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# Control of Glycemia With a Basal-Plus Regimen in People With Type 2 Diabetes Mellitus Insufficiently Controlled by Previous Treatment

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## Abstract

**Background:** Type 2 diabetes mellitus (T2DM) is often characterized by insulin resistance and progressive β-cell deterioration. With longer duration of T2DM most patients treated with oral antihyperglycemic drugs (OADs), in monotherapy or in combination, will ultimately require basal insulin therapy and even further prandial intensification later on. The basal-plus regimen is one of the proposed approaches for treatment intensification by adding one injection of prandial rapid-acting insulin to basal insulin. The CONBA+ study aimed to collect real-world data of glycemic control of T2DM patients uncontrolled on insulin/OAD therapy using the basal-plus approach in Morocco.

**Methods:** CONBA+ study was a national, prospective, non-interventional, multicenter study involving 50 endocrinologists from Morocco. The study, conducted between June 2015 and June 2017, enrolled T2DM patients uncontrolled on their previous regimen (hemoglobin A1c (HbA1c) ≥ 7.5% on two OADs, glargine 100 U/mL and OADs or once daily premixed insulin). Patients continued or newly initiated once-daily insulin glargine 100 U/mL (Gla-100) and also received one injection of insulin glulisine (Glu) at the main meal in replacing any previous treatment. Demographics, glycated hemoglobin (HbA1c), fasting blood glucose (FBG), postprandial glucose (PPG), insulin doses and the frequency of hypoglycemia were assessed at baseline and at 12 and 24 weeks after study entry.

**Results:** Overall, 854 people (46.8% men) fulfilled the inclusion criteria. At baseline, mean age was 59.0 ± 9.4 years, mean duration of diabetes 10.8 ± 6.7 years (range: 1 - 45 years), mean body mass index (BMI) 27.4 ± 4.0 kg/m$^2$ and mean HbA1c 9.50±1.51%. After 24 weeks, 33.0% of patients achieved target HbA1c < 7.0% (primary endpoint). In addition, mean FPG and postprandial blood glucose (PPBG) improved significantly at week 24 (change from baseline: -88 mg/dL and -108 mg/dL respectively; P < 0.001) while the number of reported severe hypoglycemia was low.

**Conclusions:** The use of a basal-plus regimen consisting of insulin glargine 100 U/mL and insulin glulisine injected at the main meal resulted in significant improvements of glycemic parameters. In addition, the basal-plus approach showed a good safety profile with a low risk of hypoglycemia.

**Keywords:** Treatment intensification; Insulin glargine; Insulin glulisine; Glycemic control; Hypoglycemia

## Introduction

Type 2 diabetes mellitus (T2DM) is a complex disease often associated with insulin resistance and progressive β-cell deterioration. As β-cell function declines, most patients will require insulin as they will fail to obtain and maintain an adequate glycemic control with only lifestyle changes and oral antihyperglycemic drugs (OADs) [1]. The addition of basal insulin is considered to be the simplest way to start insulin therapy in those patients [1, 2]. Nevertheless, only approximately half of all patients treated with basal insulin will achieve target glycated hemoglobin (hemoglobin A1c (HbA1c)) goals indicating a need for additional treatment [3]. Starting with premixed insulin may be an effective option, but it is frequently linked to an increased risk of hypoglycemia, weight gain and fixed meal schedules [4].

As an alternative, the approach known as "basal-plus strategy" has been developed. This approach considers the addition of a single daily prandial injection of rapid-acting insulin before the meal of the day that produces the largest postprandial glucose excursions. The effectiveness of the basal-plus regimen is supported by the fact that one major prandial glucose excursion occurs daily in patients with T2DM especially at mid-morning after breakfast [5]. In addition, several clinical trials have demonstrated the efficacy and safety of this approach as it allows achieving a good therapeutic response with a low risk of hypoglycemia and weight gain, regardless of the patient's age or BMI [6-10].

