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Efficacy of switching from basal-bolus insulin therapy to twice-daily insulin degludec/insulin aspart co-formulation plus insulin aspart in patients with poorly controlled type 2 diabetes

E. GÜNEŞ[1], M. GÜNEŞ[2]

[1]Department of Endocrinology, Metabolism and Diabetes, Health Sciences University, Bursa State Hospital, Bursa, Turkey
[2]Department of Endocrinology, Metabolism and Diabetes, Health Sciences University, Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, Turkey

Abstract. – OBJECTIVE: The aim of this study was to evaluate the efficacy of twice-daily (BID) insulin degludec/insulin aspart (IDegAsp) co-formulation + once-daily (OD) bolus insulin aspart (IAsp) injection (IDegAsp BID-Plus) as simplified intensive insulin therapy in patients with poorly controlled type 2 diabetes mellitus (T2DM) with basal-bolus insulin therapy (BBIT).

PATIENTS AND METHODS: The retrospective study included 155 patients who switched from BBIT to IDegAsp BID-Plus. After the initiation of the treatment, 73 patients continued regular follow-up and insulin doses, number of injections, hemoglobin A1c (HbA1c) levels, and other parameters were recorded from their files at baseline, 24, and 52 weeks.

RESULTS: The mean age of the study population was 54.3±10.2 years, the duration of T2DM was 9.7±5.7 years, fasting plasma glucose (FPG) was 252.7±66.7 mg/dl, and HbA1c levels were 10.5±1.5%. Among the included patients, 15 patients received five injections, 51 patients received four injections, and 7 patients received three injections per day. There was a significant decrease in HbA1c (respectively; 10.46±1.54%, 7.97±1.24%, 7.98±1.23%, baseline and 6th-month $p<0.001$, baseline and 12th-month $p<0.001$), FPG (respectively; 251.6±66.5 mg/dl, 136.1±34.7 mg/dl, 125.4±67.0 mg/dl, baseline and 6th-month $p<0.001$, baseline and 12th-month $p<0.001$) and daily dose of insulin (respectively; 102.9±29.0 Unit, 73.2±18.2 U, 63.7±20.3 Unit, baseline and 6th-month $p<0.001$, baseline and 12th-month $p<0.001$) at the end of week 24 and 52.

CONCLUSIONS: Based on real-world data, this study demonstrated that IDegAsp BID-Plus treatment provides rapid and sustainable blood glucose control with lower insulin doses and fewer injections than previous intensive insulin therapy.

Key Words:
Insulin degludec/insulin aspart, Type 2 diabetes mellitus, Basal-bolus insulin therapy, Poorly controlled type 2 diabetes mellitus.

Introduction

According to the International Diabetes Federation (IDF) Diabetes Atlas[1], 9.3% of people worldwide had diabetes mellitus in 2019. This figure is expected to reach 10.2% (578 million people) in 2030[1]. In 2019, Turkey had the highest prevalence of type 2 diabetes mellitus (T2DM) in Europe[1]. Specifically, the disease affected one in eight adults, representing 12% of the Turkish population (6.6 million people)[1]. Meanwhile, National Health and Nutrition Examination Survey (NHANES)[2] data revealed that only 36.3±7% of patients had a target hemoglobin A1c (HbA_{1c}) value <7%. Since T2DM is a progressive disease, if glycaemic regulation cannot be achieved as the disease develops, treatment is intensified by adding insulin therapy[3]. Approximately 27% of all people with T2DM take insulin[4]. Standard basal-bolus insulin therapy (BBIT) requires 4-5 separate daily injections to meet fasting and postprandial insulin needs[5]. However, this type of therapy increases the treatment burden and decreases adherence to treatment[6-10].

