MARMARA
MEDICAL JOURNAL

Original Article

https://dergipark.org.tr/tr/pub/marumj

How does an additional insulin dose for a high-fat, high-protein breakfast affect glysemic response in adolescents with type 1 diabetes?

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Submitted: 29.05.2022 **Accepted:** 13.10.2022

ABSTRACT

Objective: In this study, it was aimed to evaluate the effects of an additional insulin dose for high-fat and high-protein meal on blood glucose levels in adolescents with type 1 diabetes.

Patients and Methods: This study was single-center, crossover, and randomized. Seven adolescents with type 1 diabetes between the ages of 14 and 17 were given breakfast containing high-fat (45.9% energy) and high-protein (21.9% energy) for two consecutive days, and two different insulin doses were administered. According to the first application dose of carbohydrate/insulin ratio, the second application was given this dose of additional insulin up to 30% in postprandial 180th minute. Blood glucose was monitored for 360 minutes at 30-minute intervals using a continuous glucose monitoring system (CGMS).

Results: The average time spent in the target range (TIR) of participants was 30.6±11.83%, and time spent in hyperglycemia and hypoglycemia (time above range (TAR) and time below range (TBR)) were 67.0±14.31% and 2.4±4.89%, respectively. There was no statistically significant difference between the early (0-120th min), late (120-360th min), and total (0-360th min) glycemic responses of the applications (p>0.05). According to CGMS result, mean blood glucose, glycemic variability, and absolute blood glucose difference median and mean absolute deviation (MAD%) were found to be similar after two applications (p>0.05).

Conclusion: Insulin dose applications should be individually calculated to prevent delayed-prolonged postprandial hyperglycemia caused by high-fat high – protein intake in adolescents with type 1 diabetes.

Keywords: Type 1 diabetes, Preprandial insulin, Fat and protein counting, Meal pattern

1. INTRODUCTION

Type 1 diabetes (diabetes mellitus) is defined as a disease resulting from the autoimmune destruction of insulin-producing pancreatic beta cells [1]. Maintaining good glycemic control is extremely important in preventing microvascular and macrovascular complications associated with diabetes in the management of type 1 diabetes, whose prevalence is increasing today. Glycemic control requires insulin therapy, healthy nutrition, controlled carbohydrate intake, balanced meals in terms of macronutrients, regular exercise, and close monitoring [2]. Postprandial hyperglycemia is an important risk factor in the development of diabetes complications. Therefore, providing postprandial blood glucose control is one of the main treatment goals in reducing the risk of complications in individuals with type 1 diabetes [3].

Carbohydrates are the main nutrients that affect the postprandial blood glucose and determine the prandial insulin requirement [4]. Therefore, in the management of diabetes in individuals with type 1 diabetes who receive intensive insulin therapy, algorithms based on the number of carbohydrates in the meal are used to calculate the pre-prandial insulin dose [5, 6]. However, postprandial glycemic excursions can be seen after the consumption of meals with high-fat and high-protein with

How to cite this article: Bayindir Gumus A, Keser A, Sıklar Z, Berberoglu M. How does an additional insulin dose applied for high-fat and high-protein breakfast in adolescents with type 1 diabetes glycemic response? Marmara Med J 2023: 36(2):242-248. doi: 10.5472/marumj.1302393

ISSN: 1309-9469

http://doi.org/10.5472/marumj.1302393
Marmara Med J 2023;36(2): 242-248

insulin dose calculated based on carbohydrate counting [7-10]. Because the consumption of meals with high-fat and high-protein in children and adolescents with type 1 diabetes causes delayed hyperglycemia (which can last up to 3-6 hours after meals) and an increase in insulin requirement. In addition, high-fat and high-protein meals may cause hypoglycemia risk in the early period (1-2 hours) due to delaying gastric emptying and digestion [2]. Therefore, in determining the pre-prandial insulin doses, the effect of fat and protein on blood glucose should be considered in addition to the carbohydrate counting [7, 11, 12]. However, there is no accepted algorithm developed based on the fat and protein content of meals in addition to the amount of carbohydrates in determining the pre-prandial insulin doses. Therefore, it was aimed to evaluate the effect of additional doses of insulin on postprandial blood glucose of adolescents with type 1 diabetes after eating breakfast with high-fat and high-protein in the current study.

