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ORIGINAL RESEARCH

Switching from Multiple Insulin Injections to a Fixed Combination of Degludec and Liraglutide in Patients with Type 2 Diabetes Mellitus: Results from the Simplify Study After 6 Months

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ABSTRACT

Introduction: This study aimed to evaluate the effectiveness and safety of switching from basal bolus insulin treatment (BBIT) to a fixed combination of insulin degludec and liraglutide (IDegLira) in patients with type 2 diabetes mellitus (T2DM) who had preserved insulin secretion but inadequate glucose control. The study also aimed to assess the feasibility of implementing this therapeutic approach in common clinical practice settings.

Methods: This was a non-randomized, open-label, multicenter, prospective, single-arm study involving 234 patients with T2DM who were receiving BBIT. Inclusion criteria were duration of diabetes mellitus > 60 months, stable total daily dose of insulin (TDDI) ranging from > 20 to < 70 IU/day (approx. > 0.3 to < 0.7 IU/kg body weight/day), C-peptide levels > 10% above the lower limit, HbA1c levels > 7% and < 10% (Diabetes Control and Complications Trial), and body mass index > 25 kg/m^2. The primary endpoints were changes in glycated hemoglobin (HbA1c) and body weight at week 28 after treatment switching. Secondary endpoints included changes in the 7-point glycemic profile, hypoglycemia frequency, blood pressure, blood lipids, liver enzymes, insulin dose, and a patient questionnaire focusing on treatment satisfaction, concerns and impact on daily activities. A subgroup of 55 patients underwent continuous glucose monitoring (CGM) with the evaluation of CGM-derived parameters, such as time in range (TIR), time above range (TAR), time below range (TBR), hypoglycemia, and glucose variability.

Results: A significant decrease in HbA1c (8.6% vs. 7.6%; $p < 0.0001$) and body weight (97.8 vs. 94.0 kg; $p < 0.0001$) was observed at week 28 after treatment switching. Significant improvements were also seen in all measurements of the 7-point glycemic profile ($p < 0.0001$), reduction in the number of hypoglycemia episodes per patient, and the proportion of patients with at least one hypoglycemia event ($p < 0.001$). Furthermore, there was a significant decrease in daily insulin dose (55.6 vs. 32.7 IU/day; $p < 0.0001$), as well as improvements in blood pressure, blood lipids, and liver enzymes (gamma glutamyl transferase and alanine aminotransferase). The subgroup of patients

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who underwent CGM showed a significant increase in TIR (57.9% vs. 69.0%; $p < 0.01$) and a decrease in TAR (40.1% vs. 28.8%; $p < 0.01$), while TBR, hypoglycemia (number of episodes per patient and proportion of patients), and glucose variability did not change significantly. ***Conclusion***: The results of this study suggest that switching from BBIT to IDegLira in patients with T2DM and preserved insulin secretion can simplify treatment without compromising glycemic control. The switch to IDegLira was associated with significant improvements in various glucose control parameters, including HbA1c, glycemic profile, hypoglycemia, insulin doses, and CGM-derived parameters TIR and TAR. Additionally, it led to significant reductions in body weight, blood pressure, lipid profile, and liver enzyme levels. Switching to IDegLira may be considered a safe and beneficial approach in clinical practice settings, offering metabolic and individual advantages.

Keywords: Basal bolus insulin therapy; IDegLira; Treatment simplification; Time-in-range

Key Summary Points

Why carry out the study?

Several benefits of switching from basal-bolus insulin treatment (BBIT) to a fixed combination of insulin degludec and liraglutide (IDegLira) have been documented in trials in patients with type 2 diabetes mellitus (T2DM), but these studies were either small, monocentric, of short duration, included only patients with relatively good glycemic control, had a retrospective design using data from medical databases, and/or lacked data on the incidence of hypoglycemia; none utilized continuous glucose monitoring (CGM).

The primary aim of our study, called "Simplify," was to evaluate whether switching from BBIT to IDegLira in patients with T2DM with preserved insulin secretion but inadequate glucose control is at least as effective and safe as the preceding BBIT. A secondary aim was to determine whether such a therapeutic approach can be implemented in routine clinical practice.

What was learned from this study?

Switching from BBIT to IDegLira in patients with T2DM with preserved insulin secretion led to significant improvements in all glucose control parameters (HbA1c, glycemic profile, decrease in hypoglycemia events, decrease in insulin doses) and significant reductions in body weight, blood pressure, lipid profile, and liver enzymes. Patient satisfaction with the treatment also improved. The subgroup of patients who underwent CGM also showed a significant increase in time in range and a decrease in time above range), while time below range, hypoglycemia (number of episodes per patient and proportion of patients), and glucose variability did not change significantly.

Switching from BBIT to a fixed combination of IDegLira in patients with T2DM with preserved insulin secretion could be a beneficial and safe approach in clinical practice, offering complex metabolic and individual benefits.