Insulin non-adherence is a common problem in all countries. In line with previous research, a study by Peyrot et al[8] found that patients with T2DM had relatively low levels of adherence to insulin, which ranged from 59% in those with poor glycaemic control. One threat is that doctors

Corresponding Author: Elif Güneş, MD; e-mail: drelifgunes@gmail.com

treating patients with low adherence to insulin may prescribe higher insulin doses to control glucose levels, which could exacerbate the problem and put the patient at risk of hypoglycemia when injections are done[9]. The two most common insulin therapy-related challenges that patients face are the number of injections and taking insulin at predetermined times[8].

Uncontrolled T2DM is a major challenge for health systems. Poor glycaemic control results in increased rates of acute and chronic complications, hospital admissions, and mortality risk and shortens life expectancy[11]. To control T2DM, insulin regimens that are more effective and flexible and require fewer injections than BBIT are needed. Insulin degludec/insulin aspart (IDegAsp) is a coformulation of 70% ultra-long-acting insulin degludec (IDeg) and 30% rapid-acting prandial insulin aspart (IAsp) in the same injection pen. IDeg has been shown[12,13] to stably meet basal insulin requirements through a duration of action that exceeds 42 hours and a stable pharmacodynamic profile with four times less variability than insulin glargine. After IDegAsp is administered, IDeg forms multihexamers in the subcutaneous tissue and gradually dissociates into monomers to ensure slow, continuous delivery into circulation. IAsp rapidly dissociates from the injection site into circulation to lower postprandial glucose[14,15]. IDegAsp can be administered once daily (OD) or twice daily (BID)[16]. Compared with premix regimens, such as biphasic IAsp 30/70, IDegAsp does not require resuspension before each injection and allows flexibility in terms of the time of administration as long as it is dosed with the main meal(s) of the day[17,18].

Several studies[19-21] have shown that switching to IDegAsp is safe and effective for treating T2DM. At present, only a small number of real-world evidence studies[22,23] have explored whether IDegAsp can improve glycaemic control and lower HbA1c rates after transition. In a small retrospective study in Turkey[24], the HbA1c level of patients with uncontrolled T2DM was significantly reduced with lower bolus insulin doses and fewer injections. Furthermore, the reduction in HbA1c was greater in patients treated with IDegAsp BID than in those treated with IDegAsp OD[24].

The aim of the present study was to demonstrate the efficacy and sustainability of IDegAsp BID-Plus treatment in a real-life setting over a one-year period in patients with T2DM who had poor glycaemic control on BBIT.

Patients and Methods

Study Design

This retrospective cohort study was conducted in accordance with the Declaration of Helsinki. It was carried out between October 2020 and April 2022 in the Department of Endocrinology and Metabolism Diseases, University of Health Sciences, Bursa State Hospital.

Participants

The study's inclusion criteria were as follows: male and female patients aged ≥18 years, a diagnosis of T2DM more than one year prior to the study, treatment consisting of a BBIT regimen and oral hypoglycaemic agents (OHAs) for at least three months prior to the study and HbA1c >8.5% (52 mmol/mol) and fasting plasma glucose (FPG) >150 mg/dl at screening. The exclusion criteria eliminated patients who had acute coronary syndrome, an acute cerebrovascular event, severe heart failure (according to the New York Heart Association's class IV classification of heart failure), an organ transplant, liver failure, and liver cirrhosis as well as pregnant women and patients who missed a follow-up after the initiation of treatment. Informed consent was obtained from all individual participants included in the study.

Treatment and Follow-Up

Switching to IDegAsp BID-Plus

The present study initially included 155 patients who switched from BBIT to IDegAsp BID-Plus due to uncontrolled T2DM. However, only 73 patients met the inclusion criterion of attending regular follow-ups. The study participants used bolus insulin (glulisine, IAsp, or lispro) two or three times daily and basal insulin therapy (glargine U100, glargine U300, or detemir) once or twice daily for at least three months before switching to IDegAsp BID-Plus.

The switch to IDegAsp BID-Plus was based on expert panel recommendations and a step-by-step intensification study[25,26]. In general, IDegAsp was administered BID at the two main meals, initially at the same dose as basal insulin. It was divided into two doses (not necessarily 50:50) and then titrated to achieve optimal FPG. According to a previous study[27], during the study period, the clinician chose to skip rapid-acting insulin in eligible patients to simplify the insulin regimen.