2. PATIENTS and METHODS

Place, Time and Sample of the Study

In this study which was carried out between April 2018 and June 2018, 7 adolescents (4 males and 3 females) with type 1 diabetes mellitus for more than a year, whose ages ranged from 14 to 17, were followed up in the Child and Adolescent Endocrine Policlinic of Ankara University. These adolescents who received an intensive insulin therapy (3 times rapid-acting and one long-acting insulin per day), who had insulin requirement > 0.5 kg / U / day, who had carbohydrate counting at least for 6 months, and who had a determined carbohydrate/insulin (C/I) rate were included. Diagnosed with celiac, hyperlipidemia, gastric motility problems, and other complications related to diabetes (neuropathy, nephropathy, retinopathy), exercising 24 hours before test meals, having hypoglycemia or ketoacidosis, overweight or obese (BMI z score for age ≥1SD and ≥2SD), individuals with diabetes who were not in the follicular or periovulatory phase of the menstrual cycle were not included in the study. During the study period, adolescents with type 1 diabetes mellitus and their families who applied to the polyclinic were interviewed by the research team. In these interviews, the research team informed the participants about the process of the study and what they expect from them during this study. As a result of sixty interviews, 16 individuals and their families volunteered, while 7 volunteers who met the inclusion criteria attended.

The study was conducted with the Ethics Committee Approvals of Ankara University Clinic Studies Ethical Committee (18-1163-17) and Turkish Republic Ministry of Health Turkey Pharmaceuticals and Medical Devices Agency (93189304-514.04.01-E.245193).

Study Design

In this randomized and crossover study, the effect of two different insulin doses administered for a high-fat and high-protein breakfast on postprandial blood glucose was evaluated.

Test Breakfast and Insulin Regimes

Adolescents with type 1 diabetes mellitus were given a breakfast containing high – fat (35.6 g; 45.9% energy) and high-protein (38.2 g; 21.9% energy) for two consecutive days (Table I). Their blood glucose was followed for 360 minutes with the continuous glucose monitoring system sensor (CGMS®; Medtronic *i*Pro2 system Northridge, CA, USA). In order to eliminate the effect of other meals on blood glucose, insulin dose was intervened at breakfast [9, 13]. A correction dose was not administered at least 4 hours before breakfast.

Applications were sustained by the research team in the Nutrition Laboratory at the University. Breakfast was prepared by the researchers for each participant separately in the kitchen of this Nutrition Laboratory. On the application days, the participants were made available at 08:45 at the latest, and the breakfast was given at 09:00. Participants were asked to finish breakfast within 20 minutes, not consume food unless necessary for hypoglycemia treatment within 6 hours after consumption, and not to do excessive physical activity, and a suitable environment was provided for this. Their meals other than breakfast were not intervened, and they were informed about their routine nutritional treatment.

Table I. *Content of high-fat and high-protein breakfast*

Test Breakfast	Carbohydrate (g)	Protein (g)	Fat (g)	Energy (kcal)
200 mL whole-fat cow milk	9.4	6	6.6	121
2 whole eggs (fried in sunflower oil)	3.2	12.8	7.2	128.8
2 egg white (fried in sunflower oil)*	0.5	5.9	0.1	26.5
10 mL sunflower oil	0	0	10	90
60 g whole-fat white cheese	2.1	8.4	10.2	133.8
75 g white bread	40.9	5.1	1.5	197.5
Total	56.1	38.2	35.6	697.6
Percentage distribution of energy	32.2%	21.9%	45.9%	

**Nutrients were calculated according to the label information of foods. Data of https://fdc.nal.usda.gov/ was used only for egg white.*

In the first application, the pre-prandial insulin dose calculated according to the individual C/I ratio was administered. In the second application, the insulin dose was determined based on the studies in the international literature [11]. Accordingly, 30% of the insulin dose calculated according to the C/I ratio was applied additionally at the 180th minute, considering the recommendations made for the prevention of hyperglycemia experienced in the 3rd hour after a meal containing high-fat and high-protein. Prandial fast-acting insulin (Lispro) was injected into the area on the arm after the first blood sample was taken 10 minutes before the breakfast.

http://doi.org/10.5472/marumj.1302393
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Postprandial Glycemia and Glycemic Response

Adolescents with type 1 diabetes mellitus were invited the day before the test meal was given and CGMS was implanted subcutaneously in the brachium. The patients were said to apply insulin injection in areas at least 7 cm from CGMS during the study period. In addition, adolescents with type 1 diabetes were asked to record their capillary fasting and pre-sleep blood glucose with their own glucometer for the calibration of CGMS. During the study (6 hours), in addition to the CGMS data, blood glucose measured by the researchers at the beginning and at the 180th minute were recorded with the same glucometer. At the end of the applications, CGMS data were computerized for evaluation. From CGMS data, blood glucose at 13 measurement times between 6 hours every 30 minutes, time in range/TIR (70-180 mg/dL%), time above range (TAR) (>180 mg/dL%), time below range (TBR) (<70 mg/dL%), median absolute relative percent difference (MAD%), and mean blood glucose (mg/dL) were recorded. In addition, using the standard deviation (mg/dL) and standard deviation/mean blood glucose formula, glycemic variability/fluctuation (CV/GV) was calculated.