INTRODUCTION

Basal-bolus insulin treatment (BBIT) is generally considered to be the last therapeutic option for patients with type 2 diabetes mellitus (T2DM) [1, 2]. However, BBIT is often used prematurely due to the lack of other therapeutic options and can present as a very demanding treatment

regimen for the patient. In addition to the burden of multiple injections, frequent self-monitoring of blood glucose (SMBG), and the challenges of coordinating with dietary measures and physical activity, BBIT can lead to various clinical complications, including hypoglycemia, weight gain, peripheral hyperinsulinemia, and fluid retention [1, 3]. These factors can negatively impact patients' adherence to treatment and hinder the achievement of optimal glycemic control. Furthermore, many patients with T2DM on BBIT have preserved insulin secretion [4, 5], raising questions about the necessity of full insulin replacement.

The new American Diabetes Association/European Association for the Study of Diabetes (EASD/ADA) Consensus Report recommends that treatment with glucagon-like peptide-1 receptor agonists (GLP1-RA) precedes insulin treatment; if basal insulin was initiated first, then GLP1-RAs are considered the preferred method of intensification [1]. GLP1-RA are known for their high efficacy in glucose lowering and weight loss, along with complex cardiometabolic effects [6–8] and proven cardiovascular and renal protective benefits [9–11]. Numerous randomized clinical trials (RCTs) [12] and real-world evidence (RWE) [13] trials have demonstrated that combined therapy with basal insulin analog and GLP1-RA, also as a fixed combination [12], is non-inferior to BBIT in terms of glycemic control after treatment failure with basal insulin. Moreover, this combination has shown superiority in terms of weight reduction and lower risk of hypoglycemia, and also in the requirement for a lower total daily dose of insulin [12, 13]. Additionally, a fixed combination of basal insulin and GLP-1RA, such as insulin degludec and liraglutide (IDegLira), offers significant treatment simplification for the patient. Despite all of the above, limited data are available on whether IDegLira would also be effective in those patients with T2DM who have already been on BBIT for an extended period.

Three RWE studies [14–16] documented several benefits of switching from BBIT to IDegLira in patients with T2DM, with the more important of these being improvements in glycated hemoglobin (HbA1c), body weight, and reduction of insulin dose. However, these studies were either small, monocentric, and/or of short duration, included only patients with relatively good glycemic control, and/or had a retrospective design using data from medical databases; others lacked data on the incidence of hypoglycemia, and none utilized continuous glucose monitoring (CGM).

The aim of our study, called "Simplify", was to evaluate whether switching from BBIT to IDegLira in patients with T2DM with preserved insulin secretion but inadequate glucose control is at least as an effective and safe therapy as the previous BBIT. We also aimed to determine whether such a therapeutic approach can be implemented in routine clinical practice.

METHODS

Study Design and Participants

The Simplify study was a non-randomized, open-label, multicenter, prospective, single-arm study conducted in a real-world clinical practice setting, with a duration of 28 weeks. The main inclusion criteria for enrollment were patients who had T2DM with preserved insulin secretion, were receiving BBIT at a total daily dose of insulin (TDDI) ranging from 20 to 70 IU/day, and had HbA1c levels $> 7\%$ but $< 10\%$. The main exclusion criteria included patients with type 1 diabetes mellitus, including latent autoimmune diabetes (LADA), with any acute or chronic underlying medical conditions, and with any additional non-diabetic treatment that could potentially affect glycemic control or body weight within the 3 months prior to screening, and those unable to comply with the therapeutic regimen (Table 1).

Outcome Measures

Primary endpoints were defined as the change in HbA1c and change in body weight from baseline to week 28 after the switch from BBIT to IDegLira. Secondary endpoints included the change in the 7-point glycemic profile based on SMBG, the number of confirmed episodes of

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
HbA1c: > 7%, < 10% (DCCT); 53–86 mmol/mol (IFCC units)	BMI < 25 kg/m^2, unplanned significant weight lose
Age: > 18 years, < 80 years	Any signs of catabolism
Duration of diabetes mellitus: minimal 60 months	Type 1 diabetes mellitus including LADA
Preserved insulin secretion with C-peptide level at least 10% above the lower limit of the normal range	Planned surgery (except for minor short-term procedures) or hospitalization
BBIT with duration of at least 12 months	Acute disease < 2 weeks before prescreening with potential effect on glycemic control
Type 2 diabetes mellitus	Chronic disease detected < 3 months before prescreening or unstable with a potential effect on glycemic control or body weight
TDDI > 20 IU, < 70 IU/day (approx. > 0.3 < 0.7 IU/kg/day), with stable doses during at least 3 months ± OAD with a stable composition and dose over the last 3 months before screening	Addition of drugs < 3 months before prescreening with a potential effect on glycemia or body weight
BMI > 25 kg/m^2	Optimal glycemic control on previous insulin treatment
Ability and willingness to perform SMBG	Treatment with GLP1-RA
Ability and willingness to wear blinded CGM (3-times for 14 days)—*in a selected subgroup of patients*	Contraindication/intolerance to GLP1-RA, insulin degludec or IDegLira according to the Summary of Product Characteristics
	eGFR < 15 ml/min/1.73 m^2
	Patients unable to comply with therapeutic regimen
	Overall unfavorable condition of the patient limiting study participation

