment and Monitoring of Diabetes and its Complications (15), it is possible to initiate premixed insulin therapy OD or BID in insulin-naïve patients.

In the ADA 2017 guidelines, changes were made in the combination injectable insulin therapy algorithm for patients with T2D, reflecting the following findings of recently published studies (18):

- Basal insulin + glucagon-like peptide-1 (GLP-1) receptor agonist therapy, basal insulin + fast-acting insulin therapy and twice-daily premixed insulin therapy have equal efficacy and safety,
- TID premixed insulin and basal-bolus insulin regimens have equal efficacy and safety.

Accordingly, the recommended treatment intensification options when A1C targets cannot be achieved with basal insulin therapy are as follows: A) replacement of the treatment with twice-daily premixed insulin, B) addition of a single-dose of fast-acting insulin to basal insulin treatment after the meal resulting in highest plasma glucose level, and C) addition of a GLP-1 receptor agonist to the treatment. When treatment targets cannot be achieved despite these changes, the following can be considered for options A, B, and C respectively: A) switching from BID premixed insulin to TID, B) switching to basal-bolus treatment, and C) switching to one of the other two treatment options. If A1C levels still cannot be achieved, changes across regimens should be considered (19).

Importance of PPG control

A growing number of studies have shown that the FPG-focused approach per se is not sufficient in achieving optimal glycemic control (A1C <7%), and PPG control has equivalent significance in this regard (12,21,25). Notably, along with the epidemiological evidence on the relationship between postprandial hyperglycemia and cardiovascular risk

(26-29), PPG levels are considered to be a stronger predictor of cardiovascular risk than FPG levels in patients with T2D (21, 29, 30). Postprandial hyperglycemia is a common condition in diabetic patients and is observed even in patients whose A1C target levels have been achieved (31,32). In a study on 3,284 T2D patients, who did not receive insulin therapy, daily plasma glucose profiles over the duration of one week showed that a PPG value >160 mg/dL was recorded at least once in 84% of the patients (32).

Epidemiological studies suggest that postprandial hyperglycemia has a strong association with cardiovascular risk and outcomes (26-29). There is increasing evidence linking it with cardiovascular disease markers such as oxidative stress (33), carotid artery intima-media thickness (34), and endothelial dysfunction (33,35). Postprandial hyperglycemia has also been associated with retinopathy (36,37), cognitive impairment in elderly patients (38), and some cancer types (39-43). The combined control of FPG and PPG levels is necessary in order to achieve glycemic targets. It is reported that for patients with normal FPG levels (80-130 mg/dL) who cannot achieve A1C targets (>7%), treatment modifications to meet the target levels of PPG (<160 mg/dL) will also help attain A1C targets (18).

According to two meta-analyses evaluating the approaches targeting and not targeting postprandial hyperglycemia control, the reduction in A1C with premixed and prandial insulin regimens was 0.45% more effective compared to basal insulin regimens, and the chance of achieving target A1C levels (<7%) was 1.88 and 2.07 times higher in premixed and prandial insulin regimens, respectively (44, 45). Similarly, a systematic review cited that the reduction in PPG (mean difference, 27.02 mg/dL) and in A1C (mean difference, 0.39%) were greater after premixed insulin analog treatment compared to long-acting insulin analog treatment (46). These findings emphasize the need to include postprandial hyperglycemia as a parameter in the treatment plan for effective glycemic control (21).

Epidemiological studies show that the control of PPG increments is an important factor in reducing hyperglycemia-related mortality and morbidity (47,48). More than 25,000 subjects (1275 with diabetes mellitus) participated in the DECODE (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe) Study, which showed that an increase in the PPG led to a significant increase in mortality, regardless of FPG levels (47). Similarly, the Diabetes Intervention Study, which had an 11-year follow-up period, also found that patients with T2D who died during follow-up had a higher level of PPG compared with those who completed the follow-up period, although their initial FPG levels were similar (48). Numerous analyses have shown that a high level of PPG during T2D diagnosis is indicative of a decrease in life expectancy. Since the relative contribution of PPG levels is more important than FPG levels in glycemic control with decreasing levels of A1C, both components should be considered together in T2D treatment (49).

