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Dual-basal-insulin regimen for the management of dawn phenomenon in children with type 1 diabetes: a retrospective cohort study

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Abstract

Background: Handling of the dawn phenomenon (DP) with multiple daily insulin injection (MDII) regimen is a real challenge.

Objective: We aimed to demonstrate the effectiveness of a dual-basal-insulin (a long-acting glargine and an intermediate-acting neutral protamine Hagedorn (NPH)) regimen for the management of DP in children with type 1 diabetes mellitus (T1DM). The primary efficacy outcome was to overcome morning hyperglycemia without causing hypoglycemia during the non-DP period of the night.

Design: Retrospective cohort study.

Method: Charts of 28 children with T1DM (12 female; 42.8%, mean age 13.7 ± 2.1 years) treated with MDII were retrospectively reviewed. The median duration of diabetes was 4.5 years (range 2–13.5 years). DP was diagnosed using a threshold difference of 20 mg/dL (0.1 mmol/L) between fasting capillary blood glucose at 3 a.m. and prebreakfast. NPH was administered at midnight in addition to daily bedtime (08.00–09.00 p.m.) glargine (dual-basal-insulin regimen). Midnight, 03:00 a.m., prebreakfast and postprandial capillary blood glucose readings, insulin–carbohydrate ratios, and basal-bolus insulin doses were recorded the day before the dual-basal-insulin regimen was started and the day after the titration of the insulin doses was complete. Body mass index standard deviation scores (BMI SDS) at the onset–3rd–12th month of treatment were noted.

Results: Before using dual basal insulin, prebreakfast capillary blood glucose levels were greater than those at midnight and at 03:00 a.m. ($F = 64.985$, $p < 0.01$). After titration of the dual-basal-insulin doses, there were significant improvements such that there were no statistically significant differences in the capillary blood glucose measurements at the three crucial time points (midnight, 03.00 a.m., and prebreakfast; $F = 1.827$, $p = 0.172$). No instances of hypoglycemia were reported, and the total daily insulin per kilogram of body weight did not change. The BMI SDS remained steady over the course of the 1-year follow-up.

Conclusion: In this retrospective cohort study, the dual-basal-insulin regimen, using a long-acting glargine and an intermediate-acting NPH, was effective in overcoming early morning hyperglycemia due to insulin resistance in the DP. However, the effectiveness of the dual-basal-insulin regimen needs to be verified by prospective controlled studies using continuous glucose monitoring metrics or frequent blood glucose monitoring.

Keywords: children, dawn phenomenon, dual-basal-insulin regimen, multiple daily insulin, NPH, type 1 diabetes mellitus

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Introduction

A rise in blood glucose levels in the early morning hours without preceding hypoglycemia is known as the dawn phenomenon (DP), which is caused by inadequate insulin levels that fail to sustain normoglycemia. Although this was a known phenomenon since the 1920s,[1] the term "dawn phenomenon" was first labeled by Schmidt *et al.*[2] in 1981. An increase in insulin in the early morning hours with stable blood glucose levels is also seen in healthy individuals, indicating that it is a typical physiological requirement.[3] Current evidence indicates that early morning hyperglycemia is the result of insulin resistance, which is associated with nocturnal secretion of growth hormone.[4] Growth hormone is primarily released during night[5] and impairs hepatic and peripheral insulin sensitivity.[6] The circadian rhythm of insulin secretion is absent in patients with type 1 diabetes mellitus (T1DM) and altered in type 2 diabetes mellitus (T2DM); thus, anti-insulin effects of growth hormone remain unmet.