BBIT Basal-bolus insulin treatment, *BMI* body mass index, *CGM* continuous glucose monitoring, *DCCT* Diabetes Control and Complications Trial, *eGFR* estimated glomerular filtration rate, *GLP1-RA* glucagon-like peptide-1 receptor agonists, *HbA1c* glycated hemoglobin, *IDegLira* fixed-combination insulin degludec and liraglutide, *IFCC* International Federation of Clinical Chemistry, *LADA* latent autoimmune diabetes of adults, *OAD* oral antidiabetic drugs, *SMBG* self-monitoring of blood glucose, *TDDI* total daily dose of insulin

symptomatic hypoglycemia (< 3.9 mmol/l) or severe hypoglycemia per patient, and the proportion of patients with at least one hypoglycemic event based on SMBG. Other secondary endpoints encompassed change in TDDI, blood pressure, lipid profile, and liver enzymes (gamma glutamyl transferase [GGT] and alanine aminotransferase [ALT]). Any adverse events or reasons for patient termination in the study were recorded. Additionally, a questionnaire that focused on patient concerns related to treatment satisfaction and the impact of diabetes mellitus and its treatment on daily activities was administered.

In a subgroup of patients, changes in CGM-derived parameters, such as time in range (TIR), time above range (TAR), time below range (TBR), hypoglycemia (including the number of episodes per patient and the proportion of patients), and glucose variability were also evaluated. The interpretation of results was in accordance with the International Consensus on Time in Range [18].

The study was conducted at diabetes outpatient clinics across 37 participating centers in

Slovakia. The initial investigators' meetings for each center took place between 15 and 22 June 2021, followed by a pre-screening period. Patient screening commenced between 15 September 2021 and 15 March 2022. The study concluded on 30 October 2022.

Procedures

Pre-screening of eligible patients was conducted during the patient's routine visit to the clinic, at least 3 months prior to the screening (Fig. 1). Emphasis was placed on compliance with therapeutic recommendations, regular SMBG, and the recording of all confirmed symptomatic hypoglycemia episodes < 3.9 mmol/l in all enrolled patients. In eligible subjects, baseline clinical and laboratory parameters were collected during a screening visit scheduled 2 weeks before the patient was switched from BBIT to IDegLira. The day of switching was considered to be day 1. After the switch in treatment, the evaluated parameters were collected at weeks 14 and 28. At week 14, safety and glycemic control, including CGM-derived parameters, were recorded; at week 28, changes in the evaluated parameters from baseline to week 28 were calculated and statistically analyzed (Fig. 1).

The switch from BBIT to IDegLira was performed in a single outpatient visit. The BBIT regimen was discontinued the day before day 1, and the initial dose of IDegLira was calculated as 50% of the previous TDDI, but not exceeding 16 IU, followed by titration of ± 2–4 IU every 2–3 days. IDegLira was preferably administered in the morning before breakfast, based on evidence that most patients typically experience the highest increase in blood sugar levels after breakfast and that administering IDegLira in the morning effectively maximizes the effect of liraglutide to manage postprandial glycemia following breakfast. Treatment with metformin and gliflozins was continued, while the use of gliptins was discontinued. The decision to continue treatment with glitazones and/or sulfonylureas was left to the clinical judgment of the treating physician. Laboratory parameter analysis was conducted using standard laboratory methods in certified laboratories. Values for the evaluated parameters were collected and