Patients with very high insulin requirements and FPG were switched to IDegAsp BID-Plus as simplified intensive insulin therapy. IDegAsp BID was administered at breakfast and dinner. IDegAsp BID-Plus doses were titrated according to patients' self-monitored blood glucose, HbA1c, and plasma FPG levels at the beginning of the study (baseline) and at 3, 6, and 12 months.

The number of daily injections and the total daily insulin dose were recorded at baseline and at 3, 6, and 12 months. At the end of three and six months, treatment was further simplified to IDegAsp BID-Plus, as some patients no longer required IAsp at the third meal for blood glucose regulation. OHAs taken during BBIT and after switching to IDegAsp BID-Plus were obtained from the patients' records.

Biochemical Analyses

FPG and other biochemical parameters were analyzed from plasma samples after eight hours of fasting. Age, gender, body mass index (BMI), duration of T2DM (DT2DM), FPG, HbA1c, creatinine (Cr), thyroid stimulating hormone (TSH), alanine transaminase (ALT), aspartate transaminase (AST), low-density lipoprotein (LDL), triglyceride (TG), spot urine albumin creatinine ratio (UACR), hypertension (HT), hyperlipidemia (HL) and history of coronary artery disease or catheterization (CAD) were obtained from the patients' records. Plasma HbA1c levels were evaluated using the high-performance liquid chromatography (HPLC) method (Adams HA-8180V).

Statistical Analysis

IBM® Statistical Package for the Social Sciences (SPSS) statistics 20 (IBM Corp., Armonk, NY, USA) was used to compare the data. After the normal distribution was determined, an independent samples *t*-test was applied to data with a normal distribution, and the Mann-Whitney U test was applied to compare data that did not have a normal distribution. The Pearson's Chi-squared test was used to compare ratios, and the paired samples *t*-test was used to compare consecutive data. A *p*-value lower than 0.05 was considered statistically significant.

Results

Baseline Characteristics

The mean DT2DM was 9.7 years, and the mean HbA1c level was above 10%. The participants' baseline characteristics are summarised in Table I.

Of the 73 study participants, all patients were receiving BBIT. 39 patients switched to IDegAsp BID-Plus from insulin glargine U100, 15 switched from insulin glargine U300 and 19 switched from insulin detemir. In addition to insulin therapy, 67 patients used at least one OHA drug. Specifically, 37 patients received metformin, 5 received dipeptidyl peptidase-4 (DPP-4) inhibitors, 22 received a metformin+DDP-4 combination, and 3 received sodium glucose cotransporter-2 (SGLT-2) inhibitors.

Glycaemic Control

As shown in Table II, significant FPG reductions occurred after the transition to IDegAsp BID-Plus. The mean FPG values were 251.6±66.5 mg/dl at baseline and 117.5±29.3 mg/dl at 3 months ($p<0.001$). Likewise, HbA1c decreased significantly after switching to IDegAsp BID-Plus. The mean HbA1c values were 10.46±1.54% at baseline and 8.30±1.19% at 12 weeks ($p<0.001$). The reduction in FPG and HbA1c was maintained at 24 and 52 weeks.

Table I. Laboratory data and demographic characteristics of the participants.

Age (n=73) year	54.3 ± 10.2
Female/Male	54/19
BMI (n=53) kg/m^2	34.8 ± 7.7
DT2DM (n=54) year	9.7 ± 5.3
FPG (n=73) mg/dL	252.7 ± 66.7
HbA1c (n=73) %	10.5 ± 1.5
Cr (n=73) mg/dL	0.79 ± 0.29
TSH (n=73) µIU/mL	2.4 ± 2.3
ALT (n=73) IU/L	20.7 ± 13.7
AST (n=73) IU/L	24.3 ± 16.6
LDL (n=73) mg/dL	116.3 ± 35.2
TG (n=73) mg/dL	214.5 ± 82.0
UACR (n=38)	438.8 ± 736.8
Metformin (n)	59/73
DPP-4 (n)	27/73
SGLT-2 (n)	14/73
Insulin glargine U100 (n)	39/73
Insulin glargine U300 (n)	15/73
Insulin detemir (n)	19/73
Hypertension (n)	53/73
Hyperlipidaemia (n)	56/73
Coronary artery disease (n)	17/73

