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ORIGINAL RESEARCH

Unmet Needs in the Management of Type 2 Diabetes Mellitus Patients Starting Insulin Therapy with Basal or Premix Insulin in Routine Clinical Practice in Serbia

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ABSTRACT

Introduction: Type 2 diabetes mellitus (T2DM) is a progressive disease with declining beta cell function, ultimately necessitating insulin therapy. Timely introduction of adequate insulin improves management of diabetes. The aim of this study was to evaluate the unmet needs in the management of T2DM patients recently initiated on insulin therapy in routine clinical practice in Serbia.

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Methods: The NEED study was a cross-sectional, observational, multicenter, real-world study conducted in Serbia, involving 26 physicians, endocrinologists, treating individuals with T2DM from 17 secondary health care institutions. Study participants were newly initiated with insulin therapy, being treated with basal or premix insulin ± oral antidiabetics (OAD) for 6–12 months.
Results: Four hundred one individuals were included in the study between October 2016 and March 2017. The mean age of study patients was 61.8 ± 9.2 years with mean BMI 30.0 ± 5.0 kg/m^2, and duration of diabetes, prior to initiation of insulin therapy, was 8.4 ± 5.9 years. A basal insulin regimen was used by 287 (71.6%) and premix insulin by 114 (28.4%) subjects. The average daily dose (39.8 ± 13.9 units premix vs. 26.3 ± 13.5 units basal), dose/kg (0.47 ± 0.15 units/kg premix vs. 0.31 ± 0.17 units/kg basal), and number of injections per day were higher in the premix compared with basal insulin regimen ($p < 0.01$). The percentage of T2DM participants with at least one unmet need was high (95.8%). The majority of participants had two or three unmet needs. The most common unmet needs were: HbA1c > 7.0% (79.3%), at least one documented symptomatic hypoglycemia (≤ 3.9 mmol/l) event in the previous 3 months (63.8%), and two or more doses of insulin per day (53.1%). The mean individual HbA1c target was 6.8% in the NEED study cohort, with only

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16% of participants reaching it. Most participants [281 (70.1%)] experienced symptomatic hypoglycemia.

Conclusions: The NEED study showed that new insulin users of either basal or premix HM insulin have many unmet needs in the first 6–12 months of treatment. This confirms that in real-life settings novel insulins should be considered in the management of T2DM to reduce the number of symptomatic hypoglycemic events and reach a better HbA1c level.

Funding: Sanofi, Serbia.

Keywords: Basal insulin; Diabetes; Premix insulin; Type 2 diabetes; Unmet needs

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a progressive disease with declining beta cell function, ultimately necessitating introduction of insulin therapy. Despite well-documented benefits of timely glycemic control and consensus guidelines encouraging early use of insulin, considerable clinical inertia exists with respect to initiating appropriate insulin therapy in people with T2DM [1]. Furthermore, a significant proportion of patients already treated with basal insulin is failing to achieve glycemic targets in the real world [2].

Insulin therapy in Serbia is fully reimbursed by the government. However, there are some limitations related to the choice of insulin therapy. Full reimbursement for the introduction of insulin therapy is for human (HM) insulins only. After failure to achieve good glycemic control with HM for a period of 6 months, with documented hypoglycemia and HbA1c levels higher than 7%, insulin analogs can be introduced and fully reimbursed.

International Diabetes Federation (IDF) clinical practice recommendations define management of type 2 diabetes mellitus (T2DM) in primary practice [3]. In Serbia, HM insulin therapy is usually initiated in the inpatient setting at the secondary levels or at the outpatient clinic at the tertiary level.

The NEED study was conducted to evaluate the unmet needs in the management of T2DM patients treated with basal or premix insulins in routine clinical practice in Serbia.

METHODS

Study Design and Population

The NEED study was a cross-sectional, observational, multicenter study involving 26 physicians, endocrinologists, treating individuals with T2DM from 17 secondary health care institutions in Serbia. The participating sites were equally geographically distributed across the country to ensure a good representation of the insulin management of T2DM patients. Each physician had to include up to 20 consecutive subjects, fulfilling the inclusion/exclusion criteria. Patients were enrolled consecutively from the cohort seen by the participating physicians in their daily clinical practice. According to the non-interventional study design, all treatments and procedures were performed at the physicians' discretion and did not interfere with everyday clinical practice.