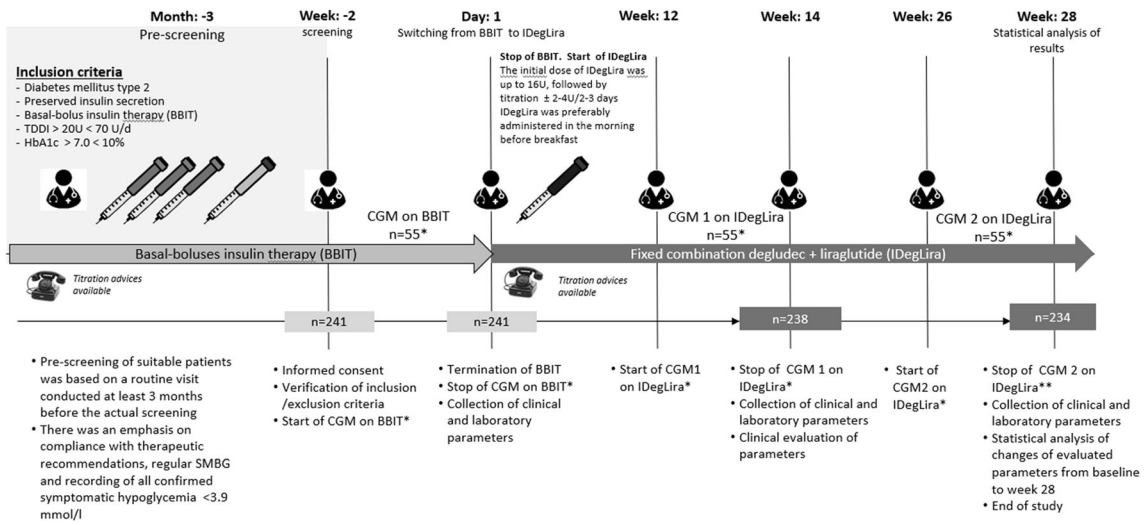

Fig. 1 Study timeline. *BBIT* Basal-bolus insulin therapy, *CGM* continuous glucose monitoring, *CGM on BBIT* CGM on basal-bolus insulin therapy, *CGM on IDegLira* CGM on IDegLira, *IDegLira* fixed combination of insulin degludec and the glucagon-like peptide-1 receptor agonist (GLP1-RA) liraglutide, *SMBG* self-monitoring of blood glucose, *TDDI* total daily dose of insulin. Asterisk refers to a subgroup of 55 patients who underwent also continual CGM

Table 2 Clinical characteristics of patients, showing change from baseline to week 28

Parameter	Patients (n = 234)			Change from baseline to week 28 (p)[a]
	Baseline	Week 14	Week 28	
Male:female (%)	49:51			
Age (years)	64.9 ± 8.2			
Duration of diabetes mellitus (years)	16.1 ± 7.5			
Body weight (kg)	97.8 ± 18.6	94.8 ± 17.8	94.0 ± 17.8	0.0001
BMI (kg/m^2)	33.9 ± 5.4	32.9 ± 5.2	32.6 ± 5.0	0.0001
C-peptide (nmol/l)	0.75 ± 0.43			
Total daily dose of insulin (IU/day)	55.6 ± 13.5	31.1 ± 9.3	32.7 ± 10.1	0.0001
Metformin (%)	85.0%	84.6%	86.8%	n.s
SGLT2 inhibitors (gliflozins) (%)	24.8%	17.9%	18.4%	n.s
DPP-4 inhibitors (gliptins) (%)	12%	0%	0%	0.0001
Sulphonylureas (%)	7.3%	9.0%	12.4%	n.s
PPARγ agonists (glitazones) (%)	0%	0%	0%	n.s
HbA1c (%, DCCT)	8.6 ± 1.0	7.7 ± 1.2	7.6 ± 1.1	0.0001
Arterial hypertension (%)	90.6%			
Dyslipidemia (%)	77.7%			
Cholesterol—total (mmol/l)	4.7 ± 1.1	4.5 ± 1.1	4.4 ± 1.0	0.01
Triglycerides (mmol/l)	2.1 ± 1.2	1.9 ± 1.1	1.8 ± 0.9	0.0001
HDL-cholesterol (mmol/l)	1.2 ± 0.3	1.2 ± 0.4	1.2 ± 0.3	n.s
LDL-cholesterol (mmol/l)	2.8 ± 1.0	2.6 ± 0.9	2.6 ± 0.8	0.01
Systolic blood pressure (mmHg)	141.4 ± 17.3	135.5 ± 14.5	135.2 ± 14.6	0.0001
Diastolic blood pressure (mmHg)	81.1 ± 9.8	79.6 ± 8.8	79.5 ± 8.6	0.05
ALT (μkat/l)	0.57 ± 0.45	0.52 ± 0.29	0.48 ± 0.25	0.001
GGT(μkat/l)	0.76 ± 0.85	0.70 ± 0.61	0.66 ± 0.61	0.001
Smoking of cigarettes (%)	12.8%			
Hypoglycemia based on SMBG				
Number of episodes of symptomatic, confirmed hypoglycemia < 3.9 mmol/l/patient/month	0.38 ± 0.10	0.05 ± 0.40	0.10 ± 0.46	0.001
Number of episodes of severe hypoglycemia/patient/month	0.03 ± 0.14	0	0	0.05

Table 2 continued

Parameter	Patients (n = 234)			Change from baseline to week 28(p)[a]
	Baseline	Week 14	Week 28	
Proportion of patients with at least 1 hypoglycemic event/month (%)	16.20	3.42	4.70	0.001

Values in table are presented as the mean ± standard deviation (SD) or as a percentage, as appropriate
ALT Alanine aminotransferase, *DDP-4* dipeptidyl peptidase 4, *GGT* gamma glutamyl transferase, *HDL/LDL* high-/low-density lipoprotein, n.s. not statistically significant, *PPARγ* peroxisome proliferator-activated receptor gamma, *SGLT2* sodium-glucose cotransporter-2
[a]Unless indicated otherwise (n.s.), values at week 28 are significantly different from those at baseline at the level indicated

electronically recorded by each participating center.