IDF has developed guidelines that include recommendations specific to PPG management in patients with T2D and suggests that patients should be given a post-meal (1 or 2h) plasma glucose target of <160 mg/dL (50), as long as hypoglycemia can be prevented. These PPG values are higher than target values defined in the previous version of the IDF guidelines (140 mg/dL) (51). The PPG values suggested by ADA/EASD and AACE/ACE are <180 mg/dL and <140 mg/dL, respectively (19, 20, 12, 52). The ADA/EASD guidelines recommend adding prandial insulin to the treatment or switching to premixed insulin in patients who achieve FPG goals under basal insulin therapy but still have elevated A1C values, or in patients whose daily basal insulin dose is over 0.5 U/kg (12). Only IDF has developed guidelines specific to PPG management, emphasizing the more significant contribution of PPG to overall glycemic control, especially in patients with relatively lower A1C levels (<8%), and the importance of PPG control in achieving target A1C levels regardless of the disease stage (50). It is recommended to select an effective agent of PPG specifically for patients with high PPG values and with A1C values between 7% and 8% (50).

Role of premixed insulin in T2D treatment

Premixed insulin offers the advantage of glycemic control in T2D patients by meeting both the basal and prandial insulin require-

ments. In addition, these treatments require fewer injections than the basal-bolus regimens and thus allow for simpler and more appropriate dose adjustments (21, 53-56). While premixed human insulin can provide sufficient glycemic control in patients with T2D, it may be insufficient to meet their physiological needs due to difficulty in administration and failure to provide sufficient peak insulin concentrations. The use of human insulin has, in fact, decreased since the introduction of analog insulins into clinical practice.

While the short-acting analogs, which are developed by modifying the human insulin molecule to overcome its limitations (57), act faster after subcutaneous injection, the maximal effect is achieved after 45-60 min of administration and the effect disappears within 4-5 h. The premixed insulin analogs have lispro and aspart bases and are available in Turkey in the following ratios: biphasic insulin aspart (BIAsp) 30/70, BIAsp 50/50, BIAsp 70/30, biphasic insulin lispro 25/75, and biphasic insulin lispro 50/50. Premixed insulin analogs are considered more advantageous in PPG control compared to human insulin (58-61). In studies with healthy volunteers, the peak serum insulin level (23.4 ±5.3 mU/L) was achieved within a median (min-max) of 60 (45-69) min and the lowest serum glucose level (3.2 ±0.5 mmol/L) was achieved within a median (min-max) of 70 (69-79) min following a single 0.2 U/kg dose of BIAsp 30 subcutaneous injection (62).

The poor compliance of patients to treatment is a major challenge in insulin therapy. In the DROPOUT studies on insulin-naïve T2D patients in Turkey (n = 433 and n = 1,456), premixed insulin treatment was shown to be associated with higher patient compliance in terms of dose-skipping (19% vs. 52%) and skipping insulin injections for more than a day (22.7% and 61.3%) as compared to basal-bolus treatment (63), as well as in terms of persistence (75% vs. 62.8%) (64). Premixed insulin is one of the basic treatment options in patients with postprandial hyperglycemia. They can be used for treatment intensification following basal insulin therapy, as well as an insulin initiation therapy since they can effectively reduce FPG and A1C levels along with controlling PPG. Premixed insulins provide a much simpler regimen than basal-bolus regimens to obtain similar PPG control (65-67), resulting in better patient compliance and less hesitancy on the part of the physicians to start insulin treatments (65,68). Although basal-bolus regimens are generally more flexible than premixed regimens (e.g., for patients with very inconsistent mealtimes or those with high levels of physical activity), premixed insulins have sufficient flexibility to maintain glycemic control in the context of a simple titration algorithm (65,69).