Statistical Analysis

The quantitative data obtained as a result of the research were expressed as mean ($\bar{x}$), standard deviation (SD), lower and upper values. The compliance of the data to normal distribution was examined with the "Shapiro Wilk test" and the change between the two applications was evaluated with the "Paired-Samples T-test". SPSS 15.0.1 statistical package program was used in the statistical analysis of the data. In the analysis of all hypothesis tests, the level of significance was set as $p<0.05$.

3. RESULTS

A total of 7 adolescents with type 1 diabetes mellitus, 3 girls and 4 boys, with a mean age of 15.3±1.11 years, continuing secondary school (n=3) and high school (n=4) education, participated in the study. Body height and BMI percentiles of adolescents for age were 50.3±15.29 and 63.9±26.69, respectively. Participants level of knowledge about diabetes is shown in Table II. Accordingly, the time in range (TIR) was determined as 30.6±11.83%, and the time spent in hyperglycemia and the time spent in hypoglycemia was 67.0±14.31%, and 2.4±4.89%, respectively during the applications. The mean HbA1c determined in the last outpatient clinic visits of the participants was 8.8±1.06%.

None of the adolescents experienced hypoglycemia during the applications. Mean postprandial blood glucose measured at intervals after the applications are shown in Table III. In both applications, the initial blood glucose was high and the mean blood glucose was above the target range. On the 180th and 210th minutes of the second application, the blood glucose was found to be statistically higher compared to the first application ($p<0.05$). There was no significant difference between the two applications at the other measurement times ($p>0.05$, Table III).

Table II. *Diabetes information of adolescents with type 1 diabetes mellitus*

Characteristics	$\bar{x}$ ±SD (lower-upper)
Age of diagnosis (year)	9.7±3.85 (5.5-14)
Age of diabetes mellitus (year)	5.6±4.36 (1-10.5)
Baseline HbA1c (%)	8.8±1.06 (7.3-10)
TIR (%)	30.6±11.83 (16-50)
TAR (%)	67.0±14.31 (46-84)
TBR (%)	2.4±4.89 (0-13)
Duration of the use of carbohydrate counting method (year)	3.8±2.94 (0.5-9)
Insulin requirement (IU/kg/day)	0.9±0.17 (0.7-1.1)
Proportion of bolus insulin dose in total daily insulin dose (%)	61.3±11.78 (38.9-73.3)
Individual C/I ratio for breakfast	6.8±3.87 (4-15)
Individual insulin sensitivity factor (mg/dL)	37.2±9.14 (29-50)
Insulin dose required for breakfast (IU)	9.7±3.71 (3.7-13.8)

TIR: time-in-range, TAR: time-above-range, TBR: time-below-range, C/I: Carbohydrate insulin ratio.

http://doi.org/10.5472/marumj.1302393
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Table III. *Mean postprandial blood glucose measured at intervals after the applications*

Postprandial Blood Glucose (mg/dL)							
Minute intervals	**First application**	**Second application**	**p***	**Minute intervals**	**First application**	**Second application**	**p***
	$\bar{X}$ ±SD	$\bar{X}$ ±SD			$\bar{X}$ ±SD	$\bar{X}$ ±SD	
Baseline	232.4±37.00	230.4±42.00	0.923	210	185.4±39.93	214.9±45.13	0.040**
30	237.9±25.75	235.0±46.79	0.906	240	179.4±44.49	196.9±47.87	0.118
60	243.4±30.81	238.1±50.34	0.843	270	172.3±49.10	180.6±52.27	0.454
90	231.9±30.47	241.4±44.93	0.687	300	187.43±68.71	167.0±52.92	0.447
120	218.7±22.49	243.6±40.70	0.195	330	169.7±42.77	154.8±41.42	0.277
150	205.0±25.34	237.7±39.77	0.056	360	176.7±37.31	166.0±36.94	0.441
180	193.1±30.85	231.0±42.6	0.023**				