BMI: Body mass index, DT2DM: duration of T2DM, FPG: fasting plasma glucose, HbA1c: hemoglobin A1c, Cr: creatinine, TSH: thyroid stimulating hormone, ALT: alanine transaminase, AST: aspartate transaminase, LDL: low density lipoprotein, TG: triglyceride, UACR: spot urine albumin creatinine ratio, DPP-4: Dipeptidyl peptidase 4, inhibitors, SGLT-2: Sodium-glucose cotransporter-2 inhibitors.

Table II. Baseline and follow-up parameters.

	Baseline	Month 6	Month 12
FPG (mg/dl)	251.6 ± 66.5[a]	136.1 ± 34.7[b]	125.4 ± 67.0[c]
HgA1c (%)	10.46 ± 1.54[a]	7.97 ± 1.24[b]	7.98 ± 1.23[c]
C Peptide µg/L	3.1 ± 1.7		2.5 ± 1.5[c]
Triglyceride (mg/dl)	215.0 ± 83.5[a]	170.9 ± 68.9	
UACR	735.7 ± 998.5[a]	251.9 ± 283.5	
Total daily insulin dose (U)	102.9 ± 29.0[a]	73.2 ± 18.2[b]	63.7 ± 20.3[c]
Weight (kg)	93.7 ± 20.5		89.2 ± 17.4[c]

[a]Comparison between baseline and 6 months: $p < 0.001$, $p < 0.001$, $p < 0.001$, $p = 0.021$, $p < 0.001$. [b]Comparison between 6 and 12 months: $p = 0.01$, $p > 0.05$, $p < 0.001$. [c]Comparison between 6 and 12 months: $p < 0.001$, $p < 0.001$, $p = 0.005$, $p < 0.001$, $p < 0.001$. FPG: fasting plasma glucose, HbA1c: haemoglobin A1c, UACR: spot urine albumin creatinine ratio.

After six months, 74.0% (54/73) of the participants fell below the HbA1c cut-off value of 8.5% (according to the initial inclusion criterion). When the HbA1c cut-off value was 7.0%, 24.7% (18/73) of the patients were below this value. At the end of the study, HbA1c was below 8.5% in 68.5% (50/73) of the participants and below 7.0%, in 24.7% (18/73) (Figure 1).

Number of Injections

Switching to IDegAsp BID-Plus significantly reduced the number of injections. Prior to the transition, 15 patients received two doses of basal insulin (five total injections per day). Specifically, 10 patients received insulin glargine U100, 1 received insulin glargine U300, and 4 received insulin detemir. Meanwhile, 51 patients received basal insulin once a day (four total injections/day). Specifically, 24 received insulin glargine U100, 13 received insulin glargine U300 and 14 received insulin detemir. After six months, 54 patients were injected 3 times a day, and 19 patients were injected 2 times daily. After one year, 38 patients were injected 3 times daily, and 35 patients were injected 2 times daily.

Insulin Dosage

There was a statistically significant decrease in total daily insulin dosage (Table II), mainly due to a decrease in the bolus dosage. The basal insulin dosage decreased from 44.8±13.8 U at baseline to 35.6±7.3 U at 6 months and 24.4±8.4 U at 12 months. Comparative analyses were conducted between baseline and 6 months (p<0.001), baseline and 12 months (p<0.001) and 6 and 12 months (p<0.001). The bolus insulin dosage decreased from 58.1±21.8 U at baseline to 21.2±7.7 U at 6 months and 17.8±8.7 U at 12 months. Comparative analyses were conducted between baseline and 6 months (p<0.001), baseline and 12 months (p<0.001) and 6 and 12 months (p<0.001) (Figure 2).