Evaluation of CGM-derived parameters was conducted using the ambulatory glucose profile (AGP) report from the latest generation of the Abbott FreeStyle Libre Pro iQ, a blinded continuous glucose monitoring system (Abbott Laboratories, Chicago, IL, USA).

Statistical Analyses

Data are shown as arithmetic means ± standard deviations (SD) or percentages. Continual variables at baseline and week 28, were compared by paired *t*-test, and the proportions were compared by Chi-square test.

Compliance with Ethics Guidelines

The study was conducted in accordance with the Helsinki Declaration of 1964 and its later amendments. Approval was granted to all 37 participating centers by the Multicentric Ethics Committee of the National Institute for Endocrinology and Diabetology n.o., in Ľubochňa, Slovakia (No. 3716/21-A.08). Written informed consent was obtained from all participants prior to their inclusion in the study.

RESULTS

A total of 241 patients were initially enrolled in the study, including 55 who underwent CGM. By week 14, following the change in treatment, three patients not in the CGM subgroup had withdrawn from the study: one due to gastrointestinal discomfort, one due to deteriorating glycemic control, and one for personal reasons that were not specified. Between weeks 14 and 28, four additional patients outside the CGM subgroup were excluded: one due to worsening glycemic control, one due to an unfortunate car accident, and two who dropped out for personal reasons that were not specified. Thus, complete data were available for 238 participants at week 14 and for 234 patients, including 55 who also had CGM-derived data, for week 28.

The clinical and laboratory data of the patients before and after the change in treatment are shown in Table 2. The average age of the patients was 64.9 years, with an average duration of T2DM of 16.1 years. Patients were not optimally controlled, with an average HbA1c of 8.6%. Most patients were obese, with a mean body mass index (BMI) of 33.9 kg/m^2. At enrollment, 91% of patients had hypertension, 77% had dyslipidemia, and 43% had known cardiovascular disease. Participants who underwent CGM did not differ from the whole group in any of the clinical characteristics assessed in Table 2 (not shown).

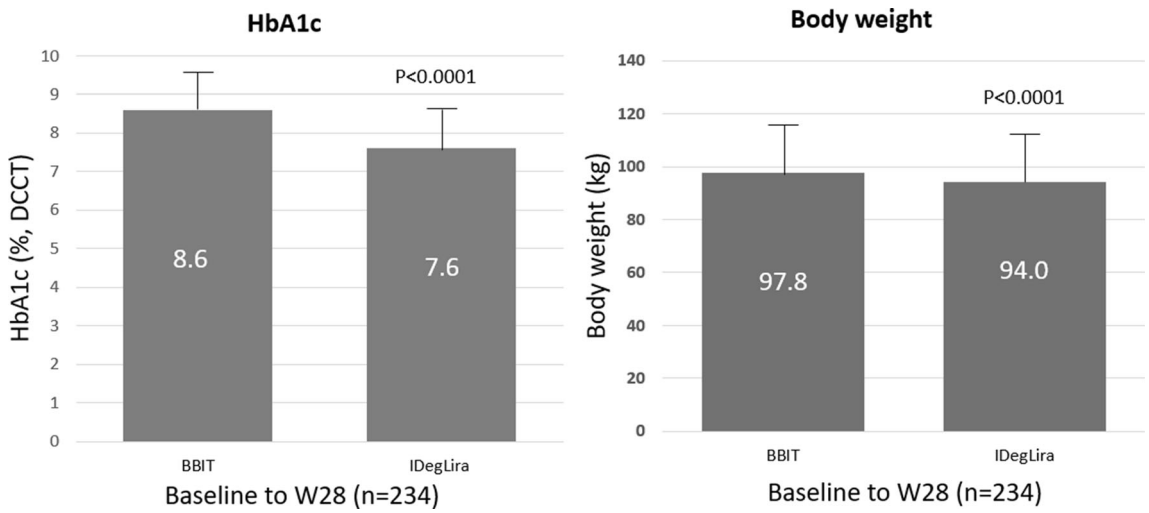

Fig. 2 Changes in HbA1c levels and body weight from baseline to week 28 after switching from BBIT to IDegLira. *BBIT* basal-bolus insulin therapy, *IDegLira* fix combination od insulin degludec and GLP-1RA liraglutide, *W28* 28 weeks after switching from BBIT to IDegLira, *p* statistical significance

