



The Impact of Adding Prandial Insulin to a Basal Based Regimen with Insulin Glargine in Type 2 Diabetic Patients

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Abstract

Background: Type 2 diabetes (T2D) is a progressive disease that should be managed with insulin in case of oral glucose lowering drugs (OGLDs) failure. If basal insulin is not sufficient, rapid acting insulin will be added before the largest meal. We assessed the impact of adding one prandial insulin to a basal based regimen and insulin glargine in patients with type 2 diabetes to measure the percentage of subjects achieving the HbA1c target by the end of 24 weeks of treatment in routine clinical practice.

Methods: This study was a 24-week observational study of patients with T2D not adequately controlled with OGLDs and basal insulin, for whom the physician had decided to initiate prandial insulin. The study endpoint was assessed at visit 1 (baseline), visit 2 at week 12 (± 1 week) and visit 3 at week 24 (± 1 week). The percentage of patients who achieved HbA1c targets was assessed at week 24. Statistical analyses were performed using IBM SPSS for Windows v 19 (IBM, Armonk, New York, USA). Logistic regression analysis was used to detect predicting factors of achieving the HbA1c target by week 24. $P < 0.05$ was considered as significant level.

Results: Four hundred and eighteen patients with a mean \pm SD age of 56.24 ± 9.85 years and a mean \pm SD duration of diabetes of 12.50 ± 7.16 years were included. The median total daily dose of basal insulin was 24 units, while prandial insulin was started with 6 (4, 10) U/day, titrating up to 10 (8, 18) U/day at week 24. The daily dose of prandial insulin was the only factor that could significantly predict achieving targeted HbA1c by week 24 [OR: 1.04; 95% CI: 1.007, 1.079; p-value: 0.019]. At week 24, 96 (22.9%) subjects achieved the HbA1c target with one prandial insulin.

Conclusion: The results of our study suggest that “basal plus therapy” can lead to good glycemic control with a low risk of hypoglycemia and weight gain in patients with type 2 diabetes.

Keywords: Safety, Treatment Outcome, Diabetes Mellitus type 2, Insulin, Short-Acting, Glycated Hemoglobin A

Conflicts of Interest: None declared

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Introduction

Lowering HbA1c to 7.0% in most patients will reduce the incidence of diabetes-related microvascular complications (1). However, the ADA/EASD guidelines emphasize

the importance of treatment individualization (2, 3). HbA1c goal is affected by several factors, including a history of severe hypoglycemia, limited life expectancy,

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↑What is “already known” in this topic:

Type 2 diabetes as a progressive metabolic disease should be managed with insulin in case of oral glucose lowering drug failure. In most situations, the first prescribed insulin is basal insulin. If basal insulin is not sufficient, rapid acting insulin will be added before the largest meal (Basal-Plus Regimen).

→What this article adds:

This study showed that a basal plus treatment regimen could lead to good glycemic control. The risk of hypoglycemia and weight gain was also low. In addition, improved glycemic control was also related to a low risk of diabetes complications.

advanced complications, extensive comorbid conditions and difficulty to reach the target (2). If lifestyle intervention and fully tolerated doses of one or two OADs fail to achieve or sustain glycemic goals, insulin should be initiated with a single injection of basal insulin (4). The progressive nature of the disease will result in insulin based combination therapy in the majority of patients with type 2 diabetes (4).

For whom basal insulin is no longer efficient, one approach is to add rapid acting insulin before the meal responsible for the highest post prandial glucose, which contains the greatest carbohydrate (2, 5). However, many clinicians do not agree with the optimal treatment approach (6).

As reported in ADA/EASD guidelines, a number of intensification treatment options are available (2, 7), and one of the most effective is to add rapid-acting insulin to basal insulin. Studies such as ELEONOR (8) & OPAL (4) investigated whether a less-intensive approach with a single injection of prandial insulin (basal-plus strategy) would be more convenient and reduce both postprandial glucose excursions as well as HbA1c levels (9). In addition, the guideline of ADA/EASD mentioned that this regimen is more flexible with less hypoglycemia and weight gain (2).

