



# Comparison between Insulin Glargine and Insulin Detemir in Adolescents with Type 1 Diabetes during Ramadan Fasting

Walid Kaplan<sup>1</sup> Bachar Afandi<sup>2</sup> Noura Al Hassani<sup>1</sup>

<sup>1</sup> Department of Pediatric, Tawam Hospital, Al Ain, United Arab Emirates

<sup>2</sup> Department of Medicine, Tawam Hospital, Al Ain, United Arab Emirates

Address for correspondence Walid Kaplan, MD, Department of Pediatric, Tawam Hospital, P. O. Box 15258, Al Ain, United Arab Emirates (e-mail: wkaplan@seha.ae).

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## Abstract

**Objectives** The aim of this study was to compare between insulin glargine and insulin detemir on glucose profile in adolescents with type 1 diabetes mellitus (T1DM) who fast the month of Ramadan.

**Materials and Methods** This was prospective, cross-over study. Subjects were randomized into Group G, in which insulin glargine was given once daily, and Group D, in which  $\frac{2}{3}$  of the total dose of insulin detemir was given before breaking the fast and  $\frac{1}{3}$  before starting it. Subjects were crossed-over after 1 week. We compared the mean interstitial glucose (IG), and the percentages of hypoglycemia ( $<70$  mg/dL) and severe hyperglycemia ( $>300$  mg/dL) between the groups.

**Results** A total of 11 adolescents were enrolled. Mean ( $\pm$  standard deviation) age was  $14 \pm 3.3$  years. There was no difference in the mean IG ( $190 \pm 46$  vs.  $198 \pm 37$  mg/dL,  $p=0.1$ ), or the percentages of severe hyperglycemia ( $13.5 \pm 12.9\%$  vs.  $13.6 \pm 9.2\%$ ,  $p=0.5$ ) in group G and Group D, respectively. Conversely, the percentage of hypoglycemia was higher in Group G than Group D ( $9.1 \pm 7.0\%$  vs.  $4.4 \pm 2.7\%$ , respectively,  $p=0.01$ ).

**Conclusion** Insulin detemir given twice daily results in less hypoglycemia than once daily insulin glargine in adolescents with T1DM during fasting in Ramadan.

## Keywords

- ▶ adolescents
- ▶ detemir
- ▶ glargine
- ▶ Ramadan fasting

## Introduction

Patients with type 1 diabetes mellitus (T1DM) who fast the month of Ramadan abstain from eating and drinking for more than 12 hours a day, and then might indulge in a binge eating between sunset meal (Iftar) and dawn meal (Sohour). While T1DM has been listed as a high-risk factor for fasting during Ramadan,<sup>1,2</sup> many patients elect to fast

regardless of the recommendations of their health care providers.<sup>3,4</sup>

Long-acting insulin analogues have substituted Neutral Protamine Hagedorn insulin during fasting due to their lower risk of hypoglycemia.<sup>5</sup> Because of the prolonged fasting period that might exceed 20 hours in some countries, the dose of basal insulin is frequently reduced to minimize the risk of hypoglycemia,<sup>6,7</sup> especially in the last few hours of

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fasting.<sup>8</sup> However, there is no consensus on the proper dose adjustment of the basal insulin. Conversely, the hyperglycemic trend that starts after breaking the fast and continues throughout the eating hours<sup>9</sup> is expected to worsen if patient takes lower dose of basal insulin. From a practical point of view, those challenges can be easily managed in the case of hybrid closed-loop automated insulin pump by reducing the basal rate in the last few hours of fasting, and increasing it after breaking the fast according to glucose changes.<sup>10</sup> However, such adjustments cannot be done with the once daily basal insulin analogues in patients on multiple daily injections (MDI).

Insulin detemir has been approved for twice daily injection<sup>11–13</sup> and its use might be of a clinical advantage in patients with T1DM who intend to fast the month of Ramadan. Theoretically, it would be beneficial to increase the dose of the basal insulin during the eating hours and reduce it during the fasting hours by giving different doses for those two respective periods. Obviously, such a variation in basal rate cannot be achieved with basal insulin that is approved for once daily dosing, such as insulin glargine.

The goal of this study was to compare glucose profile (average glucose, and percentages of hypoglycemia and severe hyperglycemia) between insulin glargine and insulin detemir in a group of adolescents with T1DM using MDI regimen during fasting the month of Ramadan.

