Official Title of the study: Comparison of Carbohydrate Counting and Food Insulin Index Methods in the Determination of Insulin Doses for High-and Low-Glycemic Index Meals in Adolescents with Type 1 Diabetes

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1. Background

Type 1 diabetes is an autoimmune disease characterized by chronic hyperglycemia resulting from an absolute endogenous insulin deficiency. In type 1 diabetes management, premeal insulin dosage and physiological insulin requireme0nt must be matched to maintain optimal blood glucose control (1). Intensive insulin therapy is the preferred treatment for individuals with type 1 diabetes. It can be an effective way of controlling blood glucose levels and minimising the risk of long term diabetic complications (2, 3). Insulin delivery is achieved subcutaneously using multiple daily injections or subcutaneous insulin infusion using insulin pumps. It provides the calculation of insulin doses according to the carbohydrate content of the meal and pre-meal blood glucose levels. It can also provide a less restricted lifestyle to individuals with type 1 diabetes by providing flexibility in meal time, quantity and frequency (4, 5).

Achieving glycemic control is important for patients with diabetes because it effects the development of diabetic complications. Diabetes control is mainly assessed according to HbA1c, fasting blood glucose and blood glucose measured two hours after meal consumption. In the control of type 1 diabetes, not only regular use of insulin is sufficient, but also important in balanced diet and regular physical activity. An individualized diet plan in particular is the corner-stone to proper metabolic control (6).

Currently, there are algorithms based on the carbohydrate content of the meal to calculate the meal insulin dose in patients with type 1 diabetes receiving intensive insulin therapy. One of these algorithms, the carbohydrate counting method (CC), is considered the "gold standard" for estimation of meal-time insulin dose. CC assumes that only carbohydrates influence the dose of insulin required and that equal portions of carbohydrate produce a similar glycemic response and require the same amount of exogenous insulin to be metabolized (7, 8). However, the effects of carbohydrates in food on increasing blood glucose levels are not equal and this concept is defined as glycemic index (GI). Studies have shown that GI is also a parameter affecting blood glucose level (9). The GI value of the food together with the CC provides the most accurate estimation of the insulin response in determining the meal insulin dose (7, 8, 10). Despite the use of insulin therapy and CC in individual with type 1 diabetes, many individuals continue to experience unanticipated hyperglycaemic and hypoglycaemic events that increase the risk for development of complications and reduce quality of life. These complications occur especially after a high-protein or high-fat meal is consumed. Although carbohydrate is the predominant macronutrient affecting postprandial blood glucose level, recent research has shown that dietary fat and protein can significantly affect the postprandial glucose excursions and thus adjusting the prandial insulin dose for these macronutrients may be beneficial (10-13).

Food Insulin Index method (FII), which is another method used to determine meal insulin dose, has been proposed which ranks foods based on the insulin response in healthy subjects relative to an isoenergetic reference food (either glucose or white bread) (14). The algorithm uses food energy as the constant, and thus all dietary components and their metabolic interactions can be considered for any food with sufficient energy density, allowing a holistic approach to determining insulin demand. It has shown that FII is more advantageous than CC in the control of postprandial blood glucose levels in people with type 1 diabetes especially after high fat and

protein meal (1, 8, 12, 13, 15). In addition, it was found that there was a correlation between meal insulin dose calculated according to FII and observed insulin response (1).

In summary, it is important to maintain blood glucose levels within the normal range in individuals with type 1 diabetes. In order to achieve this, the insulin demands of the foods consumed in the meal must be estimated accurately. Today, CC method is used in the calculation of meal insulin dose. GI is also known to affect blood glucose levels. Knowing the GI of foods together with CC provides the most accurate estimate of insulin response. However, the CC is insufficient to calculate the insulin dose, especially for high-fat or high-protein meals. It has been shown that the newly developed FII method which determines insulin demand by using energy of nutrients is advantageous compared to carbohydrate counting method in keeping blood glucose levels within normal range. However, studies have not evaluated the effect of GI on blood glucose levels when comparing CC and FII method.

2. Objective

The aim of this study is to compare the impact of carbohydrate counting (CC) method which is standard insulin dose calculation algorithm and food insulin index (FII) method which is a new algorithm on postprandial glucose following high fat and high protein meals with different GIs in adolescent with type 1 diabetes.