The common practice in Iran is to switch from basal insulin to a premixed regimen after disease progression and when basal insulin is not enough anymore. Since the basal-plus strategy has not been studied in Iran, the aim of this registry was to show the impact of adding one prandial insulin to a basal based regimen with insulin glargine in type 2 diabetic patients.

Methods

This study was a multicenter, observational (non-interventional on the therapeutic strategy), and non-comparative study in people with type 2 diabetes in real clinical practice.

Patient selection

Four hundred and forty type-2 diabetes patients were planned in 56 centers in Iran. The number of patients to be recruited was determined on a province basis.

Patients with type 2 diabetes, above 18 years old, who had $7\% < \text{HbA1c} \leq 10\%$ and $\text{FBS} < 130 \text{ mg/dl}$ and adjunct therapy with prandial insulin and willing to sign the informed consent form, were included in the study.

Each participating physician was asked to include consecutive patients during the recruitment period starting from the initiation date from August 2014 to Jun 2015. This consecutive recruitment helped to limit bias related to physician-led patient selection. Each physician recruited patients until the targeted number of patients in his/her center was reached. A screening log was implemented to document this consecutive enrolment.

The prescription of therapies was under the discretion and responsibility of the patient's physician. Treatment (insulin glargine and short/ Rapid acting insulin) was administered in routine clinical practice according to the approved indication. Due to the observational nature of

this study, there was no fixed study visit schedule and the study did not impose any additional procedures, assessments or changes to routine management of patients. The visits were done according to the routine clinical practice which is usually every 3 months for diabetic patients in Iran.

Data collection

Physicians were asked to record data for study endpoint assessments at visit 1 (baseline), visit 2 at week 12 (± 1 week), and visit 3 at week 24 (± 1 week).

The data were collected and filled in the paper case report form (CRF) by the physicians. For the eligible patients, some information including anti-diabetic therapy agents, glycemic parameters and hypoglycemia data were collected. Hypoglycemia was defined as $\text{PG} \leq 70 \text{ mg/dl}$; asymptomatic hypoglycemia was defined as hypoglycemia not accompanied by typical hypoglycemia symptoms but with measured $\text{PG} \leq 70 \text{ mg/dl}$. Severe Hypoglycemia was defined as hypoglycemia during which assistance of another person to administer carbohydrates, Glucagon, or taking other actions is required.

Patients were free to withdraw from the study follow-up schedule at any time and irrespective of the reason.

All study withdrawals were recorded by the physician in the appropriate CRF pages and in the patient's medical records when considered as confirmed (at least date of withdrawal and reason for it).

The physicians made every effort to re-contact the patient, to identify the reason why he/she failed to attend the visit, and to determine his/her health status, including at least his/her vital status. Attempts to contact such patients were documented in the patient's record (e.g., times and dates of attempted telephone contact, the receipt for sending a registered letter). Patients who did not complete the study and for whom no endpoint data were available were considered as lost to follow-up. They were not replaced. Patients who had withdrawn from the study could not be re-included.

Sample Size Calculation

The primary outcome was to show the impact of adding one prandial insulin to a basal based regimen with insulin glargine in patients with type 2 diabetes. According to the results of a previous study (10), the prevalence of subjects on OGLDs plus glargine whose HbA1c was more than 7 was 80%. G power software was used considering $\alpha = 0.05$, power = 85%, respectively; the sample size was estimated to be 240. Moreover, we found about 10-12 confounding factors; therefore, we used the rule of 10 events per variable to add to the sample size. In addition, considering the dropout rate of 20%, the final sample size was 440.

Statistical Analysis

Firstly, the data was checked. Range (minimum and maximum) of quantitative and qualitative variables were checked in SPSS software, and if they were not logical, data were double-checked and corrected or eliminated, if necessary. Baseline demographic and clinical characteris-

tics were expressed as means \pm standard deviation or frequency and percent. Numeric data were round up to two decimals. The history of diabetes-related complications was presented as frequency and percent. Normal assumptions were checked by looking at the normal curve, or Frequency histogram as well as the Kolmogorov-Smirnov test. In case of a normal distribution, we used parametric statistical tests such as t-test while we used non-parametric statistical tests such as the Friedman test in case of non-normal distribution.

