Official Title of the study: Effect of Food Insulin Index on Metabolic Parameters in Obese Adolescents

NCT number: NCT ID not yet assigned

Document Date: 2 October 2015 (The date on which the uploaded document was approved by a human subjects protection review board.)

This study was supported by the Scientific and Technological Research Council of Turkey with a project number of 116S069.

1. Background

Obesity is one of the major public health problems in the world, and adolescence is a critical period in the development of obesity [1]. Adolescent obesity has been shown to reduce health-related quality of life and to be associated with a range of health related problems, including pre- and type 2 diabetes [1,2]. It is also well known that the high body mass index seen during the adolescence tracks substantially to adulthood [1]. Therefore, treatment of obesity in the adolescence is important in terms of both protecting the existing health and preventing the diseases in the adulthood. However, little is known about the optimal dietary approach for weight loss in obese adolescents, particularly those at risk of developing type 2 diabetes. The traditional treatment approach focuses on reducing energy intake by decreasing fat and increasing carbohydrates, but this option may not be appropriate to treat obese adolescents with insulin resistance (IR). It is speculated that this diet may lead to higher levels of postprandial glycemia and/or insulinemia and may increase IR, a potential role in the development of type 2 diabetes [2]. Furthermore, restrictive dieting may be problematic during growth and development. Thus, dietary interventions that modulate appetite and food consumption may offer alternative approaches for reducing energy intake [3].

In individuals at risk of developing type 2 diabetes, diets leading to excessive insulin secretion may increase oxidative stress and accelerate the progression of beta-cell failure [4]. Carbohydrates are the major stimulus for insulin secretion, and the glycemic index (GI) is a concept to provide the most accurate prediction of likely insulin response after consuming carbohydrate-containing foods. Recently, the role of carbohydrate quality as assessed by GI in obesity management especially for individuals with a compensatory increased insülin secretion has received considerable attention [1,2]. High-GI foods may lead to impaired balance between hormones acting in appetite stimulation (such as ghrelin) and suppression (such as incretins), thus resulting in reduced satiety and obesity. Moreover, high-GI diets, due to the rapid blood glucose and insulin response following consumption, may stimulate reduced satiety and increase voluntary energy intake [1]. Additionally, the rapid increase in postprandial plasma insülin is presumed to result in chronic stimulation of the hunger accompanied by hyperinsulinemia and lipogenesis [5]. Although carbohydrates are the major stimulus for insulin secretion, it is not the only one. Dietary proteins and fats also elicit a significant insulin response, and when combined with carbohydrates, they play a synergistic role in increasing insulin levels and reducing glycemia [2,4]. The new concept of the food insulin index (FII) allows for the testing of foods with low or no carbohydrate content, since the measure of comparison is energy as opposed to carbohydrates for the GI. For the calculation, the observed insulinemic response (area under the curve, AUC) to consumption of a 1000 kJ (239 kcal) portion of the test food divided by the insulinemic response after ingestion of a 1000 kJ portion of the reference food (either glucose or white bread) [4]. The FII concept, which directly quantifies the postprandial insulin response to a test food in comparison with an isoenergetic portion of a reference food, has been suggested to be more suitable than GI in evaluating conditions related to insulin exposure, such as obesity [6].

Nevertheless, few studies have been conducted to elucidate the role of FII in obesity. In a study investigating the effect of dietary GI and FII on body composition, it was demonstrated that a

higher dietary FII during puberty (9-14 years for girls and 10-15 years for boys) was associated with a higher percentage of body fat in young adulthood (18-25 years), although dietary GI during puberty was not related to body composition in young adulthood [7]. That study suggests a prospective adverse influence of increased insulinemia rather than increased glycemia on body composition [7]. Furthermore, a recent study has shown that diets with low insulin demand may reduce energy intake and may hence assist with weight loss in obese adolescents with IR [2]. However, the effect of FII on short-term hunger, satiety or voluntary energy intake has yet to be seen. On the other hand, single food studies found the FII as a better predictor of observed insulin responses than the carbohydrate content or GI. However, it has been yet unknown whether the FII in the context of realistic mixed meals can affect the postprandial glucose and insulin responses in obese adolescents with IR.

2. Objective

The aim of this study was to determine whether the FII could affect postprandial metabolic responses and appetite sensations in obese adolescents with IR, consuming two different test meals that had similar macronutrient content and GI but a 2-fold difference in FII.