There are no data in Morocco concerning glycemic con-

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trol of T2DM patients using a basal insulin analog together with one rapid-acting insulin injection regimen at the main meal. The present real-world study aimed to collect data on the number of T2DM patients who were uncontrolled on various previous treatments including two OADs only, basal insulin with OADs, or once daily premixed insulin who achieved HbA1c < 7.0% after 6 months with a basal-plus regimen.

## Materials and Methods

### Study design and patients population

This was an open-label, prospective, observational study carried out from June 2015 to June 2017 in 50 sites that were randomly selected among 150 endocrinologists in Morocco. A total of 1,000 patients were planned to be included in the study to obtain a representative and sufficient sample size.

Physicians who agreed to participate were asked to enroll the first 20 T2DM patients aged at least 18 years, who were known to be diabetic since at least 1 year and presenting with HbA1c ≥ 7.5%, for whom the physician has recently (between one and three months prior to inclusion in the study) decided to prescribe a basal insulin (insulin glargine 100 U/mL, Gla-100) and a rapid-acting insulin injection (insulin glulisine) at main meal due to a suboptimal glycemic control with the previous regimen (two OADs, Gla-100 with OADs or once daily premixed insulin).

Patients were to be excluded if they were not willing, or not able to perform self-monitoring blood glucose or to self-titrate basal insulin under physician's guidance; if they had any serious underlying illness, were hospitalized or taking steroids or any other medication known to elevate or lower glycemia. Moreover, pregnant or breastfeeding women were not allowed to participate in the study.

All patients provided written informed consent before entering the study. The study was non- interventional; the decision to start the basal plus regimen was at physician's discretion as well as OAD therapy. No titration of insulin glulisine or insulin glargine was to be undertaken by study protocol. Dose titration, if any, was decided only by the physician.

The study was conducted in accordance with the applicable international and local laws and guidelines.

### Data collection

During the study, data were collected on standardized paper case report forms (CRFs) at three different outpatient visits: at the moment of inclusion (visit 1) then at 12 and 24 weeks after entering the study (visit 2 and visit 3, respectively). Demographics, vital signs, bodyweight, HbA1c, insulin doses, use of OADs and of concomitant non-insulin antidiabetic drugs were reported. Moreover, the frequency of symptomatic and nocturnal (defined as occurring between midnight and 6:00 am) hypoglycemia and adverse events were recorded. Finally, records for fasting (FBG) and postprandial blood glucose (PPBG) were collected.

### Statistical analysis

The statistical analysis was descriptive. Results were presented as number of available observations, means, standard deviations (SD) and minimum and maximum values for quantitative variables. Categorical variables were presented as percentages. The 95% confidence interval (CI) was given. Differences between means were assessed by the paired *t*-tests for continuous variables while the McNemar test was used for comparison of percentages. P values < 0.05 were considered statistically significant.

## Results

### Study population

Overall, 854 patients (46.8% men) fulfilled the selection criteria and were included in the study. At study entry, the mean age was 59.0 ± 9.4 years with almost half of participants (48.6%) aged over 60 years. The time between diagnosis of T2DM and inclusion in the study ranged between 1 to 45 years; and 27.3% of participants were not overweighed or obese.

The baseline patient characteristics are summarized in Table 1.

All participants were intended to receive a basal plus therapy consisting of once-daily Gla-100 and one injection of glulisine at the main meal at the discretion of the participating physician between 1 and 3 months prior to inclusion. However, a few patients were switched to twice daily (BID) Gla-100 (n = 2; 0.2%) or two (n = 46; 5.4%) or three (n = 12; 1.4%) injections of glulisine at the beginning of the study (Table 2). The number of patients with more than one glulisine injection per day further increased towards the end of the study (BID: n = 122; 14.3%; thrice daily (TID): n = 54; 6.3%). The analysis of results included all participants regardless of injection frequency of basal or prandial insulin in order to reflect daily routine practice in Morocco.