DP could be seen in both T1DM and T2DM. Investigations into the frequency of DP have produced inconsistent results because of the multiplicity of quantitative definitions[7]; however, DP affects almost half of the patients with T1DM. Insulin resistance is increased in puberty due to the increased growth hormone secretion; hence, DP is more prevalent in the adolescent age group.[8–10] Particularly when DP is "extended," high blood glucose level persists beyond the time of breakfast. It thus affects overall glycemic control, raises glycated hemoglobin (HbA1c) by 0.4%, shortens the time in range, and increases glycemic variability.[11,12] In addition to micro- and macrovascular complications, chronic hyperglycemia and glycemic variability cause alterations in gray and white matter structures of the brain, which may lead to cognitive disability.[13,14] The most effective way to manage DP is through continuous subcutaneous insulin infusion pumps (CSII), which enable varying nocturnal infusion rates.[15] Despite the availability of CSII, correcting DP still requires alternative solutions. This is particularly important for adolescents who may refuse to use CSII or face challenges getting reimbursement for devices and equipment.[16–18] Therefore, not every child or adolescent with diabetes qualifies for CSII, and multiple daily insulin injections (MDII) is ultimately required to treat the disease. However, managing DP in patients using MDII is more challenging. The control of DP cannot be accomplished with a single long-acting insulin (i.e. without a peak action throughout the day). If the dose of long-acting insulin is increased to overcome early morning insulin resistance (i.e. DP), the risk of hypoglycemia during the non-DP hours of the day and night may increase.

To treat early morning hyperglycemia in T1DM children using a basal-bolus insulin regimen with MDII, the basal insulin dose in the early morning hours must be increased. Neutral protamine Hagedorn (NPH) is an intermediate-acting human insulin with an onset of action in 1–3 h and peak action in 4–8 h.[17] The onset and peak action coincide with early morning hyperglycemia, typically between 2:00 and 5:00 a.m. when NPH is administered at midnight. Thus, the requirement for morning insulin spike can be met by using NPH at midnight. With this rationality, we have been managing DP in our clinic recently with a dual-basal-insulin regimen, consisting of long-acting insulin at bedtime (glargine) and intermediate-acting insulin at midnight (NPH). In this study, we aimed to evaluate the efficacy of a dual-basal-insulin regimen for the treatment of DP in children with T1DM.

Material and method

We conducted a retrospective cohort study. Charts of 28 children with T1DM (12 females, 16 males) who used dual-basal-insulin treatment for the management of DP were reviewed. Diagnosis of T1DM was based on ISPAD 2018 guidelines.[19] All patients were under 18, had diabetes for at least 2 years, and were using MDII. At the time of diagnosis or referral to our clinic, every child with T1DM and their parents participate in a structured training program on diabetes, types of insulin and their actions, insulin delivery systems, healthy feeding guidelines, and advanced carbohydrate counting. Insulin is initially administered at a daily dose of 0.5–1 U per kg of body weight. The initial basal insulin (long-acting, insulin glargine) dose is 25–30% of the daily total, with the remaining 70–75% administered as meal boluses (rapid-acting, insulin aspart, or lispro). Capillary blood glucose levels are measured at least eight times a day – before and 2 hours after meals, at midnight, and 03.00 a.m. The doses of long- and rapid-acting insulins are adjusted to achieve glycemic targets (preprandial 70–145 mg/dL [0.4–0.8 mmol/L], postprandial 90–180 mg/

dL [5.1–10.3 mmol/L], bedtime 120–180 mg/dL [6.8–10.3 mmol/L], and nocturnal 80–162 mg/dL [4.6–9.2 mmol/L]) and avoid hypoglycemia.[20] Insulin dose adjustments are generally carried out under a 3-day fixed carbohydrate meal plan. Prandial insulin dose is adjusted according to postprandial glucose targets, and individualized insulin–carbohydrate ratios (ICR) for each meal (breakfast, lunch, dinner) are determined. Patients and caregivers are taught to adjust rapid-acting insulin to meet the carbohydrate consumed with individualized ICR for each meal (flexible insulin regimen). Basal dose adjustment is carried out by targeting fasting morning glucose within the range of 20–30 mg/dL (1.1–1.7 mmol/L) of bedtime glucose level and >80 mg/dL (4.6 mmol/L) at 03.00 a.m. The patients and their caregivers are asked to record capillary blood glucose measurements, insulin doses, and carbohydrate counts for each meal daily. During the follow-up visits every 3 months, insulin doses, ICR, and diabetes education are reviewed based on these records.