3. Materials and methods

3.1. Study design

This was a randomized, single-blind, crossover clinical trial conducted on 2 separate days, with a 1-week washout period between each study day [8]. All participants were randomly submitted to two different test meals with the following similar glycemic index (GI) and different food insulin index (FII) amounts: a low GI and low FII (LGI-LII) content, and a low GI and high FII content (LGI-HII). The order of the test meals was determined by using a computer-generated randomization sequence before recruitment. Test meals were served as a breakfast after 12-hours fasting and participants were asked to consume the meal in full, within 15 min. Venous blood samples were collected just before breakfast (t=0 min) and at time points 15, 30, 45, 60, 90, 120, 180 and 240 min after the meal [9]. Visual analogue scale (VAS) ratings were measured at the same time points, and 4 h after the breakfast, an *ad libitum* buffet-style lunch was served to each participant [10]. The primary outcomes were postprandial responses of serum glucose, insulin and C-peptide. Subjective appetite assessment were the secondary outcomes. The study design was summarized in 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 (2015/451) on 2 October 2015, and all participants gave written informed consent.

3.2. Participants

Twenty two obese adolescents with IR 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 12-18 years, age- and sex-specific body mass index (BMI) ≥95th percentile of the growth-reference data, new diagnosis and not receiving any treatment, and HOMA-IR >3.16. Exclusion criteria included hypertension, cardiovascular

disease, diabetes mellitus or any other significant metabolic, endocrine or gastrointestinal disease, use of tobacco or alcohol, taking any medications, and having difficulties for physical activity.

3.3. Clinical evaluation

All participants underwent a detailed physical examination by the pediatric endocrinologist before included in the study. Obesity was defined according to the BMI (weight in kg/height in m^2) ≥95th percentile of the WHO 2007 growth-reference for 5-19 years [11,12]. IR was assessed through Homeostatic Model Assessment for IR (HOMA-IR) which is a valid tool for evaluating IR in children and adolescents [13]. This index was calculated as follows: HOMA-IR = [fasting insulin level (μU/mL) × fasting glucose level (mmol/L)] / 22.5 [14]. HOMA-IR>3.16 was used as a threshold for IR [15]. Furthermore, pubertal maturation was determined using Tanner-Marshall descriptive standards by the pediatric endocrinologist [16,17]. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by aneroid sphygmomanometer in the sitting position after 10 min of rest [18].

3.4.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 [19]. Waist, hip and neck circumference were measured to the nearest 0.1 cm using a non-elastic tape with the participants standing, with the face directed towards, shoulders relaxed, and the tape was positioned at a level parallel to the floor. Waist circumference was measured at the end of normal expiration and the measurement site was midway between the lowest rib and the top of the iliac crest. Hip circumference was measured at the widest part of the hip at the level of the greater trochanter [19]. Neck circumference was measured with the their head held erect, eyes facing forward and the neck in a horizontal plane at the level of the most prominent portion of the thyroid cartilage [20]. All measurements were done in duplicate for each participant. If the two measurements differed by more than 1%, a third measurement was taken. All three measurements were recorded and the mean of the two nearest measures was calculated [21]. BMI was calculated as weight (kg) divided by the square of height (m^2) [19], and converted age- and sex-specific z-score according to WHO criteria [12].

Body fatness was estimated by the bio-electrical impedance analysis method, by a segmental body composition analyser (BCA), Tanita BC-418MA (Tanita Corporation, Tokyo, Japan) [22]. Before the analysis, participants were asked to refrain from food or drink in the four hours prior to measurement, and to wear light clothes [19]. Participants stood with bare feet over the analyzer holding handgrips in each hand. The segmental BCA shows separate body mass readings for body fat (BF, kg), trunk fat (TF, kg), fat free mass (FFM, kg) and muscle mass (MM, kg). Also, body water (BW, kg) and basal metabolic rate (BMR, kcal) was determined by the BCA.