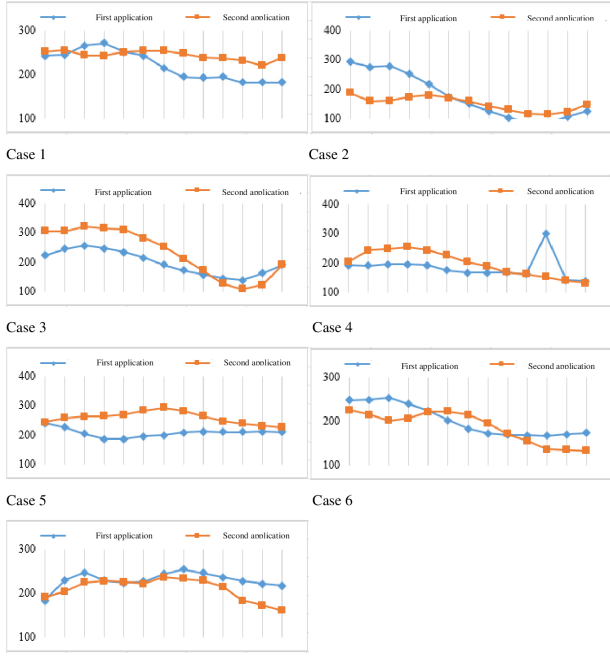
**Paired-Samples T test **p<0.05*

When the glycemic responses of participants to breakfast after different doses of insulin were examined, no significant difference was determined between the two different applications in terms of early, late and total glycemic responses (p>0.05). Mean blood glucose, glycemic variability, and MAD determined, based on CGMS data were found to be similar on the application days (p>0.05, Table IV). However, it was observed that blood glucose responses differ individually after consumption of high-fat and high-protein breakfast, and the additional dose of insulin administered for fat and protein at the 180th minute reduced hyperglycemia in four individuals (Figure 1).

Table IV. *Glycemic responses of adolescents with type 1 diabetes mellitus after two different applications*

Glycemic Responses (mg/dL*min) (AUC)	First application	Second application	p*
	$\bar{X}$ ±SD	$\bar{X}$ ±SD	
Early glycemic response (0-<120 min)	28161.4±3109.54	28545.0±5384.82	0.889
Late glycemic response (120-360 min)	44120.0±8717.92	46430.0±9679.40	0.416
Total glycemic response (0-360 min)	71830.0±7301.48	74765.0±13630.20	0.553
MBG (CGMS) (mg/dL)	195.1±43.13 (116-246)	198.1±41.10 (150-267)	0.841
CV/GV (CGMS) (%)	27.0±11.99 (9.4-44)	28.9±10.13 (13.4-46.7)	0.531
MARD (CGMS) (%)	14.7±10.00 (3.5-33.3)	26.0±26.79 (4.6-83.4)	0.274

**Paired-Samples T test, AUC: area of under the curve, MBG: mean blood glucose, CV/GV: glycemic variability/fluctuation, CGMS: continuous glucose monitoring system, MARD: median absolute relative percent difference*



** Vertical lines indicate 30-minute intervals.*

Figure 1. *Individual blood glucose monitoring results of adolescents with type 1 diabetes*

4. DISCUSSION

It was aimed to evaluate the effect of an additional 30% insulin dose calculated according to the individual C/I ratio for the breakfast with high-fat and high – protein on the postprandial blood glucose. The last measured mean HbA1c of the participants was 8.1±1.11% (Table II). According to the International Society for Pediatric and Adolescent Diabetes Clinical Practice Consensus Guidelines (ISPAD) [2], it is suggested that the

http://doi.org/10.5472/marumj.1302393
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HbA1c of type 1 diabetes patients should be kept below 7%. In addition, it is stated that with the inclusion of continuous blood glucose measurement systems in diabetes management, the glycemic control should not be evaluated only with the HbA1c, but also with the TIR, TAR, and TBR [14, 15]. Especially, the TIR was found to be associated with chronic complications of diabetes, and in the Diabetes Control and Complications Study (DCCT), a relationship was detected between the percentage of TIR, TAR, and the risk of developing diabetic retinopathy and microalbuminuria [16, 17]. In individuals with type 1 diabetes, the targets are TIR (70-180 mg/dL) >70%, TAR (181-250 mg/dL) <25%, (>250 mg/dL) <5% and TBR (54-70 mg/dL), <4%, (<54 mg/dL) <1% [18]. In this study, the mean TIR, TAR, and TBR of adolescents were determined as 30.6±11.83%, 67.0±14.31%, and 2.4±4.89%, respectively (Table II). These results show that in addition to the HbA1c, TIR and TAR ratios of participants are also high. Especially, the mean TAR was remarkably above the recommended range. Independently from HbA1c, this result points out that the blood glucose levels are above the normal range in times that are not measured from capillary blood. On the other hand, it may be difficult to reach glycemic goals due to reasons such as frequent meals outside the home, missing an insulin injection, skipping meals, not sharing diabetes management with their parents, sleeping until late hours, which are common behaviors in adolescence [2, 19]. The fact that adolescents with good diabetes management could not be reached in this study is the most important limitation of the study.