When the blood glucose measurements were similar at midnight and 03.00 a.m. and increased toward the morning, the DP was considered. Using the 3-month patient data, DP was identified and quantified by subtracting the capillary blood glucose nadir at 03.00 a.m. from the prebreakfast fasting capillary blood glucose value (07.00–09.00). The diagnosis of DP was confirmed when the patient consumed a 3-day fixed carbohydrate meal that contained 50% carbohydrate, 35% fat, and 15% protein. We settled on a 20-mg/dL (1.1-mmol/L) threshold to define DP.[21–23] The lack of difference between blood glucose measurements at midnight and 03:00 a.m. indicates the adequacy of the basal insulin dose. Patients with a history of surgery, infection, or psychological stress during the previous 6 weeks or were taking medications (glucocorticoids, beta-blocking agents, etc.) that could affect insulin sensitivity were excluded from the study. The initial NPH dose was calculated as 25% of the patient's current glargine dose. The glargine dose was reduced by 10% simultaneously when starting the NPH dose to avoid hypoglycemia. Glargine was administered at bedtime (08.00–09.00 p.m.), while NPH was administered at midnight. Titration of insulin doses was performed by changing the NPH and glargine doses by 1–2 units up or down in the following 10–14 days to achieve a prebreakfast glucose level of less than 145 mg/dL (8.3 mmol/L),[20] and a difference between prebreakfast and 03.00 a.m. capillary blood glucose less than 20 mg/dL (1.1 mmol/L), while 03.00 a.m. glucose was kept above 80 mg/dL (4.6 mmol/L). Breakfast ICR was readjusted based on target blood glucose values during this period.

Age at the diagnosis of T1DM was extracted from patient files. Tanner stages of puberty were noted.[24] Body weight and height at the onset, 3rd and 12th month of dual-basal-insulin regimen were recorded. Body mass index (BMI) and its standard deviation score (SDS) were calculated.[25] BMI SDS was assessed using Centers for Disease Control and Prevention (CDC) charts.[25] Midnight, 03:00 a.m., breakfast pre- and postprandial capillary blood glucose readings, breakfast ICR, and basal insulin doses were recorded the day before the dual-basal-insulin regimen was started as well as the day after the titration of the basal insulin doses was complete. NPH insulin was considered as basal insulin in calculations. Because of the retrospective nature of the study, we did not have other capillary glucose records during the day; thus, the change in glucose levels could not be evaluated. HbA1c and BMI-SDS at the onset, 3rd, and 12th months of the dual-basal-insulin regimen were recorded. Two periods of the study were defined as:

B1: The day when only Glargine was used (before the start of NPH)
B2: The day when the titration of the basal insulin doses was complete

Statistical analysis

All statistical analyses were carried out using SPSS 21.0 for the Windows software package (IBM Corp. Armonk, NY, USA). Normality was tested using the Shapiro–Wilk test. Descriptive analyses were presented using mean and standard deviation for normally distributed data, median, and minimum–maximum for non-normally distributed data. Mean values of continuous variables are compared using t-tests; medians are compared using the Mann–Whitney *U* test or the Wilcoxon test, as appropriate. The change of capillary blood glucose at three time points (midnight, 03.00 a.m., and prebreakfast) as well as HbA1c and BMI-SDS at 0, 3, and 12 months

Table 1. Baseline characteristics of the patients.

Gender (Female) (*n*, %)	12, 42.8%
Age (years)*	13.7 ± 2.1
Duration of diabetes (years)$	4.5 (2–13.5)
Body weight SDS*	0.0 ± 1.4
Height SDS*	−0.3 ± 1.1
BMI SDS*	0.2 ± 1.2
HbA1c	
mmol/mol*	98.4 ± 18.6
%*	9.0 ± 1.7

*Mean ± standard deviation.
$Median (minimum–maximum).
BMI, Body mass index; SDS, standard deviation score.

were analyzed using ANOVA for repeated measures.