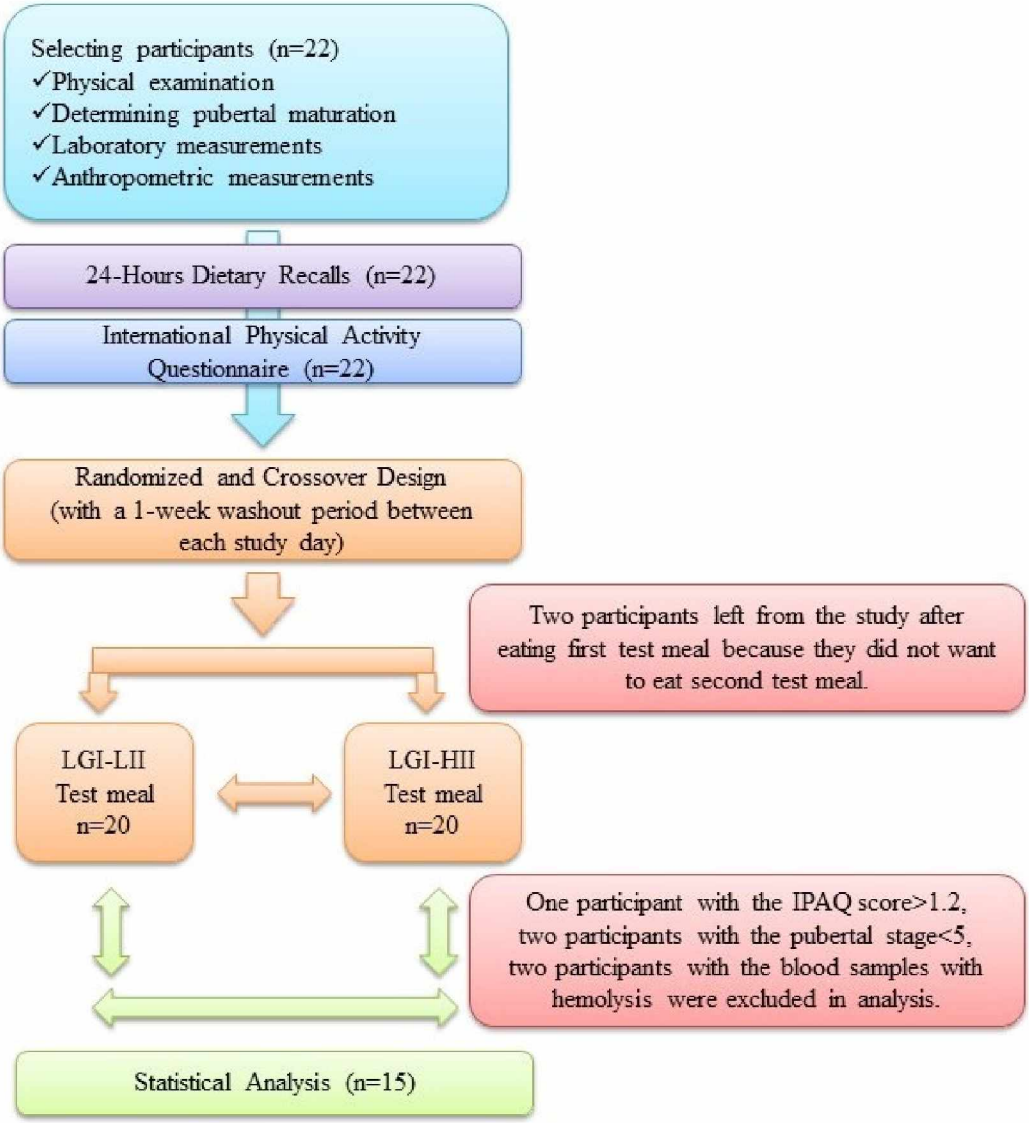

Figure 1. The study design

3.5.Dietary and physical activity assessment

Participants' dietary intakes were assessed by the 24-hours dietary recalls using a photographic atlas of food portion sizes to quantify the data in the beginning of study and on the day of each meal test [8,23]. Diet composition was analyzed by the BeBiS Nutrition Information System software version 7.2 [24]. This database contains Turkish food composition tables for all foods.

Physical activity level was evaluated by the IPAQ short form, a validated survey instrument [25]. The 7-item IPAQ records self-reported physical activity in the last seven days [26]. Responses were converted to Metabolic Equivalent Task (MET) minutes per week according to the IPAQ scoring protocol [26].

