Effects of rapid-acting insulin analogues insulin glulisine and insulin aspart on postprandial glycemic excursion with single bout of exercise in patients with type 2 diabetes

Nagaaki Tanaka and Yoshikazu Hiura

Abstract. The analogue insulin glulisine (Glu) shows both more rapid onset and shorter duration of action compared with the other rapid-acting insulin analogues. The current study investigates these properties in regard to the occurrence of hypoglycemia related to exercise. A randomized, single-center, open-label, crossover study was conducted in 12 hospitalized type 2 diabetes patients (all male, mean ± SD age of 51.9 ± 11.3 years; BMI: 25.5 ± 3.9 kg/m²; HbA1c: 11.2 ± 2.4 %). Glu or insulin aspart (Asp) was subcutaneously administered just before breakfast. Insulin dosage was determined as the usual dose of pre-prandial rapid-acting insulin for patients treated with insulin therapy or as 0.1 unit/kg for patients treated with oral anti-hyperglycemic agents. Sixty min after the start of eating, the patients began aerobic exercise on a bicycle ergometer for 30 min at 50% of maximum heart rate. Hypoglycemic episodes (plasma glucose level < 70 mg/dL with or without symptoms) were observed more frequently in Asp group (p < 0.05). Post-exercise plasma glucose levels at 90, 120, and 150 min were significantly lower in Asp group (p < 0.05). In patients with BMI < 25 kg/m² (n = 6), post-exercise blood glucose levels were significantly lower in Asp group (p < 0.05), while in patients with BMI ≥ 25 kg/m² (n = 6) the difference was not significant. Glu may therefore be a suitable choice of rapid-acting insulin for patients with type 2 diabetes who are at high risk of post-exercise hypoglycemia.

Key words: Glulisine, Exercise, Hypoglycemia

INTENSIVE INSULIN THERAPY (IIT) is one of the important and fundamental therapeutic strategies for patients with type 2 diabetes mellitus (T2DM) [1]. While IIT is an established therapeutic strategy to achieve target glycemia, hypoglycemia is still the major barrier to an optimal outcome. Severe hypoglycemia was associated with increased mortality in participants in both the standard and intensive glycemia arms of the ACCORD trial [2]. However, the relationships between the achieved HbA1c and treatment intensity were not straightforward [3]. An association of severe hypoglycemia with increased mortality was also found in the ADVANCE trial [4]. In addition, an association of self-reported severe hypoglycemia with 5-year mortality has also been reported in clinical practice [5, 6]. According to the ADA position statement of exercise recommendation, people with T2DM are encouraged to perform at least 150 min/week of moderate-intensity aerobic physical activity (50–70% of maximum heart rate), spread over at least 3 days/week with no more than 2 consecutive days without exercise [1]. Physical activity may increase the risk of hypoglycemia if medication dose or supplementary carbohydrate intake is not altered in patients with T2DM who are taking insulin and/or insulin secretagogues. Accordingly, for individuals on these therapies, supplementary carbohydrate ingestion is recommended if pre-exercise glucose levels are 100 mg/dL (5.6 mmol/L) or exercise is of longer duration than 30 min. It may be difficult to avoid post-exercise hypoglycemia by having additional snacks or modifying insulin dose just before exercise. Several lines of rapid-acting insulin analogues have become available such as insulin lispro (Lis), insulin aspart (Asp) and insulin glulisine (Glu) that may be used to address this problem. Glu is a recombinant human insulin analogue in which asparagine at position B3 has been replaced by lysine, and lysine at position B29 has been replaced by glutamic acid. Because of these modifications, Glu shows
both more rapid and sharp onset and somewhat shorter duration of action compared with the other rapid-acting insulin analogues [7, 8]. To date, no study has been conducted to directly assess the glucose excursions that occur during aerobic exercise sessions in the treatment with Glu or Asp in T2DM patients. The characteristic features of rapid onset and short duration of action of Glu might reduce the occurrence of hypoglycemia during exercise. In the present study, we investigated the effect of Glu and Asp on hypoglycemic episodes in T2DM patients who were encouraged to perform aerobic exercise.