In summary, premixed insulin analogs are effective and safe agents that can be used in diabetes treatment. They may improve compliance as they can be administered immediately before meals and require fewer injections (70), and provide an effective PPG control. The later sections in this consensus statement specifically refer to BIAsp 30 while discussing biphasic insulin analogs, since BiAsp 30 is the most extensively studied and most widely used premixed formula worldwide, having been tested in more than 60 clinical trials and used in over 2.6 million patients in the last 17 years. In addition, BiAsp 30 has been used on more heterogeneous patient populations compared to other pre-mixed formulas (66,71).

Initiation and titration of insulin treatment with BIAsp 30

The expert panel recommends starting insulin treatment with BIAsp 30 if:

- A1C is ≥10.0% or FPG ≥ 300 mg/dL or severe hyperglycemia is seen in a newly diagnosed patient
- A1C target has not been achieved even after multiple OAD regimens
- Insulin use is indicated independent of A1C value, as one of the insulin regimen options

The expert panel suggests that the BIAsp 30 initial dose titration be individualized on the basis of body mass index, activity status, insulin resistance, diet, co-morbidities, and hypoglycemia, according to the following chart (Table 3).

BIAsp 30 BID is a frequent initiation regimen and is also recommended by the Turkish Society of Endocrinology and Metabolism 2017 Guideline for Diagnosis, Treatment, and Monitoring of Diabetes Mellitus and Its Com-

Table 3. Expert Panel Recommendation 3: Guidelines for BIAsp 30 dose titration.

Lowest pre-meal plasma glucose level	Titration*
≥ 130 mg/dL	+ 2 Units
80–130 mg/dL	No change
≤ 80 mg/dL or hypoglycemia	- 2 Units

*PPG levels should be taken into consideration if the patient cannot reach the A1C target with titration according to FPG

plications (15), which is consistent with many international guidelines (21-24) (Table 4, Table 5).

It has been reported that initiation with BIAsp 30 BID resulted in a 0.5% greater reduction in A1C on an average compared to basal insulin (47,48). Meta-analyses and systematic reviews of randomized controlled trials (RCTs) on insulin analogues showed that premixed insulin treatment, when compared to basal insulin therapy, was more effective in reducing A1C (mean difference: 0.45% and 0.39%) (24,47) and was 1.88 times more likely to achieve an A1C target of <7% (mean difference: 27.02 mg/dL) (46), but was less effective in FPG control (mean difference: 16.75 mg/dL and 12.61 mg/dL) (44, 46).

The majority of clinical trials evaluating the safety and efficacy of BIAsp 30 were conducted with twice a day posology. Observational studies have also shown that physicians prefer to use BIAsp 30 predominantly twice a day, once each in morning and evening (71, 72). In the IMPROVE observational study involving 52,419 patients with T2D and 5,000 doctors, A1C reduction at 26 weeks in the treatment-naïve and OAD-treated patients (n=42,763) were 3.1% and 2.1%, respectively ($p<0.0001$), with BIAsp 30 BID used in 81% of the patients (48, 58, 71, 73).

Switching from basal insulin to BIAsp 30

The combination of basal insulin and OAD is recommended for the initiation of insulin therapy in T2D by many guidelines (12, 14, 15, 18-20, 52). However, basal insulin is not a suitable treatment for every patient. In general, basal insulin analog treatments provide short-term glycemic control, but their long-term effects in combination with OADs are insufficient as they reach a plateau over time. Even if the FPG level remains within the recommended target range, high PPG levels that become more

Table 4. Expert Panel Recommendation 4: BIAsp 30 insulin therapy initiation in insulin-naive patients.