### Changes in HbA1c levels

A significant improvement in glycemic control was observed during the study after initiation of a basal-plus regimen with Gla-100 and glulisine. HbA1c decreased from 9.50±1.51% to 8.08±1.06% at 12 weeks (P < 0.001) and to 7.37±0.88% at 24 weeks (P < 0.001). Likewise, mean change from baseline in HbA1c was -1.42% (95% CI: -1.53%, -1.30%) and -2.13% (95% CI: -2.25%, -2.02%); P < 0.001 at 12 and 24 weeks respectively (Table 3). The percentage of patients who achieved target HbA1c level < 7.0% increased from 10.2% (95% CI: 8.1% - 12.2%) at 12 weeks to 33.0% (95% CI: 29.7% - 36.1%) at 24 weeks (P < 0.001; Table 3).

Only 3.5% (95% CI: 2.3-4.8%) and 14.5% (95% CI: 12.0-16.9%) of patients achieved HbA1c values ≤ 6.5% at 12 and 24 weeks, respectively.

**Table 1.** Baseline Characteristics of the Study Participants

| Variables | N | Mean ± SD | Range |
|---|---|---|---|
| Age (year) | 848 | 59.0 ± 9.4 | 30 - 87 |
| Gender | 835 | | |
| Female | 444 (53.2%) | - | - |
| Male | 391 (46.8%) | - | - |
| Height (cm) | 846 | 167.2 ± 8.6 | 142 - 192 |
| Weight (kg) | 850 | 76.5 ± 11.8 | 43 - 117 |
| Body mass index (kg/m$^2$) | 846 | 27.4 ± 4.0 | 16.7 - 50.0 |
| Duration of diabetes (years) | 853 | 10.8 ± 6.7 | 1 - 45 |
| Heart rate (bpm) | 823 | 77.3 ± 8.6 | 54 - 128 |
| Systolic blood pressure (mm Hg) | 844 | 133.4 ± 14.8 | 93 - 230 |
| Diastolic blood pressure (mm Hg) | 838 | 75.6 ± 9.7 | 50 - 120 |

N: number of subjects/available data; SD: standard deviation. Results were reported taking into account available data. Missing data were not counted in the total number of subjects or percentages.

**Table 2.** Gla-100 and Glulisine Doses (Mean ± SD) Throughout the Study

| | Baseline | | 12 weeks | | 24 weeks | |
|---|---|---|---|---|---|---|
| | N | Units/day | N | Units/day | N | Units/day |
| Gla-100 | | | | | | |
| OD | 849 | 20.7 ± 8.5 | 837 | 22.7 ± 8.9 | 815 | 23.5 ± 9.0 |
| BID | 2 | 33.0 ± 9.9 | 3 | 28.0 ± 11.1 | 2 | 29.5 ± 9.2 |
| Glulisine | | | | | | |
| OD | 725 | 9.7 ± 4.2 | 659 | 10.7 ± 3.9 | 612 | 11.5 ± 4.9 |
| BID | 46 | 10.1 ± 4.4 | 120 | 14.4 ± 7.1 | 122 | 14.8 ± 6.9 |
| TID | 12 | 10.0 ± 4.5 | 26 | 15.6 ± 9.0 | 54 | 16.6 ± 10.3 |

SD: standard deviation; OD: once daily; BID: twice daily; TID: thrice daily. N: number of subjects/available data. Results were reported taking into account available data. Missing data were not counted in the total number of subjects or percentages.

### Blood glucose

After the 6 months observational period, mean FBG levels dropped significantly ($P < 0.001$) from 198 ± 65 mg/dL at inclusion to 148 ± 40 mg/dL at 12 weeks and to 129 ± 32 mg/dL at 24 weeks. Similarly, mean change from baseline for FBG was -57 mg/dL (95% CI: -79 to -35 mg/dL) and -88 mg/dL (95% CI: -110 to -66 mg/dL) at 12 and 24 weeks, respectively (Table 4). Mean PPBG values decreased significantly from 277 ± 72 mg/dL (baseline) to 200 ± 51 mg/dL ($P < 0.001$) at 12 weeks ($\Delta$ = -78 mg/dL) and to 168 ± 41 mg/dL ($P < 0.001$) at 24 weeks ($\Delta$ = -108 mg/dL) (Table 4).

In addition, glycemic control of T2DM patients was significantly improved regardless of the pre-treatment regimen used prior to the inclusion into the study (Table 5).