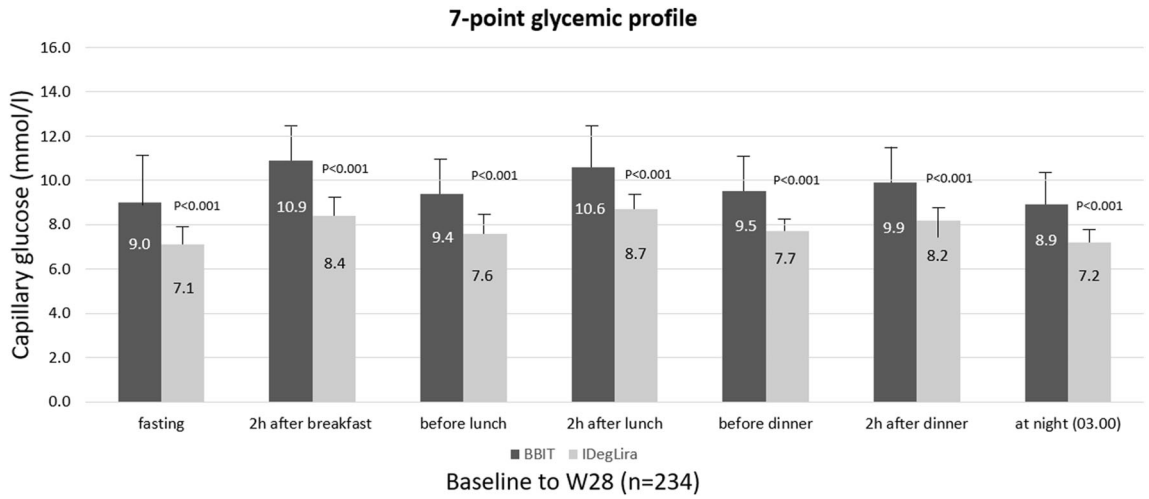

Fig. 3 Changes in 7-point glycemic profile from baseline to week 28 after switching therapy from BBIT to IDegLira. *BBIT* basal-bolus insulin therapy, *IDegLira* fix combination od insulin degludec and GLP-1RA liraglutide, *W28* 28 weeks after switching from BBIT to IDegLira, *2 h* two hours, *p* statistical significance

A significant reduction was observed for both primary endpoints. The mean decrease in HbA1c was 1.0%, and the mean decrease in body weight was 3.8 kg at week 28 (Fig. 2). There was also a significant average decrease of 2 mmol/l in the 7-point glycemic profile (Fig. 3). The number of hypoglycemic episodes per patient, as well as the proportion of patients with at least one hypoglycemic event recorded by SMBG, was significantly lower in with IDegLira than with BBIT. No severe hypoglycemic episodes occurred after the switch to IDegLira (Table 2). In the subgroup of 55 patients who underwent CGM, there was a significant 11.1% increase in TIR and a significant 11.3% decrease in TAR at week 28 (Table 3). TBR did not change significantly. CGM also showed a trend towards a decrease in both the number of episodes of

Table 3 Continuous glucose monitoring derived parameters. Change from baseline to week 28

Parameter	Patients (n = 55)			Baseline to week 28 p
	Baseline	Week 14	Week 28	
Time in range (%)	57.9 ± 25.3	68.9 ± 23.7	69.0 ± 17.5	0.01
Time above range (%)	40.1 ± 26.9	30.1 ± 24.8	28.8 ± 18.8	0.01
Time below range (%)	1.84 ± 4.00	1.00 ± 1.80	1.53 ± 2.94	n.s
Hypoglycemia—number of episodes per patient	2.55 ± 4.85	1.40 ± 2.51	1.33 ± 2.61	n.s
Hypoglycemia—proportion of patients (%)	52.7	38.2	38.2	n.s
Glucose variability (%)	28.6 ± 6.0%	25.9 ± 6.6%	27.8 ± 6.4%	n.s

Values in table are presented as the mean ± SD or as a percentage, as appropriate

hypoglycemia per patient and the proportion of patients with at least one hypoglycemic event, as well as lower glycemic variability. However, changes in these parameters did not reach statistical significance (Table 3).

Among the other evaluated parameters, a significant decrease in blood pressure, especially systolic blood pressure, was observed, as well as in blood lipids, namely triglycerides, total cholesterol, and low-density lipoprotein-cholesterol. Additionally, there was a significant decrease in the liver enzymes GGT and ALT. The insulin dose requirement was also significantly lower compared to baseline (Table 2).

There was no significant change in concomitant antidiabetic, hypolipidemic, antihypertensive, and anti-obesity treatments, except for gliptins, whose proportion decreased to zero (Table 2). Responses to questionnaires focused on patient satisfaction with treatment and the impact of diabetes mellitus and its treatment on daily activities showed that after switching from BBIT to IDegLira, patients were more satisfied with the treatment and perceived it as a significant relief from the usual burden associated with BBIT. Patients' concerns about weight gain or hypoglycemia with BBIT were not confirmed, and the new treatment approach did not raise any concerns for most respondents (Fig. 4).