Participants were adult patients with T2DM, 18 years of age or older, on basal or premix HM insulin as initial regimen for 6–12 months, with or without oral antidiabetic drugs (OADs). They had to provide HbA1c measurements, performed in the last 3 months, and a patient diary with information on insulin doses and recordings of hypoglycemic events from the last 3 months. Potential T1DM patients (< 40 years of age who started insulin within a year after diabetes diagnosis), those on systemic corticosteroids, pregnant or breastfeeding women, and those already taking part in other studies were excluded from the study. The participants signed an informed consent form prior to the conduct of any study-related procedures.

According to the cross-sectional study design, data collection was done at only one visit, and some data were collected retrospectively from the electronic records. The anamnestic and clinical data were collected, including body weight and height, HbA1c level (not older than 3 months), diabetes history and complications, other comorbidities, insulin

treatment and concomitant antidiabetic medications, individualized HbA1c target defined by the physicians, and history of severe, symptomatic, and verified symptomatic hypoglycemia (within the last 3 months prior to study entry) documented in the patient diary. The participants were asked to fill in the fear of hypoglycemia questionnaire. Participating physicians collected the data and information requested by protocol in an electronic case report form (e-CRF).

The primary objective of this study was to estimate the percentage of participants with unmet needs (at least 1 of the 5 defined needs) in T2DM patients started on insulin (basal or premix3) with/without OAD for the first 6–12 months. Unmet needs were defined as: (1) uncontrolled glycemia—participants not reaching HbA1c $\leq$ 7%; (2) severe hypoglycemia (requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions) in the previous 3 months; (3) documented symptomatic hypoglycemia ($\leq$ 3.9 mmol/l) in the previous 3 months; (4) two or more doses of insulin per day; (5) weight gain $\geq$ 3% of body weight since insulin initiation.

The secondary objectives included the proportion of patients with each unmet medical need and the combination of two or more unmet needs, proportion of patients on target HbA1c < 7%, HbA1c < 8%, and individualized HbA1c, proportion of patients on target HbA1c < 7.0% without symptomatic hypoglycemia within 3 months and weight gain $\geq$ 3% since insulin initiation, proportion of patients on target HbA1c < 7% without severe hypoglycemia within 3 months prior to study entry, incidence of hypoglycemic events within 3 months of study entry, and fear of hypoglycemia, assessed by Hypoglycemia Fear Survey II (HFS II). Signed informed consent was obtained from all participants. The study was approved by the local ethics committees and conducted in accordance with Good Clinical Practice and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Statistical Analysis

All variables are presented as continuous (scale) or categorical (nominal and ordinal) data. Continuous data are presented as mean values with standard deviations or as medians with interquartile ranges (for skewed data), and categorical data are presented by absolute numbers with percentages in descriptive statistics. Depending of the type and number of examined parameters, chi-square, Mantel-Haenszel, and Student's t tests for independent or paired samples as wll as Mann-Whitney test (non-Gaussian distribution), Wilcoxon test, ANOVA, and post hoc analyses were used. In all tests, the alpha level at 0.05 (p value < 0.05) was considered to be statistically significant. Levene's test was used to assume equality of variances. Normal distribution of each variable was for checking with the Kolmogorov-Smirnoff test. Missing data were presented in descriptive analysis with valid percent calculated. In other analysis, they were handled as missing data and excluded from analysis.

The estimated number of patients with diabetes in Serbia is 858,900 [4]. Assuming that 30% of T2DM patients require insulin therapy, the prevalence of these patients represents about 257,000. Supposing 50% frequency of unmet needs, a margin of error of $\pm$ 5.1% (44.9%; 55.1%), and confidence level of 95% (alpha: 0.05), the minimum sample size is 360 participants. This interval has a length of 10.2%, indicating a precise estimate. Considering the possibility of 10% missing data, the final sample size is corrected to 400 participants.