### Insulin doses

Of 854 patients treated with Gla-100 and glulisine, information

**Table 3.** Mean HbA1c Changes Throughout the Study and Percentage of Patients Achieving Target Values

| | Baseline (n = 851) | 12 weeks (n = 835) | 24 weeks (n = 809) |
|---|---|---|---|
| HbA1c (%) | 9.50 ± 1.51 | 8.08 ± 1.06 | 7.37 ± 0.88 |
| $\Delta$HbA1c (%) | - | -1.42 (-1.53, -1.30) | -2.13 (-2.25, -2.02) |
| HbA1c < 7.0% | 0% | 10.2% (8.1, 12.2) | 33.0% (29.7, 36.1) |
| HbA1c ≤ 6.5% | 0% | 3.5% (2.3, 4.8) | 14.5% (12.0, 16.9) |

All differences (means or percentages) between visits are significant ($P < 0.001$). Confidence intervals at 95% are presented between round brackets. HbA1c: hemoglobin A1c.

**Table 4.** Mean FBG and PPBG Values Over the Course of the Study

| | N | Baseline | N | 12 weeks | N | 24 weeks |
|---|---|---|---|---|---|---|
| FBG (mg/dL) | 810 | 198 ± 65 | 788 | 148 ± 40 | 769 | 129 ± 32 |
| ΔFBG (mg/dL) | - | - | 788 | -57 (-79, -35) | 769 | -88 (-110, -66) |
| PPBG (mg/dL) | 674 | 277 ± 72 | 678 | 200 ± 51 | 676 | 168 ± 41 |
| ΔPPBG (mg/dL) | - | - | 674 | -78 (-84, -72) | 674 | -108 (-114, -102) |

N: number of subjects/available data. Results were reported taking into account available data. Missing data were not counted in the total number of subjects or percentages. FBG: fasting blood glucose; PPBG: postprandial blood glucose.

on injection frequency and/or insulin doses was missing in 74 (8.7%) patients at baseline, and missing data further increased during the course of the study (Table 2). The mean daily glulisine and Gla-100 doses did not change significantly between the start and the end of the study in patients with available data indicating a lack of appropriate insulin titration during the study (Table 2).

### Safety

Overall, 19.5% of the participants had experienced at least one symptomatic hypoglycemic event from study entry to week 12, and 21.1% between week 12 and 24. A total of 19 severe hypoglycemic events (requiring third party assistance) were reported in 18 patients during the study: eight subjects reported one severe hypoglycemic event and one patient described two severe hypoglycemic episodes at week 12. Another nine severe hypoglycemic events were reported in nine patients until week 24. Daytime symptomatic hypoglycemia episodes were more frequently reported than nocturnal episodes.

Patients previously treated with two OADs experienced more hypoglycemic events than patients using other treatment regimens prior to study entry.

## Discussion

The basal-plus approach has been validated by several clinical trials as a simple, effective and safe method of intensifying basal insulin therapy in patients failing to meet glycemic targets on basal insulin alone or in combination with OADs [9-14].

The results of this 24-week national, open-label, observational study shows that the use of basal insulin together with rapid-acting insulin at main meal improved glycemic control in uncontrolled T2DM Moroccan patients using two OADs or basal insulin ± OAD, or once daily premixed insulin as previous therapy. Despite the fact that about 20% of participants in