## Materials and Methods

Adolescents with T1DM who expressed their intention to fast the month of Ramadan were asked to enroll in this prospective, cross-over study. Informed consent was obtained from all patients or their parents. Inclusion criteria were: (1) age 12 to 20 years, (2) duration of diabetes more than 6 months, (3) on MDI regimen, and (4) not taking other medications that interfere with glucose metabolism. Patients were randomized into two groups: Glargine Group (Group G), in which insulin glargine was maintained as the basal insulin, but the dose was reduced by 25% of the pre-Ramadan dose and the timing was changed to pre-Iftar (around 7:00 p.m.); and Detemir Group (Group D), where basal insulin was changed from glargine to detemir at the same pre-Ramadan dose, but  $\frac{2}{3}$  of the total dose was given with Iftar (6:30–7:00 pm), and  $\frac{1}{3}$  of the dose was given with Sohour (5:00 a.m.). Both groups maintained the same pre-Ramadan short-acting insulin analogue and followed the same insulin-to-carbohydrate ratio, and sensitivity factor. Patients were randomly allocated into one of the two groups for 1 week and then crossed-over for another week. We used Abbott Freestyle Libre® to monitor the interstitial glucose (IG) during all phases. We compared the mean IG, and percentages of hypoglycemia (<70 mg/dL) and severe hyperglycemia (>300 mg/dL) of the total monitoring time between the two groups. Additionally, we analyzed the hypoglycemia distribution throughout the 24 hours by dividing it into four periods of 6 hours each, related, as much as possible, to the Iftar and Sohour meals as follows: post-Iftar period from 7:00 p.m. to 1:00 a.m., peri-Sohour 1:00 a.m. to 7:00 a.m., early fasting

7:00 a.m. to 1:00 p.m., and late fasting 1:00 p.m. to 7:00 p.m. All variables are listed as mean  $\pm$  standard deviation, and the two groups were compared using Student's *t*-test. Differences with *p*-value < 0.05 were considered significant. Subjects and/or their guardians were instructed to report any episode of diabetic ketoacidosis (DKA), severe hypoglycemia (glucose less than 45 mg/dL, or hypoglycemia with seizure or coma), or diabetes-related visits to the emergency room (ER).

The study complies with all relevant national regulations and institutional policies, and was reviewed and approved by our regional Institutional Review Board, reference number CRD IRR # 459/16.

## Results

A total of 13 patients were initially enrolled, of which 2 were excluded due to not completing the study. Subjects' characteristics are listed in ►Table 1.

All subjects were able to fast 100% of the study days. The average time of glucose monitoring was similar between the two groups (148  $\pm$  60 hours for Group G and 143  $\pm$  48 hours for Group D, *p* = 0.4). There were no episodes of severe hypoglycemia, DKA, or reported ER visits in any of the subjects.

While the proportion of the basal insulin dose was lower, as expected, in Group G than Group D (0.34  $\pm$  0.8 unit/kg/day vs. 0.44  $\pm$  0.14 unit/kg/day, respectively; *p* < 0.01), there was no difference in the mean IG (190  $\pm$  46 vs. 198  $\pm$  37 mg/dL in Group G and Group D, respectively; *p* = 0.1) or the percentages of severe hyperglycemia (13.5  $\pm$  12.9% vs. 13.6  $\pm$  9.2% in group G and group D, respectively; *p* = 0.5). Conversely, the percentage of hypoglycemia was higher in Group G than Group D (9.1  $\pm$  7.0% vs. 4.4  $\pm$  2.7%, respectively; *p* = 0.01). The duration and proportion of hypoglycemia was by far the highest in the late fasting period in both groups, followed by the early fasting period, while there was barely any hypoglycemia in the post-Iftar period (►Fig. 1).