RESULTS

Characteristics of Participants

In the NEED study in Serbia, a total of 401 individuals with T2DM, newly initiated to insulin therapy, were included between October 2016 and March 2017. There were 203 (50.6%) male and 198 (49.4%) female participants. The mean age was 61.8 $\pm$ 9.2 years, with predominance of participants from 60 to 70 years. The males included in the study were significantly

younger (60.94 ± 9.3 vs. 62.9 ± 9.0 years) than females ($p < 0.05$). The mean body mass index (BMI) was $30.0 \pm 5.0 \text{ kg/m}^2$ and was significantly higher in females (females $30.5 \pm 5.0 \text{ kg/m}^2$ vs. males $29.5 \pm 5.0 \text{ kg/m}^2$; $p < 0.05$).

The mean duration of T2DM was 8.4 ± 5.9 years (median: 7.6 years), and mean duration of oral antidiabetic therapy was 8.0 ± 5.6 years (median: 7.4 years). Neuropathy was the most common microvascular complication of diabetes (55.5%), being mostly peripheral sensitive neuropathy (98.6%). Retinopathy was present in 21.5% of participants, and it led to blindness in 5.8%. Among the participants with nephropathy (13.0%), end-stage renal failure was present in 1.9%, advanced kidney disease in 23.0%, proteinuria in 21.3%, and albuminuria in 53.8%. Comorbidity was found in 286 (71.3%), dyslipidemia and arterial hypertension being most frequent (Table 1).

Insulin and Concomitant Antidiabetic Therapy

The average duration of insulin therapy was 8.99 ± 2.01 months, median 9.03 months. A human intermediate-acting basal NPH insulin regimen was used by 287 (71.6%) and HM premix 30/70 insulin by 114 (28.4%) subjects. The majority of basal insulin users [240 (84%)] took human intermediate-acting basal insulin (NPH), and 47 (16%) used basal analogs (determir or glargine). The average daily doses and number of injections per day are shown in Table 2. The average daily dose, dose/kg, and number of injections per day were higher in the premix than basal insulin regimen ($p < 0.01$).

In total, 349 (99.5%) had concomitant antidiabetic therapy. The proportion of different drug classes per insulin regimen after insulin initiation is shown in Table 2. Metformin and sulfonylureas were the predominant glucose-lowering medications taken concomitantly with insulin. The sulfonylureas were significantly more commonly prescribed in participants with basal insulin than premix insulin.

Table 1 Prevalence of comorbidities

Comorbidity	n	%
Hypertension	340	84.8
Dyslipidemia	306	76.3
Coronary heart disease	97	24.3
Acute myocardial infarction	27	6.8
Myocardial revascularization	23	5.8
Heart failure	38	9.5
Atrial fibrillation	19	4.8
Stroke	19	4.8
Peripheral vascular disease	44	11
Peripheral revascularization	8	2
Foot ulcer	9	2.3
Lower limb amputation	5	1.3
Fatty liver disease	97	24.3
Chronic obstructive pulmonary disease	29	7.3
Obstructive sleep apnea	11	2.8
Hip fracture/osteoporosis	13	3.3
Malignant disease	11	2.8
Depression	38	9.5
Severe dementia	2	0.5

Presence, Type, and Number of Defined Unmet Needs

The percentage of T2DM participants with at least one of the five defined unmet needs was 95.8%, independent of type of insulin regimen and type of basal insulin used (Table 3). Proportions of patients with documented symptomatic hypoglycemia according to insulin therapy did not show significant differences between insulin analogs [29 (61.7%)] and human intermediate [162 (67.5%)].

The most common unmet needs were: HbA1c $> 7.0\%$ (79.3%), at least one documented symptomatic hypoglycemia ($\leq 3.9 \text{ mmol/l}$) event in the previous 3 months (63.8%), and two or more doses of insulin per day (53.1%). The

Table 2 Characteristics of insulin and concomitant antidiabetic therapy

	Basal insulin	Premix insulin	Total
N/%	287/71.6	114/28.4	401/100.0
Average HbA1c (%)	7.92 ± 1.3	7.94 ± 1.2	7.92 ± 1.3
Dose (U)	26.3 ± 13.5	39.8 ± 13.9*	30.2 ± 14.9
Dose (U/kg)	0.31 ± 0.17	0.47 ± 0.15*	0.35 ± 0.18
Once daily (n/%)	182/63.4	6/5.3	188/46.9
Twice daily (n/%)	83/28.9	100/87.7[†]	183/45.6
Three times daily (n/%)	22/7.7	8/7.0	30/7.5
Metformin	251/87.4	105/92.1	356/88.8
Sulfonylureas (SU)	76/26.5	10/8.8[‡]	86/21.4
Metiglinidis (glinides)	6/2.0	0/0.0	6/1.5
Thiazolidinediones	2/0.6	0/0.0	2/0.5
GLP1 receptor agonists	2/0.6	2/1.8	4/1.0
DPP-IV inhibitors	8/2.7	0/0.0	8/2.0
SGLT-2 inhibitors	6/2.1	0/0.0	6/1.5