Materials and Methods

A randomized, single-center, open-label, crossover study was conducted in 12 hospitalized male patients with T2DM (the Japan Diabetes Society criteria of 2010 [9]). Randomization was conducted according to the order of study attendance. Sixteen patients were recruited to the study; but 4 patients could not complete the study due to the violation of the study protocol. Finally, 12 patients (7 patients started with Glu and 5 patients started with Asp) completed the study. Glu or Asp was subcutaneously administered just before standard Japanese-style breakfast (530 kcal: 55% carbohydrate, 20% protein and 25% fat) in the morning. In patients with IIT, insulin dosage of each patient was determined as the ordinary dose of pre-prandial rapid-acting insulin. On the other hand, dosage of insulin was determined as 0.1 unit/kg for patients treated with oral anti-hyperglycemic drugs (OADs). Vials of Glu (Apidra, Sanofi, Paris, France) and Asp (Novorapid, Novo-Nordisk, Copenhagen, Denmark) were purchased with the study grant. Insulin was injected subcutaneously around the periumbilical region of the abdomen using a syringe with a needle of 30 G (BD Lo-Dose™, Becton Dickinson, Franklin Lakes, NJ, USA, catalogue no. 326668) by a diabetes specialist. Sixty min after the breakfast, the patients began aerobic exercise on a bicycle ergometer for 30 min at 50% of maximum heart rate, and then took rest until the end of the study period. Exercise prescriptions were provided to the patients using the Karvonen formula. Blood samples were collected intravenously at 0, 15, 30, 60, 90, 120, 150, 180, 210 and 240 min after the meal. Within 2 to 4 days, the same procedure was repeated using the alternative insulin analogues with the same dosage (Fig. 1). Hypoglycemia was determined as blood glucose level < 70 mg/dL with or without symptoms. All patients gave their written informed consent and the study protocol was approved by the Ethics Committee of Osaka City Juso Hospital. The results were expressed as means ± standard deviation. Paired Student’s t-test and Chi-square test were used to detect the statistical significance of differences, and $p < 0.05$ was considered as statistically significant.

Results

Clinical characteristics of participants enrolled in the study are shown in Table 1. All patients were male, age: $51.9 \pm 11.3$ years; mean duration of diabetes: $4.4 \pm 4.3$ years; BMI: $25.5 \pm 3.9$ kg/m$^2$; HbA1c: $11.2 \pm 2.4$ %; fasting PG: $105.6 \pm 23.2$ mg/dL; and fasting CPR: $1.2 \pm 0.7$ ng/mL. Target heart rate for ergometer exercise was $113.5 \pm 8.9$ bpm. Six patients were treated with intensive insulin therapy, four with OADs, one
Glulisine vs aspart with exercise

Discussion

In the present study, we evaluated postprandial glycemic excursions with single bout of exercise utilizing Glu or Asp. In Asp group, postprandial glycemic excursions with single bout of exercise were significantly lower than those in Glu group. In addition to the negative area under the baseline glucose level in the post-exercise state, a higher frequency of hypoglycemic episodes occurred in Asp group during exercise. These findings support the possible benefit of Glu for patients with high risk of post-exercise hypoglycemia.

Previous reports have confirmed that Glu has a rapid and sharp onset and short duration of action compared with regular human insulin [7]. In addition, Glu has somewhat faster onset of action than Lis [10, 11] and Asp [12, 13] in obese participants with diabetes and healthy volunteers. The amino acid substitution of lysine to glutamic acid at position B29 allows Glu to have a slight faster onset of exposure (21 min for Glu, compared with 32 min for Asp and 31 min for Lis) and shorter mean duration of action (189 min for Glu, 194 min for Asp and 194 min for Lis) [8]. On the other hand, the clinical efficacy of Glu in comparison with other rapid-acting insulin analogues has yet to be established. Bolli et al. reported that Glu was associated with basal insulin plus OADs and one with liraglutide. All the study participants were hospitalized due to their poor glycemic control. Therefore we could not start the study until their plasma glucose levels were stabilized. Exam 1 was started in 17.8 ± 3.3 days after admission. Moreover, to minimize the glycemic effect of single bout of exercise and to equalize the glycemic condition between Exam 1 and Exam 2 in terms of the admission days, the time interval between Exam 1 and Exam 2 was set at 3.7 ± 0.8 days. Fasting plasma glucose level was 105.0 ± 25.1 in Exam 1 and 106.2 ± 25.7 in Exam 2 (p = 0.9052). As a result, we considered it possible to perform Exam 1 and Exam 2 under the same conditions. The average insulin dose applied in the study was 6.9 ± 1.3 units. There was no significant difference between Glu and Asp groups in pre-exercise plasma glucose excursions from baseline (time 0-60 min). However, post-exercise plasma glucose excursions at 90, 120, and 150 min were significantly lower in the Asp group than in the Glu group (p < 0.05, Fig. 2A). Total areas under baseline level of glucose curve during the post-exercise period (from 90 to 240 min) after the meal were 2182.5 mg·min/dL for Glu and -1412.5 mg·min/dL for Asp (p < 0.05, Fig. 2B). Hypoglycemic episodes were observed 7 times in Exam 1 and 6 times in Exam 2. Hypoglycemia occurrence rate was 3 in 70 measurements (4.3%) in glulisine and 4 in 50 measurements (8.0%) in aspart in Exam 1 (p = 0.3921), 1 in 50 measurements (2.0%) in glulisine and 5 in 70 measurements (7.1%) in aspart in Exam 2 (p = 0.2025). According to the insulin regimen, hypoglycemic episodes were observed more frequently in patients treated with Asp (4 times in 3 subjects in the Glu treatment group vs 9 times in 6 subjects in the Asp treatment group, p < 0.0010, Table 2). None of the episodes was symptomatic nor considered as severe as to require assistance from another person. In patients with BMI < 25 kg/m^2 (n = 6), post-exercise plasma glucose levels were significantly lower in Asp group at 90, 120 and 150 min than in Glu group (p < 0.05). However, in subjects with BMI ≥ 25 kg/m^2 (n = 6) the difference was minimal (Fig. 3).