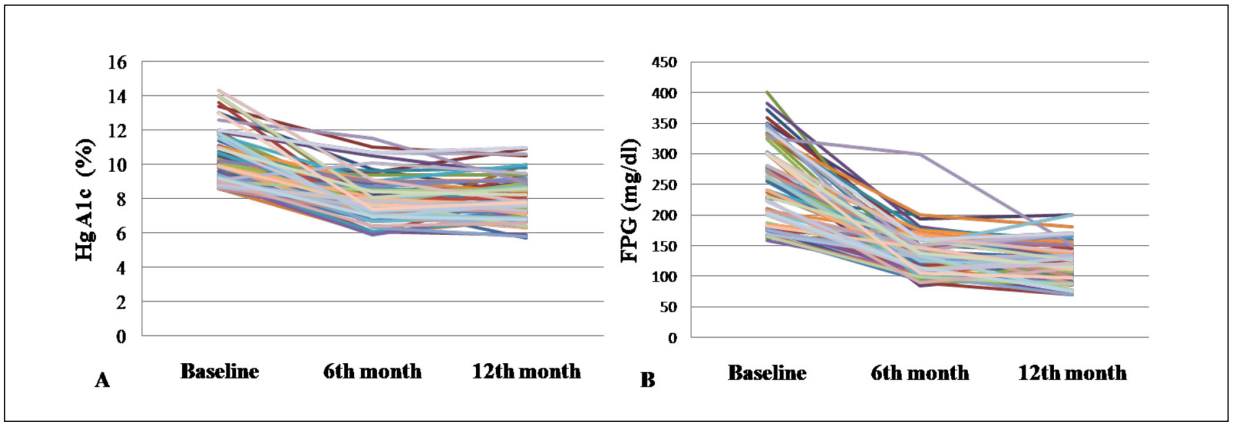

Figure 1. Changes in HgA1c (**A**) and FPG (**B**) before and after IDegAsp BID-Plus therapy.

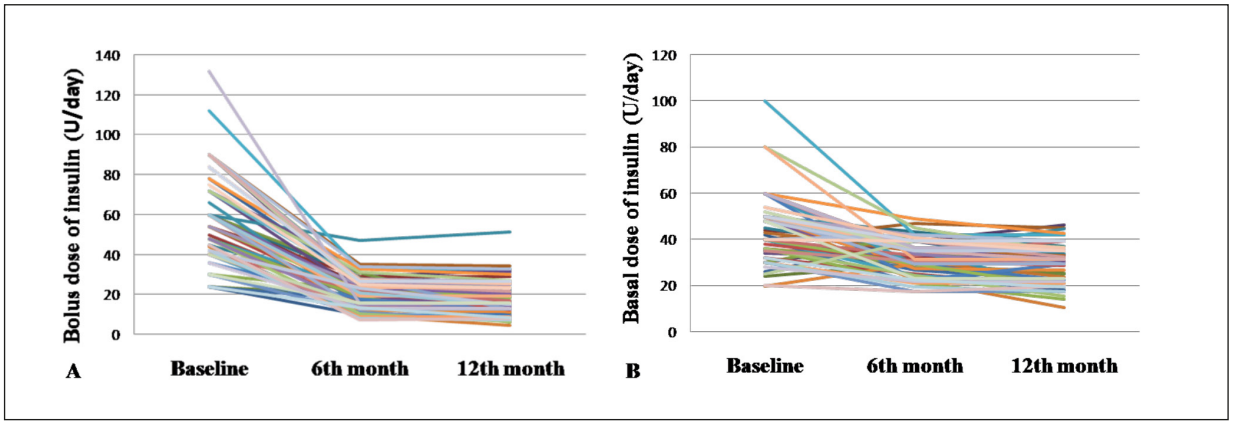

Figure 2. Changes in bolus (**A**) and basal (**B**) insulin doses per day over the studied time period.