- The total daily dose is calculated as 0.3 to 0.6 U/kg, based on body mass index, activity and nutritional status.
- The total daily dose should be split 50:50 pre-breakfast and pre-dinner; according to nutritional and activity status, the dose can be administered as 2/3 in the morning, 1/3 in the evening.
- The dose should be titrated according to Expert Panel Recommendation 3.
- If there are no contraindications, metformin should be continued. DPP4-I and SGLT2-I can be continued.
- Insulin secretory agents should be discontinued (sulfonylureas, glinides).
- Attention should be paid in terms of cardiovascular and metabolic risks when using glitazone (in terms of weight and water retention effects) and SGLT2 inhibitors (in case of normo- or hyperglycemic ketoacidosis) in combination with insulin.
- Type 1 diabetes may be misdiagnosed as type 2 diabetes and off-label use of SGLT2 inhibitors in type 1 diabetics has been reported to cause euglycemic ketoacidosis, which may be missed if ketone levels are not checked. Patients on SGLT inhibitors need to be educated on the risks of DKA, especially if dehydrated.

Table 5. Expert Panel Recommendation 5: Intensification of insulin therapy.

The expert panel recommends insulin therapy intensification in the following cases:

- If glycemic control cannot be achieved within three months in terms of FPG, PPG, and A1C with current treatment.
- If there is a difference of more than 55 mg/dL between FPG and PPG levels or if the 2-hour PPG values are above 160 mg/dL*.

* The difference is more than 30% of mean daily PPG.

apparent over time may cause suboptimal glycemic control (49, 74). Adding one or two doses of fast-acting insulin to the basal insulin therapy (basal-plus treatment) is an option for patients where glycemic targets cannot be achieved. However, this regimen may require a basal-bolus treatment in short-term, which can result in compliance problems. Therefore, premixed regimens are more appropriate when the basal insulin therapy is insufficient in patients who cannot comply with multiple insulin pens, have high PPG increments in more than one meal, have a predictable lifestyle, and have stable nutritional and activity status.

When glycemic control is not achieved under basal insulin therapy, titration of the basal insulin dose is the appropriate approach if elevated FPG levels are of concern. Twice daily premixed insulin therapy is appropriate if elevated PPG levels are encountered (Figure 1, Table 6).

Switching from BIAsp 30 BID to TID

Adding a third dose of BIAsp 30 to patients already receiving two doses of BIAsp 30 per day may be considered if:

- A1C target cannot be achieved even though FPG is under control
- Hypoglycemia occurs before lunch or before bedtime when the morning or evening insulin dose is increased
- PPG cannot be controlled after lunch

BIAsp 30 can be a better alternative to basal-bolus treatment for some patients

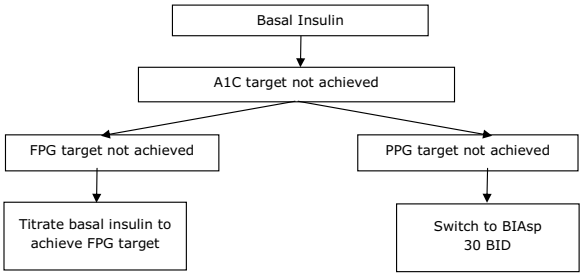

Figure 1: Algorithm for intensifying basal insulin therapy with BIAsp 30.

(e.g., elderly, living alone, with a stable lifestyle, unable to adapt to multiple insulin pens) in terms of improving compliance and requiring less injections when used thrice daily (Table 7).

In a meta-analysis comparing the efficacy of intensive insulin treatment regimens (basal-bolus and premixed) over 12 weeks in patients with T2D, no significant differences were found between basal-bolus treatments and thrice daily premixed regimens in terms of the total number of hypoglycemic episodes (0.16 episode/patient-year), body weight change (0.21 kg), or daily insulin dose (0.54 U/day) (75). The proportion of patients achieving the A1C target of <7% was 43% with basal-bolus therapy and 39% with the premixed regimen, and the likelihood to reach the target was 8% higher with basal-bolus treatment. No significant difference was found between the two treatments in terms of the reduction in A1C levels compared to the initial level (75).

Table 6. Expert Panel Recommendation 6: Switching to BIAsp 30 from basal insulin therapy.