Data are presented as X ± SD or n/%, Student's t test *$p < 0.01$ vs. basal; chi-square test [†]$p < 0.01$ vs. basal; Pearson chi-square test [‡]$p < 0.05$ vs. basal

Table 3 Proportion of T2DM patients with at least one of the defined unmet needs

	Type of current insulin treatment			
	Human intermediate	Long-acting analog	Premix insulin	Total
No unmet need	14/5.8	0/0.0	3/2.6	17/4.2
With unmet need	226/94.2	47/100.0	111/97.4	384/95.8
Total	240/100.0	47/100.0	114/100.0	401/100.0

Non-significant between different types of insulin used

proportion of participants with documented symptomatic hypoglycemia was significantly higher ($p < 0.05$), and the proportion of participants with ≥ two doses of insulin daily was significantly lower in the group with the basal insulin regimen compared with the premix insulin ($p < 0.01$) (Table 4).

The proprotion of patients with documented symptomatic hypoglycemia using SU was higher than in patients not using SU (64/86 vs. 192/315, $p < 0.05$). After excluding patients with SU, the proportion of patients with documented symptomatic hypoglycemia was similar in both insulin regimens (135/211 in the basal insulin and 57/104 patients in the premix group). The majority of participants had two (33.9%) and three unmet needs (32.7%). HbA1c > 7% with documented symptomatic hypoglycemia was the most common dual combination followed by HbA1c > 7% with ≥ 2

Table 4 Presence, type, and number of defined unmet needs per insulin regimen

	Basal insulin	Premix insulin	Total
No unmet needs	14/4.9	3/2.6	17/4.2
With unmet needs	273/95.1	111/97.4	384/95.8
HbA1c > 7%	225/78.4	93/81.6	318/79.3
Severe hypoglycemia 3 months prior to study entry	44/15.3	15/13.2	59/14.7
Documented symptomatic hypoglycemic event	191/66.5*	65/57.0	256/63.8
Documented symptomatic hypoglycemic event—patients without SU	135/63.9	57/54.8	192/61.0
≥ 2 Doses daily	105/36.5†	108/94.7	213/53.1
Weight gain ≥ 3%	76/26.5	27/23.7	103/25.7
One medical unmet need	58/20.2	5/4.4	63/15.7
Two medical unmet needs	97/33.8	39/34.2	136/33.9
Three medical unmet needs	85/2.6	4/40.4	131/32.7
Four medical unmet needs	31/10.8	18/15.8	49/12.2
Five medical unmet needs	2/0.7	3/2.6	5/1.2

Data are presented as n/%, chi-square test; *$p < 0.05$; †$p < 0.01$ vs. premix insulin

doses daily. HbA1c > 7% with documented symptomatic hypoglycemia and ≥ 2 doses daily was the most common triple combination. The participants on the basal insulin regimen most commonly had two unmet needs (33.8%), while participants with premix insulin mostly had three unmet needs (40.4%).

Proportion of Patients on Target Glycemic Control

The mean value of the last measured HbA1c (within 3 months before study entry) was 7.9 ± 1.3%. The mean individualized target HbA1c was 6.8 ± 0.4%. The most common individual HbA1c targets were under 7.0% and 7–7.5%, respectively, in 43.1% and 47.4%. Only 6.5% of patients had target HbA1c 7.5–8%, and 3% of patients had target HbA1c > 8%. The major reasons underlying physicians' decisions on setting less stringent individualized HbA1c targets were participant age (70%), patient acceptance of treatment (54%), and comorbidities (53%). Only 16.2% of study participants

reached the individualized target HbA1c level set by their physician.