As a result of the study, it was determined that breakfast with high-fat and high – protein showed individual efficacy in terms of late postprandial glycemia. Blood glucose excursions of adolescents after consuming high-fat and high-protein breakfast were clearly different from each other (Figure I). Studies in both adolescents and adults show that meals with high-fat and high-protein delay postprandial hyperglycemia and reduce early postprandial response [9, 10]. In the study of Smart et al., it was found that when both fat and protein were included in the meal, there was a significant increase and delay in the postprandial glycemic response, and the raise lasted longer [9]. In another study, high-protein meal resulted in hyperglycemia with the peak level at 3.5 hours and continued for 5 hours postprandial, while high-fat meal caused early hyperglycemia that reached the peak at 2 hours then declined within 5 hours. The results showed that the protein and fat contents of meals affect the timing and values of the peak blood glucose as well as the duration of postprandial hyperglycemia [20]. In this study, similar to the blood glucose response of participants towards high-fat, high-protein breakfast, both the peak glucose time and the peak glucose level of the patients were obviously different from each other (Figure I). According to the results of the study by Keating et al., the total mean insulin requirements of adolescents with type 1 diabetes mellitus for the high – protein and high-fat meal were significantly greater almost than for the low protein and low-fat meal [21]. These results, similar to our study, prove that high protein and high fat content meals definitely cause an increase in blood glucose levels and require additional bolus insulin doses in type 1 diabetes. This situation may have various reasons. For instance, dietary fats and free fatty acids cause increased glycemic response and prolonged blood glucose peak time by delaying gastric emptying and digestion, reducing insulin sensitivity, and increasing hepatic glucose levels [2, 9, 22]. Also, protein causes delayed hyperglycemia through increased glucagon secretion and gluconeogenesis [9]. These explain why meals with high – fat and high-protein increase the insulin requirement. However, the biggest problem in this issue is that how many additional insulin doses are required for high-protein high-fat meals, and when should these additional insulin doses be applied.

In this study, the test breakfast was given to the participants and blood glucose was monitored for 360 minutes continuously. According to this, it was found that only the blood glucose measured at the 180th and 210th minutes between the two applications was statistically different, and blood glucose was significantly lower on the first application ($p<0.05$) (Table III). This result shows that the additional insulin application did not completely exhibit the expected effect on blood glucose. One of the most important reasons for this result is that additional insulin application was not responsible for the high levels at this minute, since the additional dose of insulin was administered at the 180th minute. The fact that the blood glucose was already high at the 180th minute on the day of the additional dose of insulin may explain the increase in the next measurement, which was the 210th minute measurement. At this point, the closure of the significant difference between the two applications with additional insulin doses, especially between 240-360 minutes, suggests that the additional dose of insulin may have an effect on delayed postprandial hyperglycemia. It also shows that the amount of fat and protein in meals should be taken into account in the calculation of the prandial insulin dose. However, the lack of significant difference between the two insulin applications in early, late, and total glycemic responses, the similar mean CGMS values (blood glucose, glycemic variability, and median absolute relative percent difference) also create a contradiction (Table IV). This may be due to the fact that the participants had high initial blood glucose on the application days and they did not use the continuous subcutaneous insulin infusion, and the additional insulin dose was administered as bolus rather than as spreading. The reason for delayed and prolonged postprandial hyperglycemia after meals with high-fat and high-protein is especially the administration of insufficient doses of insulin [23]. While there is no common recommended consensus regarding the calculation of the pre-prandial insulin dose and the time of administration when a mixed meal is consumed, some researchers give some recommendations based on their clinical experience [9, 10, 24-26]. One of these suggestions is to increase the prandial insulin dose by 30-35% and to give this dose by spreading or dividing in various combinations [24]. In another study, it was stated that for a meal with high-fat and high-protein, up to 65% of the prandial insulin dose can be added [25]. One of the most important recommendations to be taken into account is that the glycemic response to fat and protein may differ individually and therefore the prandial bolus dose should be calculated individually based on postprandial glucose monitoring for up to