For comparison between baseline, week 12, and week 24 in quantitative variables, we used repeated measure analysis and a probability value of $P \leq 0.05$ as significant. In addition, post hoc analysis (LSD: Least Significant Difference) for two-way comparison was done. In the case of non-normal distributions, the data were presented as median and interquartile ranges. In these post hoc analyses, the Wilcoxon rank sum test was used and the level of significance of the p-value was corrected by the Bonferroni correction test ($0.05/3=0.017$). (The Bonferroni correction is a multiple-comparison correction used when several dependent or independent statistical tests are being performed simultaneously. In order to avoid a lot of spurious positives, the alpha value needs to be lowered to account for the number of comparisons being performed)

Logistic regression analysis was done to detect predicting factors of achieving the HbA1c target by week 24. In this analysis, the dependent variable was categorical HbA1c (<7 , ≥ 7). This model reported the odds ratio of achieving the HbA1c target considering other variables.

Qualitative variables such as the use of metformin (yes/no) were tested in three repeated measures with the Cochran Q test. For post hoc in this situation, we used McNemar's test with the Bonferroni correction.

To test the difference between occurring hypoglycemia at the end of the first visit and the second one, we used McNemar's test because hypoglycemia is a variable with two outcomes (yes/no) and was questioned two times. The significant level of the testes was considered as $p < 0.05$, except in the Bonferroni correction that was considered 0.017.

Results

Study participants

A total of 418 subjects with type 2 diabetes poorly controlled with basal insulin Glargine (mean \pm SD; HbA1c: $8.58 \pm 0.83\%$, FBS: 115.7 ± 15.8 mg/dL) were included in this study. Two hundred and fifty-one (60%) were female. The mean age was 56.2 ± 9.8 years, and the mean duration of diabetes was 12.5 ± 7.1 years. Table 1 shows baseline demographics and clinical characteristics of the study population.

Among participants, 230 (55%) had a history of hypertension and 42% were suffering from sensory neuropathy. Retinopathy was detected in 98 (23.4%) subjects and 15% had a history of micro-albuminuria. Table 2 demonstrates the history of diabetes and related complications in the study population.

Regarding medication, 89.5% of patients were treated

Table 1. Baseline Demographics and Clinical Characteristics of Study Population

Patients (n)	418
Age (y)	56.24 \pm 9.85
Female, n (%)	251 (60%)
Patient's Living area (Urban), n (%)	349 (83.5%)
Level of Education (University), n (%)	51 (12.2%)
Health Insurance (No), n (%)	27 (6.5%)
Smoking, n (%)	
Never	362 (87.4%)
Former	21 (5.1%)
Current	24 (5.8%)
Passive	7 (1.7%)
Duration of Diabetes (y)	12.50 \pm 7.16
History of Diabetes in the 2 nd or 3 rd generation, n (%)	217 (60%)
Body Weight at diagnosis (kg)	76.62 \pm 14.41
Body Weight at Entrance to the Study (kg)	74.73 \pm 12.50
BMI at Entrance to the Study (kg/m ²)	28.30 \pm 6.01
FBG (mg/dL)	115.73 \pm 15.84
HbA1c (%)	8.58 \pm 0.83
HbA1c (mmol/mol)	70.30 \pm 9.12
Total Chol (mg/dL)	171.84 \pm 42.46
HDL (mg/dL)	44.86 \pm 22.24
LDL (mg/dL)	98.48 \pm 34.05
TG (mg/dL)	155.69 \pm 77.76
Diastolic Blood pressure (mmHg)	78.89 \pm 11.75
Systolic Blood pressure (mmHg)	130.65 \pm 19.67

The data are presented as mean \pm SD unless otherwise stated.