**Table 5.** Sub-Analysis of Glycemic Control in Participants According to Their Previous Type of Antidiabetic Treatment

| Treatment | Baseline | 12 weeks | 24 weeks | P |
|---|---|---|---|---|
| Basal insulin ± OADs (n = 470) | | | | |
| HbA1c < 7.0% | 0% | 9.2% | 31.6% | - |
| HbA1c ≤ 6.5% | 0% | 3.0% | 12.8% | - |
| HbA1c (%) | 9.29 ± 1.40 | 8.06 ± 1.06 | 7.41 ± 0.90 | < 0.001 |
| FBG (mg/dL) | 178 ± 63 | 140 ± 39 | 126 ± 32 | < 0.001 |
| PPBG (mg/dL) | 264 ± 72 | 191 ± 48 | 163 ± 39 | < 0.001 |
| 2 OADs (n = 272) | | | | |
| HbA1c < 7.0% | 0% | 13.3% | 33.2% | - |
| HbA1c ≤ 6.5% | 0% | 5.5% | 16.0% | - |
| HbA1c (%) | 9.77 ± 1.51 | 8.06 ± 1.03 | 7.37 ± 0.85 | < 0.001 |
| FBG (mg/dL) | 223 ± 62 | 158 ± 40 | 134 ± 33 | < 0.001 |
| PPBG (mg/dL) | 293 ± 68 | 213 ± 52 | 175 ± 40 | < 0.001 |
| Premixed insulin ± OADs (n = 35) | | | | |
| HbA1c < 7.0% | 0% | 8.6% | 51.4% | - |
| HbA1c ≤ 6.5% | 0% | 0.0% | 31.4% | - |
| HbA1c (%) | 9.13 ± 1.16 | 7.98 ± 0.93 | 6.98 ± 0.89 | < 0.001 |
| FBG (mg/dL) | 199 ± 47 | 148 ± 34 | 122 ± 24 | < 0.001 |
| PPBG (mg/dL) | 252 ± 55 | 193 ± 40 | 174 ± 50 | < 0.001 |

FBG: fasting blood glucose; OAD: oral antihyperglycemic drugs; PPBG: postprandial blood glucose; HbA1c: hemoglobin A1c.

this study received a more intensified treatment than just basal-plus (more than one injection of glulisine per day), the significant improvements in glycemic control after 12 and 24 weeks of treatment with Gla-100 and glulisine are very comparable to results previously reported in several basal-plus studies [9-14].

Overall, 33% of patients achieved the primary endpoint of the study of HbA1c levels < 7.0% after 24 weeks of treatment. However, only 14.5% of participants achieved target HbA1c ≤ 6.5% at 24 weeks. This might be explained by a high baseline HbA1c at study entry (9.5%). The absolute mean HbA1c was considerably lowered by -2.13% at 24 weeks indicating a good effectiveness of the basal-plus strategy in real-world practice in Morocco.

The percentage of people achieving target HbA1c < 7.0% (33%) or ≤ 7.0 % (38%) at 6 months in our real-world study were slightly lower to that one observed after 6 months in the OPAL clinical study using a basal-plus regimen with Gla-100 and glulisine as well [14]. In the OPAL study, 44% of patients achieved HbA1c ≤ 7.0% at the end of the study. However, the OPAL study showed a high proportion of patients (30%) achieving an HbA1c target of 6.5% in comparison to our study. This may be due, in part, to the different selection criteria used in relation to baseline HbA1c levels. In fact, while subjects had to show HbA1c values > 6.5-9.0% to be eligible for the OPAL study, the CONBA+ study required HbA1c values > 7.5% at study entry. Moreover, our study was of non-interventional, observational nature without providing any guidance on proper insulin titration compared to the OPAL interventional study design. Therefore, it is not surprising that in our study, the mean daily glulisine and Gla-100 doses did not change significantly throughout the study indicating a lack of adequate insulin titration during the observational period. Moreover, in the CONBA+ study, patients on basal-plus regimen received a higher mean daily glulisine dose at study start (9.7 ± 4.2 U/day) compared to patients in the OPAL study (5.0 ± 2.3 U/day), while glulisine doses at end of study, were comparable between OPAL and CONBA+ (OPAL: 12.0 ± 7.0 U/day CONBA+: 11.5 ± 4.9 U/day). In contrast, Gla-100 doses were higher in the OPAL study both at start and end of study (26.5 ± 13.2 U vs. 20.7 ± 8.5 U at study start and 26.9 ± 13.2 UI vs. 23.5 ± 9.0 UI at end of study for OPAL and CONBA+ study, respectively). In addition, a total of 58 patients were already treated with more than one daily injection of glulisine at the beginning of the study and increased to 176 patients at the end of the study. On the other hand, in our study, the change from baseline to the end of study for HbA1c was greater than the values observed in clinical trials assessing the efficacy of the basal-plus approach. The analysis of pooled data from four multicenter clinical trials where patients with poor glycemic control on OADs have initiated a basal-plus regimen for up to 6 months, showed a significant decrease of -0.4% in HbA1c (vs. -2.13% for the CONBA+ study) over a follow-up of 6 months [14]. However, patients included in this analysis were already receiving once-daily injection of basal insulin (and OADs) and the single injection of insulin glulisine at the main meal was added at patient's inclusion in the corresponding studies.