BMI and Hypoglycaemic Events

The mean BMI decreased from 93.7±20.5 kg at baseline to 89.2±17.4 kg at 12 months (p<0.001). At the end of the 12th month, 54 patients were reached *via* telephone and asked about how often they experienced symptomatic hypoglycemia. Three patients had one symptomatic hypoglycemia attack per month, and two had two symptomatic hypoglycemia attacks per month.

Discussion

The real-world data collected in this study showed that IDegAsp BID-Plus treatment effectively reduced HbA1c and FPG levels in patients with poor glycaemic control on BBIT. Furthermore, the treatment involved lower insulin doses and fewer injections than previous intensive insulin therapy. Moreover, the findings at the end of the one-year study period showed that the achieved glycaemic control could be maintained with a lower total daily insulin dose and fewer injections.

The most remarkable result of switching to IDegAsp BID-Plus is the possibility of a powerful therapeutic intervention with fewer injections. Physicians are often forced to switch patients with uncontrolled T2DM to complex insulin regimens, leading to an increase in the number of daily injections and patient compliance problems. A flexible insulin regimen is defined as a regimen with variable injection-meal time intervals. Regarding basal insulins, detemir can be injected in the evening or at bedtime but must be administered at the same time every day[28]. Glargine can be injected at any time of the day but must be administered at the same time every day[29]. IDeg can be injected at any time of the day, but there must be an eight-hour break between doses[30].

IDegAsp BID-Plus is the most flexible type of insulin available today; the administration timing can be changed, and it increases person-centredness. A flexible administration treatment regimen philosophy considers patient well-being without causing harm to the extent possible. In patients with uncontrolled T2DM, small changes to insulin regimens that allow flexibility in pharmacokinetic and pharmacodynamic effects as well as psychological (frequency and timing of injections) and social (work profile, lifestyle) considerations can contribute greatly to achieving the goals of this beneficial management[31].

The significant decreases in the total daily insulin dose at 12 and 24 weeks and the maintenance of the reduction after one year compared to baseline are in line with findings from previous research[32,33] on the effect of switching to IDegAsp in real-life clinical settings and target-to-treat randomized controlled trials evaluating IDegAsp in comparison with ongoing insulin regimens in people with T2DM. Furthermore, the significant bolus insulin dose reduction, the basal insulin dose reduction as FPG stabilized and the significant total daily insulin dose reduction are consistent with reports from the BOOST clinical trial programme[33]. The transition from higher to reasonable insulin doses not only resulted in lower healthcare costs but also may have increased patient confidence and adherence to treatment.

The present study found a statistically significant improvement in HbA1c at 3, 6 and 12

months compared to baseline. The most dramatic decrease in HbA1c was seen in patients with high baseline HbA1c who were receiving high doses of insulin. IDegAsp has been used in clinical trials[33-35] in patients with T2DM that were inadequately controlled with OHAs and an alternative insulin regimen, i.e., basal-only insulin detemir, insulin glargine administered OD or BID, a premix analogue insulin regimen administered BID or an insulin regimen with a rapid-acting component. Similar reductions in HbA1c and fewer hypoglycaemic episodes were detected, basal-prandial compared to intensification with IDegAsp BID, premix BID following IDegAsp BID treatment, HbA1c <7% ranged from 48.2% to 56.5%.

Babakar et al[16] used the IDegAsp BID regimen to intensify a basil-only regimen, i.e., insulin glargine OD, in inadequately controlled T2DM patients. After 26 weeks of IDegAsp treatment, 67% of the patients were successfully treated[36]. Meanwhile, in a small group of patients with persistent poor glycemic control at the end of the study[36], the following treatment strategies were applied: (a) the addition of a single bolus injection to the IDegAsp BID regimen or (b) a switch to a complete BBIT regimen through the addition of IAsp OD to the IDegAsp BID regimen. These changes resulted in HbA1c level maintenance over the 26-week period. Moreover, switching to IDeg OD+IAsp three times per day reduced HbA1c by 0.49%[16]. In another study, Kawaguchi et al[20] used the flash glucose monitoring system to demonstrate that glargine U300/insulin glulisine (BBIT regimen) was superior to IDegAsp in terms of efficacy and safety[20].