DISCUSSION

In the present study, switching patients with T2DM from BBIT to IDegLira resulted in a mean reduction in HbA1c level of 1.0% and a body weight decrease of 3.8 kg at 28 weeks after the switch. This change of treatment also improved the 7-point glycemic profile and resulted in reduced blood pressure, lipid levels, and liver enzymes GGT and ALT. It also led to a decrease in the proportion of patients experiencing at least one episode of hypoglycemia, as well as a reduction in the number of episodes of hypoglycemia per patient while reducing the average daily insulin dose by 23 IU/day.

The subgroup analysis of patients who also underwent CGM revealed that there was a significant increase in TIR in these patients, from 58% at baseline to 69% (+ 11%) at week 28, together with a significant decrease in TAR, from 40% to 29% (− 11%), at the same time point. There was also a non-significant trend towards a lower number of hypoglycemic episodes per patient, a smaller proportion of patients with at least one hypoglycemic episode, and lower glucose variability.

Regarding concomitant treatment, the use of gliflozins, metformin, sulphonylureas, and glitazones did not significantly change from baseline to week 28, except for gliptins, whose usage decreased to zero as per study protocol. Additionally, no substantial modifications were made to antihypertensive and lipid-lowering treatments. No specific pharmacological

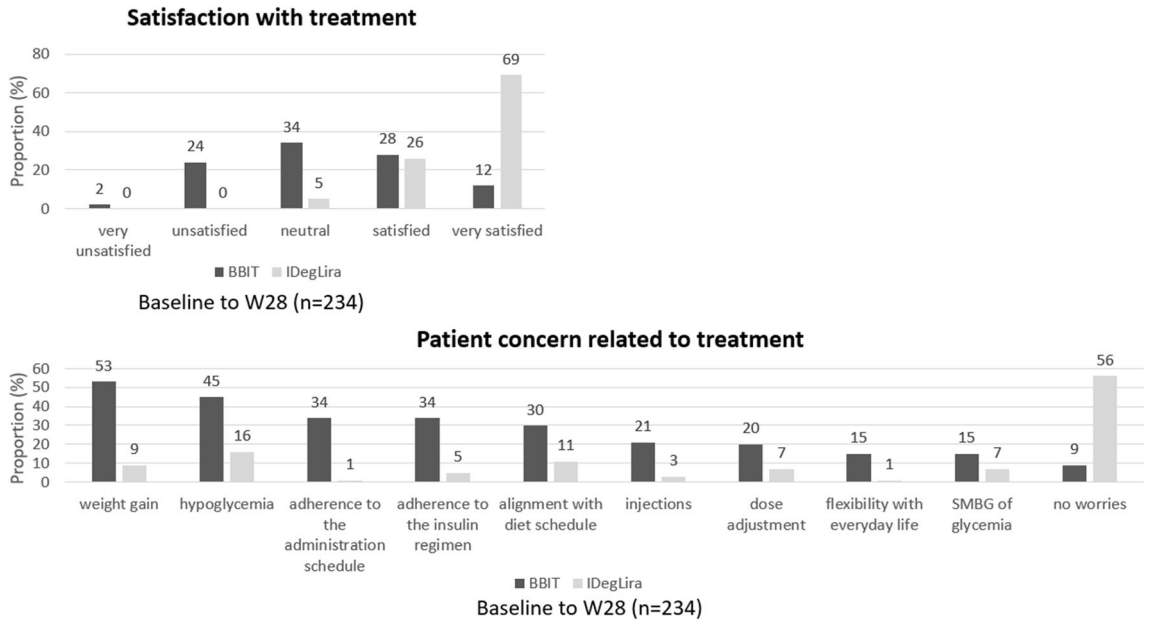

Fig. 4 Satisfaction with treatment, the impact of diabetes and its treatment on daily activities and concerns related to the treatment at baseline and at the week 28 (n = 234). *BBIT* basal-bolus insulin regimen, *IDegLira* fix combination of insulin degludec and GLP-1RA liraglutide, *W28* 28 weeks after switching from BB to IDegLira, *2 h* two hours, *p* statistical significance

treatments for obesity were initiated. Therefore, the improvements in glycemic control, weight, lipid levels, and blood pressure cannot be attributed to adjustments in the concomitant treatment. Lastly, the transition from BBIT to IDegLira led to increased patient satisfaction, less concern about their treatment, and a reduced impact of their disease and its treatment on daily activities.

In terms of adverse events during the study, one enrolled subject discontinued the study shortly after enrollment due to gastrointestinal discomfort. Two patients declined to participate in the study due to worsening glycemic control. Three patients discontinued participation for personal reasons, and one died in a car accident. No other adverse event was reported.