Both FBG and PPBG contribute to HbA1c levels, and therefore, inadequate control of either parameter will have a negative impact on overall glycemic control. Normalizing FBG is a long-established goal of basic glycemic control in the treatment of T2DM. Nevertheless, evidence suggests that postprandial glucose (PPG) levels are the major contributor to overall glycemic control in patients with well-to-moderately controlled HbA1c (< 7%) in patients with T2DM [15]. In our study, after 24 weeks, both mean levels of FBG and PPBG decreased significantly in comparison to baseline levels. These results are in agreement with those described in other studies [9-14].

Finally, as described in previous studies [9-14], the CONBA+ study has shown that the basal-plus approach, as a first step in introducing prandial insulin therapy, was well tolerated with a low rate of severe hypoglycemia and no specific safety concern. For those needing further intensification of insulin therapy given individual clinical requirements based on diabetes duration, age and risk of macrovascular disease; advancing to full basal-bolus treatment may be needed [16, 17].

Our study has some limitations given its observational non-controlled design. Some of the data were missing for a number of variables and subjects. The hypoglycemic events were self-reported by the study patients leading to a potential underestimation of the frequency of these events. Furthermore, the effect of the basal-plus approach on patients' weight could not be assessed during our study as this variable has not been reported at final visit. In addition, the study population included 58 patients on the basal-bolus regimen. Lastly, although the results of our study were examined in view of those reported in published clinical trials, a direct comparison of the CONBA+ study outcomes with other studies cannot be established due to differences in trial design, primary endpoints and assessed patient populations.

Nevertheless, despite these limitations, the results of this study have shown that the basal-plus approach using insulin glulisine in addition to basal insulin glargine is a relevant option for T2DM patients even when considering the most recent 2018 recommendations from the American Diabetes Association (ADA), where the preferred option for intensification of insulin therapy is the addition of GLP-1 receptor agonists to basal insulin. As a matter of fact, the ADA states that compared with basal-plus insulin, "basal insulin plus GLP-1 RAs are associated with less hypoglycemia and with weight loss instead of weight gain but may be less tolerable and have a greater cost" [18]. Tolerability and particularly treatment cost may indeed be important factors for treatment decision making in the population of Moroccan T2DM patients.

In conclusion, the results of our study suggest that, following the real-life clinical practice, the use of the basal-plus approach in Moroccan patients with uncontrolled T2DM on previous therapy, improves significantly glycemic control while showing a good safety profile with a low risk of severe hypoglycemia. However, additional educational initiatives are needed to further improve insulin titration practice and overall glycemic control in Morocco.

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## Conflict of Interest

H. Iraqi received grant support and/or served as a consultant for Sanofi, Eli Lilly and Novo Nordisk, Servier, Abbott, Merck, MSD and Astra-Zeneca. N. El Ansari received grant support and/or served as a consultant for Sanofi, Eli Lilly, Novo Nordisk, MSD and Astra-Zeneca.

## Informed Consent

Obtained.

## Author Contributions

H. Iraqi: validation of the protocol, analyzing the data, and writing; N. El Ansari: review of the manuscript.

## Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author.