Results

Twenty-eight children with T1DM (12 females; 42.8%) were included in the study. At B1, the mean age was 13.2 ± 2.4 years in girls and 14.2 ± 1.7 years in boys, the median duration of diabetes was 4.5 years (range 2–13.5 years), and the mean BMI SDS was 0.2 ± 1.2. All patients were pubertal, and Tanner stages ranged from 2 to 5. Mean HbA1c was 98.4 ± 18.6 mmol/mol [9.0 ± 1.7%]. Baseline characteristics of the patients are presented in Table 1.

At B1, prebreakfast capillary blood glucose level was higher than those at midnight and 03.00 a.m. ($F = 64.985$, $p < 0.01$; shown in Figure 1). There was no difference between midnight and 03.00 a.m. capillary blood glucose levels ($p = 0.647$; shown in Figure 1). The median daily insulin dose was 1.09 U per kg body weight (range 0.73–1.7), and basal insulin at B1 was 31.7% (range 18–50%) of total daily insulin.

On the day of the start of NPH, the initial median NPH dose was 0.08 U per kg body weight (range 0.04–0.12 U/kg). After titration of glargine and NPH insulin at B2, the NPH dose was decreased to a median of 0.07 U per kg of body weight (21% of initial glargine dose instead of 25%; range 0.03–0.27 U/kg). The final glargine dose was decreased by a median of 5% (range 0-21.4) of B1. The total amount of basal insulin (glargine + NPH) increased to a median of 37.3% (range 23.0–58.3%) of the total daily insulin at B2, which was significantly higher than B1 (31.7%; $p < 0.01$; shown in Figure 2).

After titration of the two basal insulin at B2, there were no statistically significant differences in the capillary blood glucose measurements at three time points (midnight, 03.00 a.m., and prebreakfast; $F = 1.827$, $p = 0.172$; shown in Figure 1). The magnitude of DP was improved in all patients, and 54% were out of DP at B2. Also, 54% of the patients had their prebreakfast blood glucose within the target range at B2. No instances of hypoglycemia were detected at any time point.

Table 2 shows the changes in insulin doses, blood glucose measurements, and insulin requirements after the dual-basal-insulin regimen. ICR at breakfast decreased in 54% of the cases, indicating the need for less insulin for the same amount of carbohydrate. Median ICR at breakfast was 1:4 (range 1:2–1:11) at B1 and 1:5 (range 1:2.5–1:12) at B2 ($p < 0.01$). Postbreakfast capillary blood glucose measurements decreased significantly during B2 compared to B1 ($p < 0.01$). The total daily insulin dose per kg (median 1.07 U/kg, range 0.73–1.49 U/kg) during B2 was similar to B1 ($p = 0.833$; Table 2). BMI-SDS did not change during the first 12 months of B2 (0.2 ± 1.2, 0.3 ± 1.3, and 0.2 ± 1.5, $p = 0.709$ at baseline, 3rd, and 12th month, respectively) ($F = 0.174$, $p = 0.712$). Although the change in HbA1c during 1-year follow-up was not statistically significant, there was a decrease at the 12th month [98.4 ± 18.6 mmol/mol (9.0% ± 1.7%), 98.6 ± 19.7 mmol/mol (9.02 ± 1.8%), and 95.1 ± 16.4 mmol/mol (8.7% ± 1.5%) at baseline, 3rd, and 12th month, respectively] ($F = 0.494$, $p = 0.542$). There were no diabetic ketoacidosis or severe hypoglycemia episodes during the 12-month follow-up.