■ Following one-to-one dose transfer from basal insulin, the total daily dose should be split 50:50 pre-breakfast and pre-dinner; according to nutritional and activity status, the dose can be administered as 2/3 in the morning, 1/3 in the evening.
■ Dose should be titrated according to Expert Panel Recommendation 3. For dose titration, the evening dose should be adjusted first, then the morning dose.
■ If there are no contraindications, metformin should be continued. DPP4-I and SGLT2-I can be continued.
■ Insulin secretory agents should be discontinued (sulfonylureas, glinides).
■ Attention should be paid in terms of cardiovascular and metabolic risks when using glitazone (in terms of weight and water retention effects) and SGLT2 inhibitors (in case of normo- or hyperglycemic ketoacidosis) in combination with insulin.
■ Type 1 diabetes may be misdiagnosed as type 2 diabetes and off-label use of SGLT2 inhibitors in type 1 diabetics have been reported to cause euglycemic ketoacidosis, which may be missed if ketone levels are not checked. Patients on SGLT inhibitors need to be educated about the risks of DKA, especially if dehydrated.

Table 7. Expert Panel Recommendation 7: Switching from BIAsp 30 BID to TID.

- Add 10% of the total dose or 4–6 U before lunch, in which case the morning dose may require 2–4 units or a 10% reduction in some patients (due to hypoglycemia before or after lunch).
- The dose should be titrated according to Expert Panel Recommendation 3, which is preferably done every 3–4 days.
- If there are no contraindications, metformin should be continued.
- BIAsp 30 should be administered immediately before meals.
- Doses should be reduced in cases of severe hypoglycemia or recurrent mild-moderate hypoglycemia. In trials with BIAsp 30 TID, the dose ratio is approximately 2:1:3.

Special Conditions

Initiation of Insulin Therapy with BIAsp 30 OD

When glycemic control cannot be achieved with OAD treatments, adding BIAsp 30 to therapy can be a favorable insulin initiation regimen with the advantage of a single dose per day (76-78).

It is possible to overcome the patient's resistance to initiate insulin therapy by addressing their (usually false) fears regarding the drawbacks of insulin treatment. The most common patient concern related to insulin therapy initiation is hypoglycemia and weight gain. Furthermore, patients fear that switching to insulin treatment is a sign of progression to a more advanced stage with serious complications such as blindness, amputation, renal insufficiency, or of treatment failure. Finally, there is often patient reluctance to track plasma glucose levels (79-81). As an alternative to the initiation of basal insulin in such patients, treatment with a single dose of BIAsp 30 per day may be initiated and if necessary, switching to a two-dose daily regimen may help the patient get used to the treatment and improve compliance. In a study comparing single-dose basal insulin and biphasic insulin aspart in patients with A1C between 7% and 11%, and without adequate metabolic control under OADs, both treatment groups resulted in a similar reduction in A1C levels, total hypoglycemia rates and weight gain (82). Another study (1-2-3 Study) reported that with a single dose of BIAsp 30, 21% patients reached the AACE target A1C level of ≤ 6.5%, while 41% reached A1C <7% (70).

In a study comparing patients who received one or two doses of BIAsp 30 per day in addition to ongoing metformin + sitagliptin therapy, 46.5% of the patients reached the ADA target of A1C <7% with a single daily dose of BIAsp 30 add-on therapy (83). With the addition of an evening dose of BIAsp 30 OD to OAD treatment in a 28-week study, A1C reduced by 1.24% and 46% of the patients achieved the A1C <7% goal. However, approximately half of the patients with A1C levels >8.5% received a second dose (at breakfast) of BIAsp 30 on the 14th week of treatment (78). This result is important as it shows that initiation with a single dose of BIAsp 30 per day is a temporary, short-term approach for patients with adequate reserves and patients with high carbohydrate intake in their evening meals.

The expert panel's view is that although this treatment is not generally considered, it can be used for patients that refuse to start insulin therapy for a limited period of time, in order to persuade them that plasma glucose levels can be controlled even after a heavy meal.