## References

1. Riddle MC, Rosenstock J, Gerich J, Insulin Glargine Study I. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care. 2003;26(11):3080-3086.
2. Hermansen K, Davies M, Derezinski T, Martinez Ravn G, Clauson P, Home P. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naive people with type 2 diabetes. Diabetes Care. 2006;29(6):1269-1274.
3. Dalal MR, Grabner M, Bonine N, Stephenson JJ, DiGenio A, Bieszk N. Are patients on basal insulin attaining glycemic targets? Characteristics and goal achievement of patients with type 2 diabetes mellitus treated with basal insulin and physician-perceived barriers to achieving glycemic targets. Diabetes Res Clin Pract. 2016;121:17-26.
4. Raskin P, Allen E, Hollander P, Lewin A, Gabbay RA, Hu P, Bode B, et al. Initiating insulin therapy in type 2 Diabetes: a comparison of biphasic and basal insulin analogs. Diabetes Care. 2005;28(2):260-265.
5. Franc S, Dardari D, Peschard C, Riveline JP, Biedzinski M, Boucherie B, Petit C, et al. Can postprandial blood glucose excursion be predicted in type 2 diabetes? Diabetes Care. 2010;33(9):1913-1918.
6. Dailey G, Rosenstock J, Moses RG, Ways K. Insulin glulisine provides improved glycemic control in patients with type 2 diabetes. Diabetes Care. 2004;27(10):2363-2368.
7. Garber AJ, Wahlen J, Wahl T, Bressler P, Braceras R, Allen E, Jain R. Attainment of glycaemic goals in type 2 diabetes with once-, twice-, or thrice-daily dosing with biphasic insulin aspart 70/30 (The 1-2-3 study). Diabetes Obes Metab. 2006;8(1):58-66.
8. Inzucchi SE, Matthews DR, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2015;38(1):140-149.
9. Raccah D, Haak TJ, Huet D, Monnier L, Robertson D, Labard P, Soler J, et al. Comparison of stepwise addition of prandial insulin to a basal-bolus regimen when basal insulin is insufficient for glycaemic control in type 2 diabetes: results of the OSIRIS study. Diabetes Metab. 2012;38(6):507-514.
10. Lankisch MR, Del Prato S, Dain MP, Mullins P, Owens DR. Use of a basal-plus insulin regimen in persons with type 2 diabetes stratified by age and body mass index: A pooled analysis of four clinical trials. Prim Care Diabetes. 2016;10(1):51-59.
11. Owens DR, Luzio SD, Sert-Langeron C, Riddle MC. Effects of initiation and titration of a single pre-prandial dose of insulin glulisine while continuing titrated insulin glargine in type 2 diabetes: a 6-month 'proof-of-concept' study. Diabetes Obes Metab. 2011;13(11):1020-1027.
12. Riddle MC, Rosenstock J, Vlajnic A, Gao L. Randomized, 1-year comparison of three ways to initiate and advance insulin for type 2 diabetes: twice-daily premixed insulin versus basal insulin with either basal-plus one prandial insulin or basal-bolus up to three prandial injections. Diabetes Obes Metab. 2014;16(5):396-402.
13. Del Prato S, Nicolucci A, Lovagnini-Scher AC, Turco S, Leotta S, Vespasiani G, on behalf of the ELEONOR Study Group. Telecare Provides comparable efficacy to conventional self-monitored blood glucose in patients with type 2 diabetes titrating one injection of insulin glulisine-the ELEONOR study. Diabetes Technol Ther. 2012;14(2):175-182.
14. Lankisch MR, Ferlinz KC, Leahy JL, Scherbaum WA, Orals Plus Apidra and LANTUS (OPAL) study group. Introducing a simplified approach to insulin therapy in type 2 diabetes: a comparison of two single-dose regimens of insulin glulisine plus insulin glargine and oral antidiabetic drugs. Diabetes Obes Metab. 2008;10(12):1178-1185.
15. Monnier L, Colette C. Contributions of fasting and postprandial glucose to hemoglobin A1c. Endocr Pract. 2006;12(Suppl 1):42-46.

16. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zinman B, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2009;32(1):193-203.
17. Davidson MB, Raskin P, Tanenberg RJ, Vlajnic A, Hollander P. A stepwise approach to insulin therapy in patients with type 2 diabetes mellitus and basal insulin treatment failure. Endocr Pract. 2011;17(3):395-403.
18. American Diabetes Association. 8. Pharmacologic approaches to glycemic treatment. Diabetes Care. 2017;40(Suppl 1):S64-S74.