Table 2. History of Diabetes-related Complications in Study Population

Retinopathy (n=400)	98 (24.5%)
Sensory Neuropathy (n=409)	175 (42.8%)
Micro Albuminuria (n=402)	62 (15.4%)
Proteinuria (n=407)	32 (7.9%)
Renal Insufficiency (n=409)	16 (3.9%)
Dialysis (n=410)	1 (0.2%)
Amputation (n=410)	3 (0.7%)
Foot Ulcer (n=410)	18 (4.4%)
Angina pectoris (n=409)	50 (12.2%)
Myocardial Infraction / Acute Coronary Syndrome (n=409)	25 (6.1%)
Heart Failure (n=410)	5 (1.2%)
Stroke with Partial Recovery (n=409)	5 (1.2%)
Stroke with Full Recovery (n=407)	5 (1.2%)
Peripheral Vascular Disease (n=407)	14 (3.4%)
History Of Revascularization (n=410)	39 (9.5%)
Other Complication (n=394)	5 (1.3%)
Hypertension (n=411)	230 (56%)

Data are presented as n (%).

with Metformin (1500 mg; median daily dose), 35.5% had received Glibenclamide (15 mg; median daily dose), and about 15% were on Repaglinide (6 mg; median daily dose) or Pioglitazone (30 mg; median daily dose) or Acarbose (150 mg; median daily dose) at inclusion. Moreover, the total daily dose of basal insulin was 24 units (17.75, 30) in the study population at inclusion. Insulin glargine was only used as basal insulin in the study population.

Insulin Dose and Metabolic Outcomes

Blood glucose improved significantly by week 24. The HbA1c dropped from $8.58\% \pm 0.84$ at baseline to $7.46\% \pm 0.98$ at week 24 in the participants (Table 3). In 284 (68.1%) patients, the HbA1c target was defined to be $\leq 7\%$; while it was defined to be $\leq 8\%$ in 31.9% of the participants due to the duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, history of minor or major hypo-

Table 3. Comparison of Anthropometric Variables, Clinical Characteristics and Medications at baseline, Week 12 and Week 24

	Visit 1 (Week 0)	Visit 2 (Week 12)	Visit 3 (Week 24)	P-value
Body Weight (kg)	74.42±12.54	74.46±12.67	74.97±12.04	0.08
Systolic Blood Pressure (mmHg)	131.07±18.28	128.36±16.61	126.87±14.97	<0.001 ^{1,3}
Diastolic Blood Pressure (mmHg)	78.78±11.57	78.79±8.58	77.75±9.33	0.09
	8.58±0.84	7.84±1.06	7.46±0.98	<0.001 ^{1,2,3}
Glycemic Control:				
HbA1c (%)				
HbA1c (mmol/mol)	70.30±9.12	62.16±11.62	58.07±10.70	<0.001 ^{1,2,3}
Achieved targeted HbA1c, n (%)	-----	100 (25.8)	160 (42.3)	<0.001
OADs, n (%)				
Metformin	374 (89.5)	254 (60.9)	216 (51.7)	<0.001 ^{1,2,3}
Sulfonylureas	150 (35.5)	52 (12.5)	36 (8.6)	<0.001 ^{1,2,3}
Glinides	21 (5)	7 (1.7)	6 (1.4)	<0.001 ^{1,3}
Thiazolidinediones	25 (6)	8 (1.9)	5 (1.2)	<0.001 ^{1,3}
α-Glucosidase inhibitors	17 (4.1)	4 (1)	1 (0.2)	<0.001 ^{1,3}
OADs, median daily dose (25 th , 75 th percentile)				
Metformin (mg)	1500 (1000, 2000)	1500 (1000, 2000)	1500 (1000, 2000)	NA
Sulfonylureas (mg)	15 (10, 20)	10 (10, 20)	10 (10, 20)	
Glinides (mg)	6 (3, 6)	3.5 (3, 6)	4 (3, 5)	
Thiazolidinediones (mg)	30 (15, 30)	30 (15, 30)	30 (22, 45)	
α-Glucosidase inhibitors (mg)	150 (100, 300)	125 (100, 150)	150 (NA)	
One / two / >two (%)	52.2 / 36.1 / 4.8	47.4 / 13.2 / 1.2	42.1 / 9.6 / 0.7	<0.001 ^{1,3}
Insulin				
Number of injection (basal)*, n (%)	1 (1, 1)	1 (1, 1)	1 (1, 1)	>0.99
Number of injection (prandial)*, n (%)	1 (1, 2)	1 (1, 2)	2 (1, 3)	<0.001 ^{1,3}
Daily dose of basal insulin*	24 (17.75, 30)	25 (18, 32)	24 (16, 32)	<0.001 ^{1,3}
Daily dose of prandial insulin*	6 (4, 10)	8 (6, 16)	10 (8, 18)	<0.001 ^{1,2,3}