http://doi.org/10.5472/marumj.1302393
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6 hours [10]. Exactly at this point, the results of our study also support these data. Considering the individual variability of the blood glucose response to a high-fat and high – protein breakfast, it indicates that it may be more appropriate to determine the additional dose according to the individual response. Therefore, Figure 1 clearly shows the differences in glycemic response after consumption breakfast with high – fat and high-protein. In new algorithms for excursions in postprandial glucose caused by high fat and high protein-containing meals, it is recommended that the additional insulin dose that is calculated for fat and protein in the meal should be given as spreading [27]. However, the results of the studies conducted and the fact that this application causes clinically significant hypoglycemia is accepted as a limitation of this method [11, 13, 27]. In this study, it should be kept in mind that the effects of different fat and protein types on blood glucose may be different, as may be the reason why the expected effects of additional doses of insulin as a bolus were not observed. There are studies showing that animal protein has a greater effect on postprandial glycemic response [28, 29]. Also, it has been reported that saturated fatty acids increase postprandial blood glucose more than unsaturated fatty acids by decreasing insulin sensitivity and thus increasing HbA1c [30, 31]. Thirteen individuals with type 1 diabetes using insulin pumps participated in the study investigating that the type of fat in meals with high and low glycemic index affects the postprandial blood glucose response. In the randomized controlled study, postprandial blood glucose after consuming a meal with olive oil was significantly lower compared to blood glucose after consuming a low-fat and butter meal ($p<0.0001$) [30]. In this study, sunflower oil rich in unsaturated fatty acids was used as visible oil in test breakfast. Therefore, it may be important and necessary to consider the source of fat and protein as well as the amount of fat and protein in the meal in calculating the prandial insulin dose.

Calculating the prandial insulin dose by considering the amount of fat and protein in addition to the number of carbohydrates in the meal in individuals with type 1 diabetes may affect the postprandial glycemic response. However, postprandial blood glucose should be monitored continuously and individually for at least 6 hours in order to determine the effect of a meal with high-fat and high-protein on blood glucose and increased insulin requirement. For this reason, it is an important requirement that children and adolescents with type 1 diabetes and people responsible for their care be educated at regular intervals by creating a common language with a specialist diabetes team. Within the scope of this training, it should be emphasized that especially the importance of adequate and balanced nutrition and the consumption frequency and number of foods with high fat should be reduced as much as possible. In addition, further studies with more participants are needed to be conducted to determine the additional insulin dose applied for observing effects of high-fat and high-protein meals on glycemia in adolescents with type 1 diabetes mellitus.

Strengths of the study: Participants were followed for 6 hours to observe the long-term effects of high-fat and high-protein breakfast on their blood glucose in the study. During these applications, their blood glucose values were continuously monitored by using the sensor. Depending on the sensor results, not only their blood glucose but also their parameters such as TIR, which have recently become a criterion in the metabolic control of diabetes, were evaluated.

Limitations of the study: There are some limitations to the study. Firstly, in this study, a prandial 30% additional dose was not applied. In order to compare the effects of different additional insulin regimens on blood glucose applied for the high-fat and high-protein, this application should be added. Secondly, data of anthropometric measurements and body composition of the adolescents would have been guided the interpretation of the results. However, these parameters should be questioned in future studies. Finally, we believe that the food consumption and physical activity records of adolescents should be taken and determined. However, in this study, none of the participants were amateur or professional athletes. It was ensured that physical activity was minimized only during the study.

Compliance with Ethical Standards

Ethical Approval: This study was conducted in accordance with the Helsinki Declaration and was approved by Ankara University Clinic Studies Ethical Committee (18-1163-17) and Turkish Republic Ministry of Health Turkey Pharmaceuticals and Medical Devices Agency (93189304-514.04.01-E.245193). All the participants and their parents were informed about the study and their verbal and written consent was obtained.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: This research was funded by Ankara University Scientific Researches Projects (Project No. 18L0241003).

Authors' Contributions: ABG and AK: Study design, data analysis, writing the article, ABG, AK, and ZS: Data collection, AK, ZS, and MB: Supervision. All authors read the article and approved the final version of the article.

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