In total, 17.2% of participants had HbA1c < 7.0% and 59.6% HbA1c < 8.0%; 82.3% of participants were high risk (participants ≥ 65 years old or with evidence of any of the comorbidities/characteristics such as chronic complications and cardiovascular comorbidities, prior severe hypoglycemic events, and professional driving). Among high-risk participants, significantly fewer participants had HbA1c < 7% (14.8%) compared with low-risk participants (28.2%). There was no significant difference in the proportion of participants having HbA1c < 8% according to the level of risk.

Only 24 (6%) participants had the target HbA1c level (< 7.0%) without symptomatic hypoglycemia in the previous 3 months and no weight gain ≥ 3%. The analysis showed no statistical difference between the group on the basal insulin regimen (9 subjects, 6.6%) and the group on premix insulin (5 subjects, 4.4%). Sixty-three (15.7%) participants achieved the target HbA1c (< 7.0%) without severe

hypoglycemia within 3 months prior study entry, with no difference between basal insulin regimens.

Incidence of Hypoglycemic Events and Fear of Hypoglycemia, Assessed by HFS

In the last 3 months, prior to study entry, most participants [281 (70.1%)] experienced symptomatic hypoglycemia. Documented symptomatic events were registered in 256 (63.8%) and severe hypoglycemic events in 59 (14.7%) participants. There were 12.83 symptomatic hypoglycemic events, 9.01 documented symptomatic events, and 0.77 severe hypoglycemic events per patient-year. The average HFS total score was 67.2 ± 27.3.

DISCUSSION

This observational study gives an overview of the unmet needs in the insulin management of newly initiated T2DM patients in everyday clinical practice in Serbia. The NEED study has shown that there were no major differences in baseline characteristics of subjects introduced to insulin in Serbia compared with other observational studies performed in Europe. As expected, patients with T2D were older (mean age 61.8 ± 9.2 years) with males significantly younger than females. Mean BMI was 30.0 ± 5.0 kg/m^2 and significantly higher in females. Similar data were obtained from another observational study in different parts of Europe; however, the duration of T2DM in our study was shorter than in data in European countries [5]. Duration of diabetes when starting insulin therapy seems to be around 10 years worldwide [6], but duration of uncontrolled hyperglycemia before insulin initiation is still questionable. Hence, the prevalence of vascular complications is variable between studies. The ADHOC study in France [7] showed a relatively high prevalence of diabetic complications (neuropathy: 25%; fundus' abnormalities: 27%, angina pectoris: 13%; myocardial infarction: 10%; stroke: 6%; lower-limb arteritis: 15%) and risk factors, particularly hypertension (77.5%)

and dyslipidemia (71%). The NEED study in Serbia registered more microvascular complications (neuropathy in 55.5% of patients) than in the French cohort, which could indicate poor metabolic control in participants. Hypertension and dyslipidemia were also more prevalent than in the French study.

Normalizing blood glucose level is the important factor for preventing vascular complications. When the HbA1c target is not reached while on OADs, insulin therapy is introduced (since the local reimbursement policy does not allow GLP-1RA initiation). Factors influencing the initial choice of insulin therapy were evaluated in a large international non-interventional study [8]. In this study, insulin was started as basal insulin alone in 51.6% (15.7 ± 11.0 U/day), basal $\pm$ mealtime insulin 14.6% (23.3 ± 17.0 U/day), or premix alone in 23.1% (20.9 ± 14.1 U/day). Physicians preferred basal insulin when HbA1c was less elevated and with prior secretagogue therapy. A similar pattern in choosing initial insulin regimens, but with higher insulin doses, was observed in the NEED study. The average daily dose and number of injections per day were significantly higher in the premix than basal insulin regimen in the NEED study, similar to the mentioned study. Contrarily, the basal insulin regimen was associated with a higher starting HbA1c level compared with premix insulin. In our study, 88.8% of the patients were taking metformin together with insulin and only 21.4% were using sulfonylureas. Similar to other observational studies, the sulfonylureas were more commonly prescribed in patients on basal insulin regimens and less often in patients on premix insulin [5].