¹ Significant difference in Post hoc visit 1, 2² Significant difference in Post hoc visit 2, 3³ Significant difference in Post hoc visit 1, 3

The data are presented as mean ± SD unless otherwise stated.

*Median (25th, 75th percentile)

glycemia, hypoglycemia unawareness, and/or individual patient considerations. About 42% of the entire participants reached to HbA1C target by the end of the study, while this figure was 25.8% at week 12.

The total daily dose of basal insulin in the first visit was 24(17.75, 30) U/day. This number did not changed at the last visit (24 (16-32) U/day). Regarding prandial insulin, the starting dose was 6 (4, 10) U/day titrating up to 10 (8, 18) U/day at week 24.

After initiating prandial insulin, metformin was continued in around 52% of people by week 24, while only 8.6% of people starting prandial insulin continued using sulfonylureas.

Among participants, 16.9% achieved the glycemic target with one prandial insulin injection, 4.2% with two prandial insulin, and 4.5% with three prandial insulin injections over 12 weeks. By week 24, 22.9% of subjects

achieved the HbA1c target with one prandial insulin, 9.7% with two prandial insulin, and 9.3% with three prandial insulin injections.

The changes in mean body weight were neither statistically nor clinically significant over 12 as well as 24 weeks for the total participants (74.42±12.54 vs. 74.97±12.04 Kg; Table 3).

The logistic regression analysis of the variables affecting HbA1c showed that only a daily dose of prandial insulin could significantly predict achieving targeted HbA1c by week 24; each unit increase in prandial insulin increases the rate of achieving HbA1c by 4% [OR: 1.04 (CI: 1.007, 1.079); p-value: 0.019] (Table 4).

Self-Monitoring of Blood Glucose

Among participants, 356 (85.2%) had a glucometer device and 353 (84.4%) stated that they checked blood glu-

Table 4. Predicting factors of Achieving HbA1c target by Week 24

	B	S.E.	P value	OR	95% CI for EXP(B)	
					Lower	Upper
Sex	0.445	0.266	0.095	1.561	0.926	2.632
Duration of Diabetes	0.005	0.019	0.788	1.005	0.968	1.043
BMI at inclusion	-0.012	0.022	0.596	0.988	0.946	1.033
Daily dose of Basal Insulin	0.016	0.011	0.139	1.016	0.995	1.038
Number of basal insulin Injection	0.033	0.450	0.942	1.033	0.428	2.496
Daily dose of Prandial Insulin	0.042	0.018	0.019	1.042	1.007	1.079
Number of Prandial insulin Injection	-0.122	0.190	0.519	0.885	0.610	1.283
Experience any episode of symptomatic Hypoglycemia	-0.479	0.386	0.214	0.619	0.291	1.319
Constant	-0.792	1.060	0.455	0.453	-----	-----

cose using their own glucometer. The median (interquartile range (IQR)) of blood glucose testing during the past year was 3 (2, 4). Two hundred eighty-five (68.2%) mentioned the cost of strips as a limiting factor for regular SMBG. Seven points SMBG was collected for three days during the last week prior to each visit from those patients had available data. Significant improvements were seen both at the meals and overall from a visit to visit. The results are presented in Table 5.