Discussion

It is well known that DP increases glucose exposure and glycemic variability. Insulin therapy aims to mimic pancreatic insulin secretion patterns, and CSII is the best management tool for DP. However, an alternative treatment approach is necessary for patients with T1DM using an MDII regimen. In the current study, we demonstrated

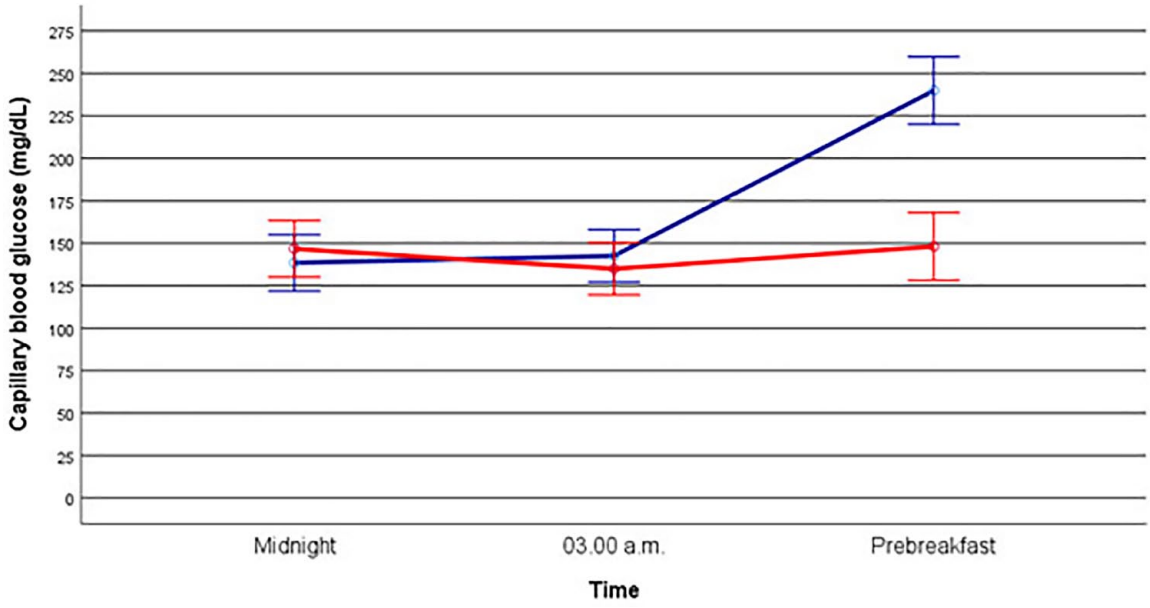

Figure 1. Capillary blood glucose at midnight, 03.00 a.m., and prebreakfast before and after the dual-basal-insulin regimen. The blue line represents B1 and the red line represents B2. The change of capillary blood glucose at three-time points (midnight, 03.00 a.m., and prebreakfast) was analyzed using ANOVA for repeated measures.

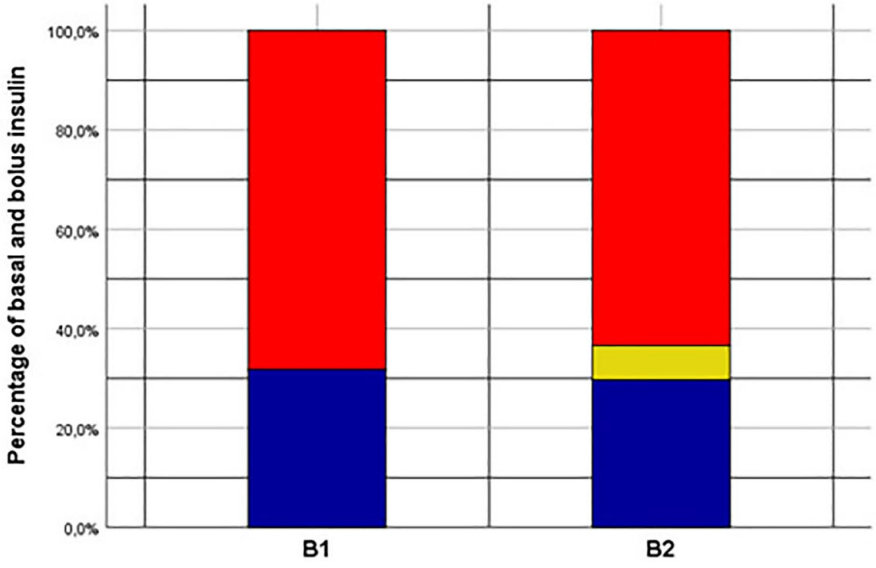

Figure 2. Percentage of basal insulin before (B1) and after (B2) the initiation of NPH. The blue bar represents glargine, the yellow bar represents NPH insulin, and the red bar represents bolus insulin. The ratio of basal insulin to the total daily insulin was significantly higher at B2 compared to B1 ($p < 0.01$).