3. Materials and methods

3.1. Study Design

A home-based, randomized, single-blind and crossover trial included 14 adolescents aged 14-18 years with type 1 diabetes. All participants were sent to their homes for 4 consecutive days with a different glycemic index breakfast. The insulin doses of the meals were calculated according to CC and FII methods. Test breakfasts with different GIs and insulin requirements calculated with different algorithms are as follows: High GI calculated by CC (CHGI), low GI calculated by CC (CLGI), high GI calculated by FII (FHGI) and low GI calculated by FII (FLGI). The order of the test meals and insulin algorithms was determined by using a computer-generated randomization sequence before recruitment. The test diets prepared by the dietitian were given to the participants by the diet company before the test day. Test meals were served as a breakfast after 8-hours fasting and participants were asked to consume the meal in full, within 20 min. The breakfast plates were collected and weighed after the test day. On the day before each test meal, participants were instructed to eat an evening snack meal at 22:00 h and to refrain from eating and/or drinking (except for water) and/or doing any physical activity beyond that of their typical daily activities. Participants started to consume test meals at 07.00 h. They were asked not to consume any food other than breakfast for postprandial 240 min. Participants maintained their normal activity levels during the study days. The classification of meals according to insulin dose calculation methods is shown in the Figure 1.

This study was conducted according to the guidelines laid down in the Declaration of Helsinki. The Clinical Research Ethics Committee of the Erciyes University approved the protocol (2018/607) on 21 November 2018, and all participants gave written informed consent.

3.2. Participants

All participants underwent a detailed physical examination by the pediatric endocrinologist before included in the study. Fourteen adolescents with type 1 diabetes who attended the outpatient clinic of the Pediatric Endocrinology, at the Child Hospital of Erciyes University, Kayseri, Turkey were selected on the basis of the following criteria: aged between 14-18 years adolescents, type 1 diabetes diagnosed for at least one year (1, 8, 11, 14-16), performing self-monitoring of blood glucose and doses of insulin at least four times daily (17, 18), HbA1c ≤ 9.6% for the last three months (19), negative fasting C-peptide (<0.1 nmol/L) (20), total daily insulin use of ≥ 0.5 U/kg (19), World Health Organization BMI/age z-score of -1 to below 3 (21). Exclusion criteria included complications of diabetes or other medical conditions including celiac disease (11, 13), treatment with oral hypoglycaemic agents (11), food allergies, intolerances, or eating disorder (1, 8, 17), intestinal malabsorption (22), delayed gastric emptying (20), viral or bacterial infection, physical or mental disability (22, 23), clinical condition related to impaired digestive system such as cystic fibrosis (19, 22).

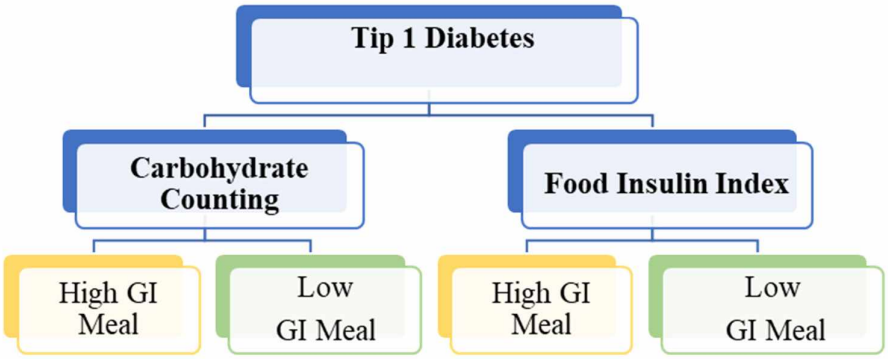

Figure 1. The classification of meals according to insulin dose calculation methods

3.3. Test Meals

The energy content of the test meals was calculated according to the recommended energy requirement for adolescents between the ages of 14-18 in Turkey's Dietary Guidelines. In addition, according to the principles of adequate and balanced nutrition, breakfast meals should meet 1/4-1/5 of daily energy requirement (24, 25). Therefore, the energy of the test meals was determined about 560 kcal. The energy, carbohydrate, protein, fat and FII of the test meals were the same; GI were different. The participants were given 75 ml of whole milk, 22 g hot dog, 60 g cheddar cheese, 75 g white bread and 8 g seedless raisins for breakfast with high glycemic index; 30 g Ezine cheese, 65 g boiled eggs, 13 g peanut, 20 g whole grain bread, 55 g apple, 185 g strawberry yogurt and 100 ml skimmed milk for breakfast with low glycemic index. The energy and macronutrient composition of the test meals is given in the Table 1.