Almost all participants (95.8%) had at least one defined unmet need, independent of type of insulin used. The most common unmet need was HbA1c $> 7.0\%$, found in almost 80% of participants. Documented symptomatic hypoglycemia was present in two thirds and use of ≥ 2 doses of insulin per day in half of the participants. Around 15% of patients reported severe hypoglycemia. The majority of participants had two (33.9%) or three unmet needs (32.7%). The participants on basal insulin regimens most commonly had two unmet needs

(33.8%) while participants with premix insulin most commonly had three unmet needs (40.4%).

The mean individual HbA1c target was 6.8% in the NEED study cohort, and only 16% of participants reached their individual HbA1c target, regardless of initiated insulin regimen. In total, 17.2% participants had HbA1c under 7.0% and 59.6% had HbA1c under 8.0%. Symptomatic hypoglycemia was experienced by 70% of our participants. There were 0.77 severe hypoglycemic events/patient/year, more than in the Fremantle diabetes study [8]. This can be explained by the use of HM insulins (84% of basal regime users were on HM insulin, and this group represents 71.6% of all NEED study participants) and great prevalence of neuropathy, which could blunt hypoglycmemia symptoms [9]. Irrespective of intrinsic differences between data sources, 24–54% of patients with T2DM globally had residual hyperglycemia with HbA1c not at target, despite achieving FPG control [10]. A similar study design showed documented hypoglycemia in 28–39% of patients with premix insulin and 35–41% with basal insulins [11], almost half of the prevalence registered in the NEED cohort. This difference indicates a gap that might be explained by different participant educational levels and adherence to the insulin titration recommendation given by physicians. Other authors found that contributing factors to this effective treatment gap likely include lack of health education and poor medicine adherence by some patients [12]. In addition, it is possible that the type of insulin being used (human intermediate-acting or human premix), as per current reimbursement limitations in Serbia, contributes to these findings of a high prevalence of participants with present unmet needs. Use of sulfonylureas may have have contributed to the hypoglycemic events in very few subjects as the dose of these drugs is always reduced from maximal to optimal on starting insulin.

A similar proportion of patients had HbA1c < 7.0%, no symptomatic hypoglycemia, and no weight gain ≥ 3%, including the proportion of patients with HbA1c < 7.0% and without severe hypoglycemia, according to type of insulin therapy. Although no significant difference in any hypoglyemic prevalence and composite targets (including weight gain ≥ 3%) was found between the groups in the NEED cohort, the meta-analysis of other studies confirmed that HM + OAD has a better safety profile than premix + OAD [13]. The literature data confirm that weight gain occurs early with the initiation of insulin therapy and has been reported to vary from 0.3 to 6.4 kg. Therapy with basal insulin induces less weight gain than premix insulin [14].

A significant proportion of patients experienced symptomatic and documented symptomatic hypoglycemic events with poor HFS total scores. This indicates a need for improved titration algorithms, better insulin therapy education of patients, and development of newer insulin formulations aimed at reducing the proportion of patients experiencing hypoglycemia.

The study may have been limited by several factors: the observational design of the study with a relatively short time frame and the retrospective nature of hypoglycemia collection, not using standardized patient diaries and HbA1c. Perhaps the main limitation was that the results are mainly derived from HM insulin treatment and sulfonylurea derivates, mostly outdated in other European counties, because of current local reimbursement restrictions. Due to the reimbursement criteria in Serbia, we included a relatively small number of patients with basal analogs in the study. This could be a limiting factor in the statistical analysis as well as an explanation for the high hypoglycemic event incidence and relatively small number of patients reaching the target HbA1c.

However, our results provide a useful perspective on the management of early insulin users by diabetologists in Serbia and the need for novel therapeutic agents in achieving better glycemic control with fewer adverse events.

CONCLUSION

The NEED study in Serbia has shown that new insulin users of either NPH basal or HM premix insulin are mainly older subjects, with long duration of diabetes and presence of chronic

complications and comorbidities. The majority of patients did not reach HbA1c targets 6–12 months after insulin initiation, experienced symptomatic hypoglycemia, and presented with at least one unmet medical need regardless of insulin regimen. This confirms that in real-life settings, novel insulins should be considered in the management of T2DM to reduce symptomatic hypoglycemic events and to reach a better HbA1c level.

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Compliance with Ethics Guidelines. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all subjects prior to inclusion in the study.

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

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