the effectiveness of dual basal insulin, a long-acting glargine and an intermediate-acting NPH, for managing DP in children with T1DM to reduce morning hyperglycemia. The dual-basal-insulin regimen increased the basal insulin safely without causing hypoglycemia during the non-DP period

Table 2. Insulin doses, midnight, 03.00 a.m., and morning capillary blood glucose, and HbA1c values before and after the initiation of dual basal insulin.

Variables	B1	B2	*p*
Total daily insulin (unite/kg/day)*	1.09 (0.73–1.7)	1.07 (0.73–1.49)	0.833‡
Basal/total insulin ratio (%)*	31.7 (18–50)	37.3 (23.0–58.3)	<0.01‡
Midnight capillary blood glucose (mg/dL), [mmol/L]$	138.4 ± 40.6, [7.9 ± 2.3]	146.7 ± 40.2 [8.4 ± 2.3]	0.734§
03.00 a.m. capillary blood glucose (mg/dL), [mmol/L]$	142.5 ± 37.8 [8.3 ± 2.1]	134.8 ± 37.1 [7.7 ± 2.1]	0.831§
Morning preprandial capillary blood glucose (mg/dL), [mmol/L]$	239.9 ± 55.6 [13.7 ± 3.2]	148.1 ± 40.1 [8.4 ± 2.3]	<0.01§
Morning postprandial capillary blood glucose (mg/dL), [mmol/L]$	210.1 ± 70.1 [12 ± 4]	126.8 ± 33 [7.2 ± 1.9]	<0.01§
Morning insulin–carbohydrate ratio*	1:4 (1:2–1:11)	1:5 (1:2.5–1:12)	<0.01‡

*Median (minimum–maximum).
$Mean ± standard deviation.
‡Wilcoxon test.
§Paired samples *t*-test.

of the night. Although total basal insulin increased with dual-basal-insulin therapy, total daily insulin remained the same, possibly due to a decrease in morning bolus insulin. Accordingly, NPH effectively overcame the early morning insulin resistance associated with DP.

DP, one of the causes of morning hyperglycemia, can impact overall glycemic control. Monnier *et al.*[11] reported the impacts of DP on HbA1c and 24-hour mean glucose as 0.4% and 12.4 mg/dL (0.7 mmol/L), respectively. Li *et al.*[12] reported a lower time in range and higher coefficient of variation in patients with DP compared to non-DP. Wang *et al.*[26] reported an independent association between glycemic excursions and DP. Also, a significant correlation was reported between poor sleep quality and the magnitude of DP.[27] It is crucial to address insulin resistance linked to DP based on these observations. However, increasing the glargine dose while targeting fasting morning glucose levels may result in hypoglycemia during the non-DP portion of the day. King *et al.*[28] reported that more than 10% of the continuous glucose monitoring (CGM) readings were less than 70 mg/dL (4 mmol/L) when the insulin glargine dose was titrated to achieve a basal glucose goal of <130 mg/dL (7.4 mmol/L) for all day instead of the non-DP period of the day. Therefore, increasing the long-acting insulin dose is not the best strategy to overcome insulin resistance of DP in order to control blood glucose levels in the early morning.

NPH, an intermediate-acting human insulin, has been used as basal insulin in conventional insulin regimens to provide for insulin needs between meals and overnight. However, NPH insulin is no longer widely used as basal insulin after the introduction of long-acting insulin analogs in the early 2000s.[17] Nevertheless, NPH insulin is ideal for the control of DP due to its peak effect and duration of action. The findings of our study are encouraging in terms of pointing to a novel application for NPH insulin. After NPH was commenced, morning blood glucose excursions were blunted, and the ICR decreased (indicating the need for less insulin for the same amount of carbohydrate) in the current study. Despite the total basal insulin dose increase, overall daily insulin did not change.