GI and FII of foods in test meals were estimated by using the GI and FII for 1000-kJ portions of foods tables published by Bao et al. (26), with glucose as the reference food. The average meal GI and FII were calculated as follows (27):

$$\text{Meal GI} = \frac{\sum_{a=1}^{n} \text{GI}_a \text{ x } \text{AvCHO}_a \text{ x } \text{Frequency}_a}{\sum_{a=1}^{n} \text{AvCHO}_a \text{ x } \text{Frequency}_a} \quad \text{Meal II} = \frac{\sum_{a=1}^{n} \text{II}_a \text{ x } \text{Energy}_a \text{ x } \text{Frequency}_a}{\sum_{a=1}^{n} \text{Energy}_a \text{ x } \text{Frequency}_a}$$

	Meal with high glycemic index	Meal with low glycemic index
Total energy (kcal)	555	561
Carbohydrate (g)	61.8	61.6
Carbohydrate (%)	45	45
Protein (g)	22.6	22.3
Protein (%)	17	17
Fat(g)	23.1	23.3
Fat (%)	38	38
Glycemic Index	64	35
Food Insulin Index	45	45

Table 1. The energy and macronutrient composition of the test meals

3.4. Calculation of insulin dose of test meals:

The insulin dose of the meals was calculated by 2 different methods.

3.4.1. Carbohydrate Counting

Insulin carbohydrate ratio (ICR) was determined for each participant. The participant's individualized ICR, expressed as insulin units per 15 g carbohydrate portion, was used to calculate insulin dose (28, 29).

3.4.2. Food Insulin Index

Insulin dose was calculated from the Food Insulin Demand (FID). The FID is the mathematical product of the FII and the energy content (kJ) per serving divided by 1000 (FID = FII x kJ per serving/ 1000). The FID was scaled up by a factor of 100/59 (FID of 1000 kJ of pure glucose/grams of carbohydrate in 1000 kJ of pure glucose) so that insulin could be dosed in the same ratio as each participants' individualized ICR (1, 11)

4. Measurement of blood glucose

Postprandial glycemia was measured for 240 min with both continuous glucose monitoring and glucometer. Participants attended the clinic prior one day of the study for insertion of CGM (Medtronic iPro2) (11). CGM data was download and reviewed after completion of the study. Capillary blood testing was performed just before breakfast (t=0 min) and at time points 30, 60, 90, 120, 150, 180, 210 and 240 min after the meal with glucometer (Accu-Check Performa Nano) (8, 11). Participants were also required to keep these blood glucose values.

Hypoglycaemic event, defined as a blood glucose level drop to < 3.9 mmol/l (30), confirmed on fingerstick. Data was excluded for the times after the participant had a hypoglycaemic event for the rest of the study period (11).

5. Anthropometric measurements

Body height and weight were measured using an automatic height gauge scale (DENSI GL150, Istanbul, Turkey) sensitive to 10-200 kg±50 g and 90-200 cm±1 mm. The measurements were made with the participants in the minimum clothing possible, without shoes, standing barefoot, keeping shoulders in a relaxed position, arms hanging freely and head in the Frankfort horizontal plane (31). BMI was calculated as weight (kg) divided by the square of height (m^2) (31), and converted age- and sex-specific z-score according to WHO criteria (32).

6. Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (version 22.0; IBM SPSS Statistics) software. Data were expressed as the number (n) and percentage (%) for categorical variables, and means ± SDs, medians (25th-75th percentiles) for continuous variables. Normality was assessed using the Shapiro- Wilk test. Furthermore, continuous variables were examined for skewness and kurtosis, and log-transformed before analysis and reported back-transformed geometric means (G) ± standard error (S.E) when required (33). Differences between groups were tested using t-tests. The blood glucose profile during the 4-h postprandial period was quantified as area under the curve (AUC) calculated according to the trapezoidal rule. A one-way repeated measure was used to analyse between the comparable test conditions. For all statistical analyses, p values less than 0.05 were considered to have statistical significance (8).

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