Hypoglycemia

No severe or nocturnal hypoglycemia was reported. The reported number of overall symptomatic hypoglycemic episodes during the first 12 weeks was 63 (15.9%) compared to the second 12 weeks of the study that was 43 (10.3%) (p-value: 0.015) for all patients who included in the study. The median daily dose of prandial insulin was not statistically different between the patients who had an experience of hypoglycemia compared to the patients who did not have hypoglycemic symptoms at week 12 as well as week 24 (Fig. 1).

Adverse drug reactions and adverse events

During the study, 106 adverse drug reactions (ADRs) were reported due to hypoglycemic events. No severe hypoglycemic event was reported.

Discussion

Considering ADA/EASD guidelines (2, 3), there are different treatment strategies to be considered in patients with type 2 diabetes not achieving an agreed HbA1c target by OGLDs and basal insulin. One available option is to consider premixed formulations of intermediate and short/rapid-acting insulins in fixed ratios (11) which are simple but less flexible compared to other strategies. The other available option is the combination of basal insulin with glucagon-like peptide-1 (GLP-1) mimetics; however, the cost is the limiting factor. An alternative option is to administer short acting insulin before each meal which closely mimics the normal physiological pattern of insulin secretion (11-13); however, it may be too complex to apply for some patients. Another option is to use a basal plus regimen involving a single injection of prandial insulin before the largest meal which is easy to apply.

This present study was a 24-week, national, multicenter, observational (non-interventional on the therapeutic strategy) study conducted to determine the impact of adding prandial insulin to a basal based regimen with insulin glargine in patients with type 2 diabetes in routine clinical practice in Iran. It also assessed the safety of the basal plus/bolus regimen. Overall, a limited number of reported hypoglycemia was seen in all patient populations. Irregularity in snacking may have resulted in the occurrence of

Table 5. Self-Monitoring of Blood Glucose

	Visit 1 (Week 0)		Visit 2 (Week 12)		Visit 3 (Week 24)		P-value
	N	Mean \pm SD	N	Mean \pm SD	N	Mean \pm SD	
Fasting	272	124.08 \pm 27.20	273	122.44 \pm 36.46	269	117.10 \pm 27.12	0.004 ^{2,3}
2-h after breakfast	291	208.31 \pm 53.40	247	186.64 \pm 58.64	238	167.35 \pm 41.75	<0.001 ^{1,2,3}
Pre-lunch	121	183.19 \pm 46.50	134	161.39 \pm 50.24	142	151.01 \pm 34.56	<0.001 ^{1,3}
2-h after lunch	218	236.42 \pm 64.63	213	191.58 \pm 46.70	210	183.02 \pm 43.57	<0.001 ^{1,2,3}
Pre-dinner	155	193.24 \pm 55.86	166	172.93 \pm 49.18	168	160.05 \pm 46.61	<0.001 ^{1,2,3}
2-h after dinner	197	229.81 \pm 63.85	204	188.09 \pm 52.25	197	176.73 \pm 48.76	<0.001 ^{1,2,3}
Bedtime	119	191.12 \pm 63.03	124	165.23 \pm 48.18	126	162.21 \pm 49.24	<0.001 ^{1,3}

The data are presented as mean \pm SD of the three days' glucose measurement using a glucometer during the last week prior to each visit.