Switching from BIAsp 30 TID to Basal-Bolus Therapy

Monitoring of A1C and the plasma glucose profile is essential in diabetes treatment. Intensification of the treatment with basal-bolus therapy should be considered in patients who have uncontrolled glucose levels despite three doses of BIAsp 30 daily. The criteria summarized in Expert Panel Recommendation 2, such as the risk of hypoglycemia, education level, lifestyle, and treatment compliance should be considered before switching to this regimen. The expert panel summarizes the reasons and methods for switching from BIAsp 30 to basal-bolus treatment as follows:

If A1C is above 1% of the target
If hypoglycemia occurs when the dose is increased
If the PPG levels are high when pre-prandial glucose is within the normal range
If meal habits have changed
In the presence of persistent hyperglycemia in the morning
If increasing the dose to control hyperglycemia in the morning causes hypoglycemia around midnight or early in the morning (possibility of Somogyi effect should be excluded by checking plasma glucose levels at approximately 03:00-04:00 am) (Table 8).

Switching to BIAsp 30 Treatment from Basal-Bolus Therapy

Hospitalizing patients in order to provide glycemic control is still widely used in Turkey although it is controversial in terms of cost-effectiveness. Patients under basal-bolus therapy, either admitted to the hospital or treated in outpatient clinics, sometimes cannot reach the targets because of compliance problems, hypoglycemia, and inadequate education. In such special cases, twice or thrice daily BIAsp 30, which provides ease of administration, may be considered to provide more effective glycemic control due to increased patient compliance (Table 9).
Statistically significant improvements in glycemic control and health-related quality of life were observed at the end of 24 weeks in the observational A1chieve study conducted on patients who switched to BIAsp 30 while they were on basal-bolus treatment (84).

Conclusions

This comprehensive consensus statement is an update of the previous statement published in 2011 (1), and contains recent data and that on some special conditions. It has been prepared by a panel of expert endocrinologists from different regions of Turkey. In this statement, views on T2D insulin treatment, the significance of timely insulinization in terms of disease and related complications, and the role of controlling elevated PPG levels have been emphasized. In line with these views, recommendations are provided for selecting the appropriate insulin regimens and monitoring FPG and PPG levels for glycemic control. Recommendations of insulin treatment initiation, titration, and intensification algorithms are presented on the basis of the appropriate insulin initiation regimen, glycemic targets suitable for titration, and intensification criteria. The expert panel observations specific to BIAsp 30 treatment indicate that premixed insulin is an effective and safe treatment option, along with advantages such as targeting both FPG and PPG, and better patient compliance for achieving glycemic control. In addition, recommendations are presented on the initiation of BIAsp 30 treatment, titration and intensification (switching from basal insulin

Table 8. Expert Panel Recommendation 8: Switching from BIAsp 30 TID to Basal-Bolus Therapy Regimen.

■ The switch must be done while transferring the total daily dose of one-to-one.
■ The daily dose is divided as 50% bolus and 50% basal insulin. The calculated bolus dose is divided equally into three meals, and dose titration is done according to patient needs.

Table 9. Expert Panel Recommendation 9: Switching to BIAsp 30 from Basal-Bolus Therapy.

■ Decision on switching to either BIAsp 30 BID or BIAsp 30 TID should be made according to the patient's daily insulin requirement. Patient compliance is usually more important than the number of daily injections when switching the treatment regimen.
■ For the patients with a daily insulin requirement of >1 U/kg/day, BIAsp 30 TID may be the preferred regimen. Doses should be divided as 2:1:3.
■ For the patients with a daily insulin requirement of <1 U/kg/day BIAsp 30 BID may be the preferred regimen. Doses should be divided as 1:1, and the total daily dose should remain the same.

to BIAsp 30, switching from BIAsp 30 BID to TID) algorithms, and special conditions specific to treatment switching (insulin initiation with BIAsp 30 OD, switching from BIAsp 30 TID to basal-bolus therapy, and switching from basal-bolus therapy to BIAsp 30 therapy).

The information in this article is only a recommendation and can provide guidance to physicians. It emphasizes the importance of taking into account individual patient factors and preferences so that the choice of insulin regimen is individualized in the same way that glycemic targets are now individualized.

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