The results of our study align with those reported in similar studies [14–17]. In a post-hoc analysis of the RCT trial DUAL II Japan study [17], a 26-week treat-to-target study evaluated the effectiveness and safety of IDegLira treatment in 39 patients with T2DM who switched from a biphasic insulin regimen to IDegLira versus to basal insulin degludec. Switching to IDegLira led to an improvement in both fasting and postprandial glycemia and to a decrease in HbA1c and body weight. The incidence of severe or confirmed hypoglycemia and the number of insulin doses were also lower. A non-randomized Hungarian study evaluated the transition from multiple doses of insulin to IDegLira in 62 patients with T2DM with relatively good glycemic control (HbA1c < 7.5%) and an insulin dose < 0.6 IU/kg body weight [14], for an average of 3 months. The mean HbA1c value and mean body weight in patients enrolled in this study decreased by 0.3% and 3.1 kg, respectively. The need for insulin had decreased from 0.47 IU/kg body weight to 0.23 IU/kg body weight at the end of the follow-up, with an average dose of IDegLira of 20.8 units. The proportion of patients who experienced at least one documented or confirmed hypoglycemic event decreased from 45% to 10% [14]. The international multicenter, retrospective, non-interventional RWE study EXTRA [15], which analyzed the medical records of patients who

had switched to IDegLira from various previous therapeutic regimens, including a regimen with multiple doses of insulin, found that the HbA1c value decreased by 0.7% and body weight decreased by 2.4 kg after 6 months of treatment. Switching to IDegLira treatment resulted in a reduction in insulin doses from 66 to 45 IU/day. The overall incidence of hypoglycemia was low and became even lower after 6 months of IDegLira treatment (0.28 vs. 0.06 events per patient per year) compared to the incidence during the previous treatment with multiple doses of insulin. Lastly, in the RWE study by Italian authors [16], treatment with IDegLira proved to be more effective than the previous treatment with BBIT, with results similar to our study. HbA1c decreased from 8.4% to 7.4%, fasting blood glucose from 8.8 to 6.9 mmol/l, body weight from 94 to 93 kg, and average insulin dose from 42 to 22 IU/day.

There are several differences between our study and the aforementioned RWE studies. Compared to the Hungarian study [14], which had a similar prospective single-arm design, our study enrolled nearly fourfold more patients, had a longer duration, and included patients with unsatisfactory glycemic control. The Italian study [16], which yielded similar results to ours, was monocentric and did not report the incidence of hypoglycemia. In contrast to the retrospective non-interventional database analysis of the European chart review study EXTRA [18], our study employed a prospective design. Lastly, a post-hoc analysis of the RCT Dual II Japan study [17] assessed the safety and efficacy of transitioning patients from a biphasic insulin regimen to IDegLira. Our study was unique in that it included a subgroup of patients who underwent CGM and it evaluated patient satisfaction with the treatment, concerns about the treatment, and the impact of their disease and its treatment on their daily activities.

BBIT is usually considered to be the last therapeutic option for patients with T2DM. Nevertheless, our study has showed that for patients with preserved insulin secretion, switching from BBIT to IDegLira can lead to improvements in all glucose control parameters, such as HbA1c, glycemic profile, decreased incidence of hypoglycemia, reduced insulin doses, and improved CGM-derived parameters. Furthermore, the switch resulted in a significant reduction in body weight, blood pressure, lipid profile, and liver enzymes, while also simplifying treatment requirements and enhancing patient satisfaction. The change in treatment was safe and generally well-tolerated. Hence, for patients with T2DM who have preserved insulin secretion, switching from BBIT to IDegLira can be viewed as a beneficial and safe strategy in clinical practice, offering comprehensive metabolic and individual benefits. Moreover, as demonstrated by other authors, IDegLira is more cost-effective than the BBIT regimen [19].

A limitation of the present study is that it did not use a randomized design to compare the continuation of BBIT with a change to IDegLira. Moreover, this study only included patients with a TDDI of < 70 IU/day and with HbA1c levels of $< 10\%$; thus, it is not clear whether the same approach could be successful in patients with high insulin resistance.

CONCLUSION

In conclusion, the results of our study are encouraging and suggest that switching from BBIT to IDegLira can also be beneficial for patients with T2DM who have been on BBIT for an extended period but still have preserved insulin secretion. This approach was associated with significant improvements in all glucose control parameters, as well as a reduction in the number of hypoglycemic episodes and insulin doses. It also led to a decrease in body weight, blood pressure, lipid profile, and level of liver enzymes. Thus, switching from BBIT to IDegLira in patients with T2DM with preserved insulin secretion can be considered a useful and safe approach in clinical practice settings, offering complex metabolic and individual benefits.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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