¹ Significant difference in Post hoc visit 1, 2

² Significant difference in Post hoc visit 2, 3

³ Significant difference in Post hoc visit 1, 3

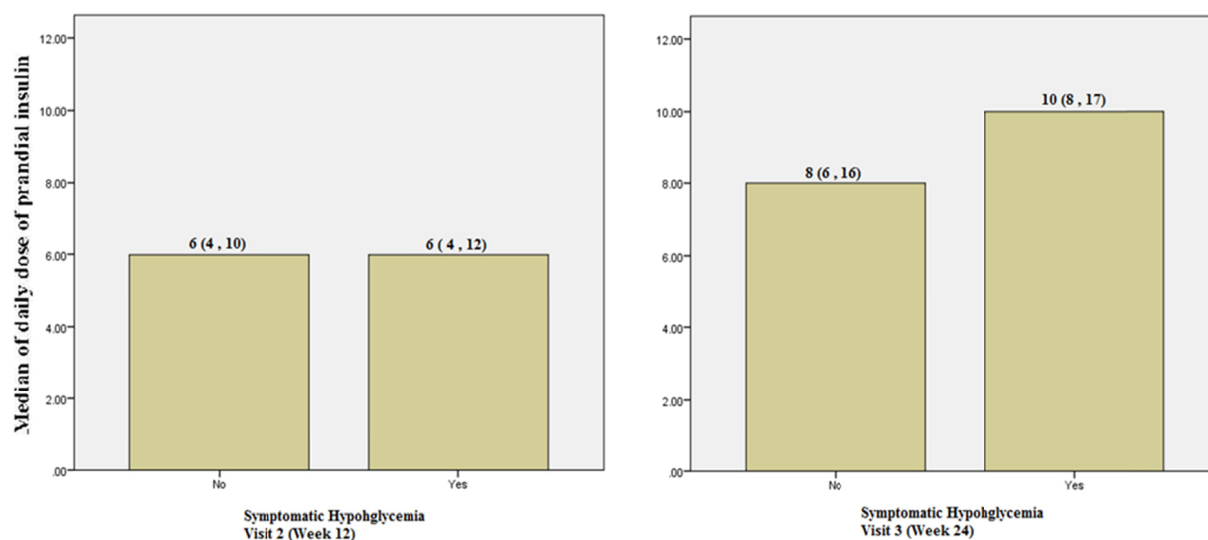


Fig. 1. Median (IQR) of daily dose of prandial insulin in patient who experienced and who did not experience symptomatic hypoglycemia in visit 2 and visit 3

hypoglycemia (14, 15). The number of hypoglycemic attacks decreased in the second 12 weeks compared to the first 12 weeks of the study. Our findings showed that initiating or adding insulin prandial was effective with noticeable improvements in glycemic control (as measured by HbA1c). Improved glycemic control is associated with a lower risk of chronic micro and macrovascular complications (1, 16) as well as decreasing overall mortality and morbidity (17, 18).

Changes in body weight were neither statistically nor clinically significant. The neutral effect of prandial insulin on body weight in this study may be due to better self-management, changes in lifestyle and nutritional status of the participants (19). Additionally, this study showed significant improvements in seven-point glucose profiles following the prandial injection, both at the meals and overall.

The results of multivariate regression analysis indicate that the only important factor associated with better glycemic control was daily dose of prandial insulin.

In line with our study, the results of previous studies (4, 8, 20, 21) also demonstrated that intensification of insulin with basal plus regimen can effectively lead to better glycemic control.

The strength of this study was that existing basal insulin therapy was optimized before the addition of prandial insulin. In eligible individuals, insulin glargine was titrated to optimize fasting blood glucose control during three months before recruitment, after which those whose HbA1c was not in target yet were included in the study. But due to the observational design, there were some limitations including lack of control group and standard treatment protocol as well as unknown circumstances under which the participants were recruited and came under the care of the investigators.

Conclusion

This observational study conducted in Iran showed that among T2DM subjects with insufficiently controlled diabetes on basal insulin glargine + OGLDs, intensified treatment regimen with one injection of insulin prandial (Basal Plus) led to improved glycemic control by reducing the mean HbA1c level and improving patient glycemic profile thereby enabling 4 of 10 subjects to reach their individual HbA1c target. In patients with reduced number and dose of OGLDs during the study period, body weight remained stable and no increase in hypoglycemia incidence was reported. The basal plus therapy as a stepwise insulin treatment regimen involving a single prandial injection, on a background of basal insulin (glargine), given before the main meal, may be effective and safe. Moreover, it could be a basis for an effective and flexible treatment strategy which is basal-bolus, if necessary.

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Ethical Approval

All procedures performed in studies involving human

participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

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

Conflict of Interests

The authors declare that they have no competing interests.

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