The present study's findings contradict previous studies[20] assertions about the superiority of BBIT over IDegAsp preparations. Unlike the sample populations in such studies[37], the present study examined patients with unregulated T2DM, very high HbA1c levels at baseline and multiple insulin regimen+high FPG despite BBIT+OHA. Therefore, the striking results of the present study may be due to IDeg's strong efficacy as well as its ability to improve adherence in a difficult patient population that cannot adapt to living with insulin.

In a real-world comparison of IDegAsp and glargine U300, IDegAsp BID bolus insulin and glargine U300 BBIT were both found to be effective and safe[37]. In a prospective multicentre study[32], statistically significant HbA1c improvements were found in six countries. Meanwhile, Özçelik et al[38] retrospective study found that a transition from an intensive premix insulin regimen to IDegAsp BID significantly decreased HbA1c values in both groups in patients with T2DM[38].

In the present study, participants had lower HbA1c levels at six months compared to baseline, with 24.7% achieving a target of <7.0% and maintaining that level at the end of one year. Although an uncontrolled T2DM population that probably has poor treatment adherence is relatively unlikely to achieve and maintain this goal, the present study demonstrates that IDegAsp can improve outcomes in a real-world setting. Furthermore, in routine clinical practice, HbA1c targets can be higher than 7.0%; at the end of one year, 68.5% of the study participants had achieved an individual treatment goal of HbA1c <8.5%. The present study's findings are encouraging for the long-term outcomes of patients with T2DM. Hazard model[39] estimates based on 10-year outcomes observed in UKPDS data suggested that a sustained mean glycemic level reduction of 0.511 points would lead to a 10.7% reduction in diabetes complications.

Meanwhile, the decrease in BMI observed at 52 weeks in the present study was possibly due to participants' increased adherence to the diet and reduced carbohydrate snacking due to reduced hypoglycaemia[40]. Another reason for this finding could be the lower total insulin dose, since insulin is an anabolic hormone[41].

The present study makes an important contribution to research on the transition to IDegAsp BID-Plus by using real-world data to study a challenging group of patients who have tried complex treatment regimens that are common in real life. In this difficult patient group, IDegAsp BID-Plus may be preferable to the basal plus insulin regimen as a simplified intensive insulin treatment regimen with lower resource utilisation (fewer needles and blood glucose monitoring tests required) and greater flexibility, especially when fear of injections is a barrier to treatment[42].

Limitations

There are some basic limitations that should be considered when interpreting the study findings, including the study's retrospective design and small sample size. In addition, the data were collected from hospital records, and information on hypoglycemia and BMI changes was missing for some participants.

Conclusions

Using real-world data, the present study showed that IDegAsp BID-Plus treatment resulted in effective and sustained HbA1c and FPG level reductions through lower insulin doses and fewer injections compared to previous BBIT in patients with uncontrolled T2DM. In the future, it may be recommended as a simplified intensive insulin therapy before switching to complex insulin regimens in patients with difficult-to-treat T2DM.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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No allowance or funding was received for the costs of the research. The expenses of the study were covered by the researchers.

Ethics Approval

The present study was approved by the Ethics Committee of the Health Sciences University, Bursa State Hospital, "23.03.2022 2022/4-12, E-13012450-514.05.99". In light of the retrospective nature of the study, all procedures were performed as part of routine care. The researchers affirm that they adhered to the Declaration of Helsinki.

Authors' Contribution

Elif Güneş: Conceptualization, methodology, data curation, writing-original draft preparation, visualization, investigation. Mutlu Güneş; Supervision, software, validation, writing- reviewing and editing.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

ORCID ID

Elif Güneş: 0000-0002-5441-2604
Mutlu Güneş: 0000-0001-9756-2285

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