Insulin is an anabolic hormone that increases glucose utilization, lipogenesis, and protein and glycogen synthesis.[29] Thus, improvement of glycemic control with intensive insulin treatment could result in weight gain.[30] According to Valeria *et al.*,[31] high insulin doses per unit of body surface

area and the waist-to-height ratio are risk factors for metabolic syndrome. Maintaining a normal body weight should be advised for people with T1DM because abdominal obesity is a risk factor for cardiovascular disease in female teenagers, and there is a U-shaped link between BMI and mortality.[31,32] In the current study, increased basal insulin with the addition of NPH covered only the DP portion of the day and did not cause an increase in the total daily insulin dose; also, BMI SDS did not increase during the 1-year follow-up in our patients. Thus, the dual-basal-insulin regimen did not pose a risk for obesity.

Our study is the first report of a dual-basal-insulin regimen for the management of DP to the best of our knowledge. There is only one report comparing semilente and NPH insulin, which states that semilente is superior to NPH insulin for the suppression of DP in adolescents with T1DM.[33] However, in that study, only a single basal insulin was used at bedtime.

HbA1c has been the gold standard for monitoring glycemic control in diabetic individuals. In individuals with T2DM, Monnier *et al.*[11] reported that DP increased HbA1c levels by 0.4%. Although there was no statistical significance, the current study observed a 3% reduction in HbA1c after 12 months of follow-up. On the other hand, HbA1c estimates average blood glucose levels over the preceding 2–3 months; it does not reflect glycemic variability.[34,35] Glycemic variability is considered to be more critical than HbA1c in the development of diabetic vascular complications.[34] Based on the limitations of HbA1c and the significance of glycemic variability, there is a trend for CGM metrics to be the gold standard method for the assessment of glycemic control.[36] Riddlesworth *et al.*[37] reported that 14 days of CGM data could provide a reliable estimation of glucose metrics for the prior 3-month period. So, given all these limitations of HbA1c and the importance of glycemic variability, it would be more accurate to evaluate the effectiveness of dual basal insulin by CGM.

This study has several limitations. We could not evaluate the effect of long-acting insulin, which we reduced the dose of throughout the day. As the study was retrospectively designed, we did not get all the glucose readings except for breakfast; therefore, we only included the time from midnight to breakfast. Also, we did not evaluate the effectiveness of NPH insulin by CGM metrics, which could provide more valuable data regarding glycemic variability. Also, we did not perform validated methods of measures of insulin sensitivity to evaluate the effectiveness of dual-basal-insulin therapy. As our purpose was to compare the insulin sensitivity before and after the dual-basal-insulin therapy, not to define exact insulin sensitivity, we used the ICR as an indirect indicator of insulin sensitivity.

In conclusion, the dual-basal-insulin regimen, using a long-acting glargine and an intermediate-acting NPH, was effective in overcoming early morning hyperglycemia due to insulin resistance in DP. However, the effectiveness of the dual-basal-insulin regimen needs to be verified by prospective controlled studies using CGM metrics or frequent blood glucose monitoring.

Declarations

Ethics approval and consent to participate

The study protocol was approved by Hacettepe University Faculty of Medicine ethics committee (Approval Number: 2022/13-18, Project Number: GO 22/758). Informed consent was waived due to the retrospective nature of the study.

Consent for publication

Not applicable.

Author contributions

Nur Berna Celik: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing – original draft; Writing – review & editing.

Dicle Canoruc Emet: Conceptualization; Investigation.

Merve Canturk: Conceptualization; Investigation.

Z. Alev Ozon: Data curation; Investigation; Supervision; Validation; Writing – original draft; Writing – review & editing.

E. Nazli Gonc: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Supervision; Validation; Writing – original draft; Writing – review & editing.

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Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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