Table 1 Characteristics of patients enrolled in the study (n = 12)

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Total</th>
<th>BMI &lt; 25 kg/m^2</th>
<th>BMI ≥ 25 kg/m^2</th>
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<tr>
<td>N / Sex</td>
<td>12 / all male</td>
<td>6</td>
<td>6</td>
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<tr>
<td>Age (years)</td>
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<td>53.5 ± 9.7</td>
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<tr>
<td>Duration (years)</td>
<td>4.4 ± 4.3</td>
<td>4.8 ± 4.7</td>
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<tr>
<td>Height (cm)</td>
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<td>166.3 ± 6.8</td>
<td>167.6 ± 10.2</td>
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<tr>
<td>Weight (kg)</td>
<td>71.1 ± 12.5</td>
<td>61.4 ± 7.9</td>
<td>80.8 ± 7.5</td>
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<tr>
<td>BMI (kg/m^2)</td>
<td>25.5 ± 3.9</td>
<td>22.1 ± 1.4*</td>
<td>28.8 ± 2.3</td>
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<tr>
<td>HbA1c (%)</td>
<td>11.2 ± 2.4</td>
<td>11.7 ± 2.7*</td>
<td>10.7 ± 2.2</td>
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<tr>
<td>Fasting PG (mg/dL)</td>
<td>105.6 ± 23.2</td>
<td>110.9 ± 29.8</td>
<td>100.3 ± 13.4</td>
</tr>
<tr>
<td>Fasting CPR (ng/mL)</td>
<td>1.2 ± 0.7</td>
<td>1.3 ± 1.0</td>
<td>1.1 ± 0.4</td>
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<tr>
<td>Insulin dose for the study (units)</td>
<td>6.9 ± 1.3</td>
<td>7.0 ± 1.7</td>
<td>6.8 ± 0.9</td>
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</table>

Data are shown as the mean ± SD. IIT, intensive insulin therapy; OADs, oral antihyperglycemic drugs; BOT, basal insulin plus oral agents. *: p < 0.01 vs BMI ≥ 25 kg/m^2.
Fig. 2  (A) Post-exercise blood glucose excursions from baseline at 90, 120 and 150 min were significantly lower in the aspart group than those in the glulisine group ($p < 0.05$). (B) Total glucose areas under baseline level during the post-exercise period (from 90 to 240 min) ($\text{GUB}_{90-240}$) after the meal were 2182.5 mg·min/dL for glulisine and -1412.5 mg·min/dL for aspart. *: $p < 0.05$ vs aspart, #: $p < 0.05$ vs baseline.

Table 2  Comparison of hypoglycemic episodes

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Hypos</th>
<th>Incident rate (%)</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glu 120</td>
<td>4</td>
<td>3.33</td>
<td></td>
</tr>
<tr>
<td>Asp 120</td>
<td>9</td>
<td>7.50</td>
<td>0.010</td>
</tr>
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</table>

Hypoglycemic episodes were observed more frequently in patients treated with Asp (4 times in the Glu treatment group vs 9 times in the Asp treatment group, $p = 0.010$). Hypos: hypoglycemic episodes, Glu: insulin glulisine, Asp: insulin aspart.

Fig. 3  In subjects with BMI$<25$ kg/m$^2$ (n = 6), post-exercise blood glucose levels were significantly lower in the Aspart group (*: $p < 0.05$), while in subjects with BMI $\geq 25$ kg/m$^2$ (n = 6) the difference was not significant.
with lower glucose levels during the first one hr after a standard meal, but the remaining glucose profiles (from 60 to 360 min after insulin injection and standardized meal) were equivalent [12]. Moreover, that study was performed without exercise. In the present study, Glu did not reduce the post-exercise glycemia lower than the baseline plasma glucose level, while it induced fewer hypoglycemic episodes than Asp. Glu is a rapid-acting insulin analogue that mimics the sharp rise of physiological postprandial insulin secretion more closely than regular human insulin and other insulin analogues [14]. In addition, Glu might be applied both pre- and post-meal status, providing patients with more flexibility regarding meal content and timing [15]. In patients with T2DM, multiple trials, including observational studies, have demonstrated that Glu (combined with insulin glargine or OADs) is superior to regular human insulin in terms of glycemic control, patient satisfaction and quality of life. According to the recommended use, patients can safely intensify their basal-bolus regimen without loss of efficacy and increased risk of hypoglycemia.