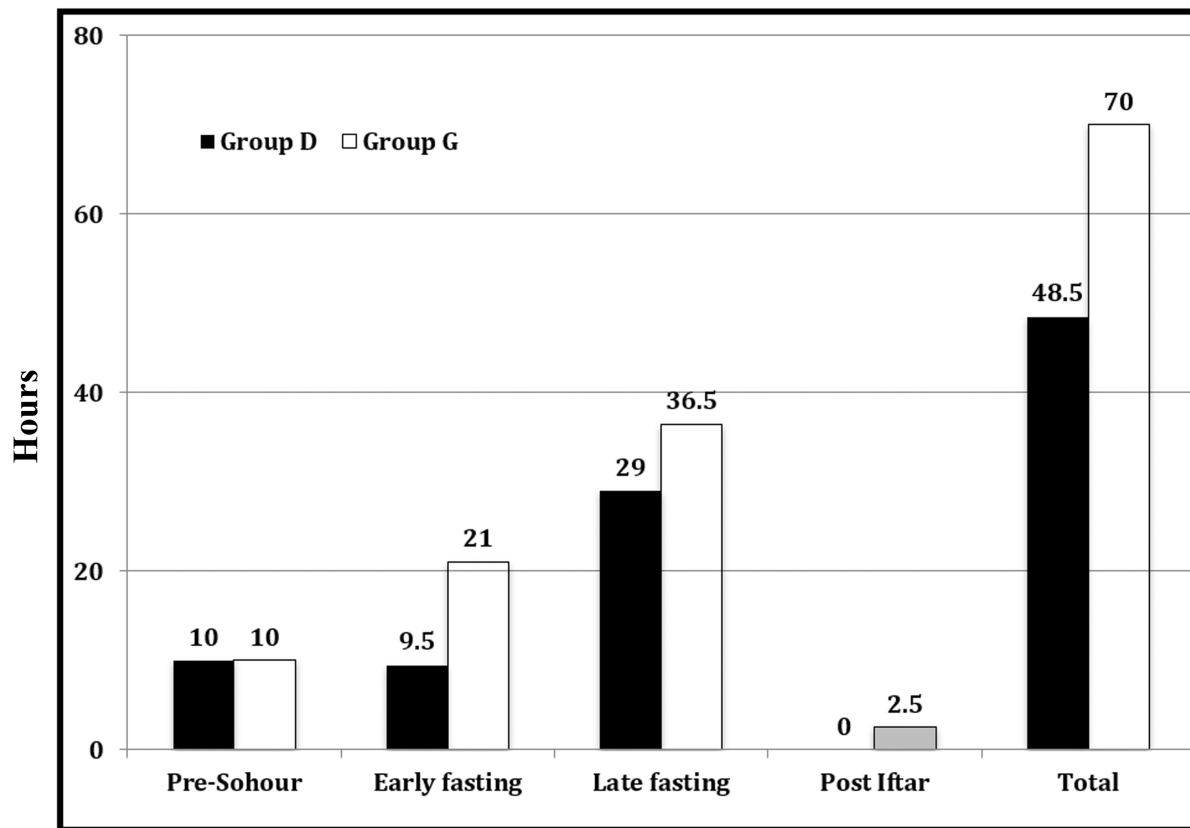
## Discussion

The prolonged abstinence from drinking and eating during Ramadan fasting increases the risk of hypoglycemia in patients with T1DM. While the reduction in basal insulin dose or changing its time is expected to lower the risk of hypoglycemia during fasting hours,<sup>2</sup> few studies reported no benefit of such an adjustment.<sup>14,15</sup> Nonetheless, this approach is endorsed by most of the current guidelines,<sup>2,16,17</sup> but there is no consensus on the rate and duration of the dose reduction; additionally, the observed postprandial

**Table 1** Subjects' characteristics

Characteristic	Mean $\pm$ standard deviation
Age (year)	14 $\pm$ 3.3
Duration of diabetes (year)	5 $\pm$ 3.9
HbA1c (%)	8.8 $\pm$ 1.9

Abbreviation: HbA1c, hemoglobin A1c.



**Fig. 1** Time spent in hypoglycemia.

hyperglycemia after breaking the fast<sup>9</sup> is expected to worsen when the dose of the basal insulin is reduced.

The use of insulin pump during fasting has been increasingly promoted to minimize the risk of hypoglycemia and the probability of breaking the fast,<sup>15,18–20</sup> or to reduce glucose variability<sup>19</sup> particularly when using the low-glucose suspension feature.<sup>21</sup> However, this option is unavailable for the majority of patients due to its financial burden and limited health care resources. We have presented in this study an option of MDI regimen with lower incidence of hypoglycemia, and a potential reduction in glucose variability during fasting.

Insulin detemir has been approved by the U.S. Food and Drug Administration for once or twice daily administration.<sup>11</sup> When compared with insulin glargine in a clamp study, once daily detemir had similar effect in the first 12 hours, but a lower effect during the last 12 hours of the day,<sup>12</sup> which might provide a superior option during Ramadan fasting where most of the hypoglycemic events were reported toward the end of the fasting hours.<sup>8</sup>

We have shown in this study that insulin detemir may help in reducing the duration of hypoglycemia during fasting by splitting its daily dose into two unequal proportions and giving the smaller proportion before the fasting starts. The proposed proportions of  $\frac{1}{3}$  and  $\frac{2}{3}$  of the total dose in our study were arbitrary and not based on any previous data. The occurrence of hyperglycemia after breaking the fast and

hypoglycemia in the early fasting periods in Group D implies that further adjustment of the proportions and timing of injections might be more effective in minimizing glucose fluctuation. Further studies with a larger number of subjects would be helpful to shed more light on this issue.

Despite giving a higher dose of basal insulin per body weight in Group D than Group G, the mean IG and the percentage of severe hyperglycemia were similar between the two groups, while hypoglycemia was significantly lower in Group D. This indicates less glucose fluctuation with insulin detemir compared with insulin glargine; however, our study was not designed to measure glucose variability. It would be very helpful to assess this parameter in a future study due to its link to diabetes morbidity and future complications.

While nonsevere hypoglycemia was reported in both groups, no one acted according to the official DaR guidelines<sup>2</sup> and broke their fast. We should emphasize more clearly that fasting despite having hypoglycemia is very unsafe and should be avoided.

The main limitation of this study is the small sample size; however, its cross-over design and the use of intermittently scanned continuous glucose monitoring (isCGM) increase the credibility of our findings. The study results are promising that an alternative MDI regimen could be applicable to underprivileged patients with T1DM who insist on fasting the month of Ramadan but cannot or do not want to use insulin pump.

**Author's Contribution**

All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

**Compliance with Ethical Principles**

The study complies with all relevant national regulations and institutional policies, and was reviewed and approved by our regional Institutional Review Board, reference number CRD IRR # 459/16.

**Funding and Sponsorship**

None.

**Conflict of Interest**

None declared.

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