In the present study, the advantage of Glu in avoiding post-exercise hypoglycemia was shown especially in lean patients. Obesity is frequently associated with T2DM, and insulin resistance associated with obesity is a hallmark of T2DM. Slower absorption of insulin is observed with an increase in subcutaneous fat layer, and insulin sensitivity decreases due to the lipid burden related to increased visceral fat, requiring larger insulin doses in order to achieve sufficient glucose-lowering efficacy [16]. Heise et al. reported in their crossover study that Glu showed a faster onset of action than Lis, independent of BMI and dose [10]. However, they made no mention of shorter duration of action. Obese patients exhibit a considerably lower VO2max relative to body mass [17]. When the same exercise intensity such as VO2max50% is provided, leaner patients can perform a higher intensity aerobic exercise that induces a stronger glucose-lowering effect. Since leaner body composition requires lower insulin secretion, those with leaner body composition are more likely to be required to intensify their external insulin supply.

The pre-exercise glucose excursions of Glu and Asp were similar in the present study, but our findings show an apparent difference with previous reports [12]. We evaluated glucose excursions only every 15 min before starting exercise, so it is possible that we might have failed to detect the peak of glucose excursion precisely. Indeed, the efficacy of faster onset of action with Glu than the other rapid-acting insulin analogues has yet to be established. In addition, no difference has been reported in time to reach peak glucose excursions of Glu and Asp (60 min and 59.5 min, \( p = 0.3328 \)), or in peak value of delta glucose from baseline (33 mg/dL and 40 mg/dL, respectively, \( p = 0.0634 \)) [12]. Another report showed that maximum glucose excursion of Glu and Lis at breakfast was equivalent (3.39 mmol/L and 3.72 mmol/L, respectively, \( p = 0.26 \)) [11]. Our data are compatible with these findings.

It is important to ask whether the ideal dose of rapid-acting insulin was administered in this study. Other studies used a different insulin regimen of 0.15-0.4 units/kg body weight [7, 8, 10, 12, 13]. In our study, the patients were administered the same insulin dose as they were accustomed to receiving every morning if they were treated with IIT, or 0.1 units/kg body weight if they were treated with OADs. Therefore, 7.0 \( \pm \) 1.5 units were injected for patients with IIT and 6.8 \( \pm \) 1.2 units for the other therapies (\( p = \text{NS} \)), whereas body weight was 69.4 \( \pm \) 10.1 kg and 73.5 \( \pm \) 16.2 kg (\( p = \text{NS} \)), respectively. These results suggest that our insulin doses for the study in patients without ITT therapy are acceptable.

In our study, the peak values of delta glucose were 59.3 \( \pm \) 21.7 mg/dL in Glu and 50.7 \( \pm \) 32.4 mg/dL in Asp, respectively (\( p = 0.4535 \)). Relatively lower dose of insulin injection (0.1 unit/kg in our study vs 0.2 unit/kg in Bolli et al. [12]) might have resulted in the higher peak glucose values seen in our study. Nevertheless, we confirmed that the rate of postprandial hypoglycemia after single bout of exercise was significantly lower in Glu than Asp. We conjectured that the shorter duration of action rather than the faster onset of action in Glu was what prevented hypoglycemic episode after the single bout of exercise. The pharmacokinetic and pharmacodynamic differences between Glu and Asp might be reflected in the postprandial state after exercise.

There are some limitations to our study. First, the number of the participants was small. It is necessary to confirm these findings in future studies with a larger number of participants. Second, this is an open-label, single-center study, hence the bias induced by examiners or inclusion bias was not eliminated.

In conclusion, after aerobic exercise, patients with Glu had significantly lower risk of hypoglycemia compared with those with Asp. These beneficial effects were more likely for patients with BMI < 25 kg/m².
Glu may therefore be a suitable choice of short-acting insulin analogue to use just before exercise for its lower risk of post-exercise hypoglycemia in patients with T2DM.

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**Contributions**

NT wrote the manuscript, researched data and contributed to data collection. YH supervised conducting the study.

**Disclosure**

This study was supported by grants for medical research from Osaka City Juso Hospital. The authors declare that they have no conflicts of interest.

**References**