3.6.Study protocol

At the first visit, clinical, nutritional and physical activity evaluations were performed. Visits 2 and 3 were the test days. Participants received each test meal in a randomly assigned order on two different mornings separated by a washout period of 1-week when they were asked to maintain their usual diet and physical activity [27]. On the day before each test meal, participants were instructed to eat a standard evening meal at 20:00 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 [28]. Moreover, female participants were tested within the follicular phase of their menstrual cycle (3–10 d after onset of menses) to avoid any effect of menstrual cycle phase on appetite [29-31].

On the each testing day, participants arrived in the testing room at 08.00 h following a 12-h fast and were asked by the dietitian to record their 24-h food and beverage consumption. Participants' body weight, height, body composition and baseline appetite were measured before eating the test meal [8]. Also, a catheter was introduced in an antecubital vein by a registered nurse and a first blood sample was immediately drawn for baseline measurements (time zero) [32]. At 08:30 h participants received the test meal blinded to its nutritional characteristics and were asked to consume within 15 min [9,33]. During the postprandial period, participants remained at rest in the testing room and blood samples were obtained at time points 15, 30, 45, 60, 90, 120, 180, and 240 min [9]. Appetite scale was applied at the same time points [10]. Moreover, participants were asked to assess the organoleptic characteristics (visual appeal, smell, taste, aftertaste and palatability) of test meal by VAS at 15 min (immediately after consuming test meal) [34]. No food or drink other than water was allowed following consumption of the test meal until the ad libitum lunch. Water was available ad libitum throughout the first trial; however, the volume consumed was measured and the participants drank the same volume during the second trial [35,36]. Participants were permitted to watch movies, read, or play with electronic devices (laptop computer, mobile phone etc.) or undertake other similar sedentary activities throughout each study day but were not allowed to sleep [10,28,37].

At 240 min after the test breakfast, participants were presented with an *ad libitum* lunch following blood sample collection and appetite sensation measurement [28,38]. Participants selected from a buffet-style meal consisting of a variety of foods from each food group (meatballs, chicken nuggets, pasta with tomato sauce, potatoes salad, carrots salad, yoghurt, white bread, grain bread, cookies, apple, mandarin and banana) [27,28,39] with bottled water and some fruit juices (black cherry juice and peach juice) as a beverage [29,40]. These foods were determined according to their preference for adolescents to consume, frequent consumption in the Central Anatolia region, and be widely preferred in similar studies. During the lunch, participants were left alone in a quiet room with controlled lightning and ambient room temperature, and asked to consume whatever they wanted and to eat until they felt comfortably full [28,38]. Foods were weighted or measured to the nearest 0.1 g before consumption, and any remaining food was reweighed to determine intake at lunch. Energy and macronutrient values were calculated using The National Food Composition Database (TurKomp) [41] and manufacturer labelling. Moreover, the first food to start eating, all foods

selected by participants, and duration of meal were recorded at lunchtime. All foods served at breakfast and lunch were prepared by the research dietitian in the kitchen of the Nutrition Laboratory in the Faculty of Health Sciences, Erciyes University, Kayseri, Turkey on the day of each test meal.

3.7.Test meals composition

Test meals were matched for macronutrients and GI but had a 2-fold difference in FII. The nutritional composition and weight of the test breakfasts was shown in 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. [42], with glucose as the reference food. The average meal GI and FII were calculated as follows [6]:

$$\text{Meal GI} = \frac{\sum_{a=1}^{n} (GI_a \times AvCHO_a \times Frequency_a)}{\sum_{a=1}^{n} (AvCHO_a \times Frequency_a)}. \quad \text{Meal II} = \frac{\sum_{a=1}^{n} (II_a \times Energy_a \times Frequency_a)}{\sum_{a=1}^{n} (Energy_a \times Frequency_a)}.$$

where n is the number of foods consumed, GI_a is the GI for food a, II_a is the II for food a, $AvCHO_a$ is the available carbohydrate content per serving of food a, $Energy_a$ is the energy content per serving of food a, and $Frequency_a$ is the consumption frequency of one serving of food a during the meal.

Table 1. Nutritional composition, GI, and FII of the component foods in test meals

	Weight (g)	**Energy (kJ[kcal])**	**AvCHO*** **(g)**	**Protein (g)**	**Fat (g)**	**GI (%)**	**FII (%)**
LGI-LII							
Grain bread	25	217(52)	9.6	2.4	0.4	50	41
Egg (boiled)	42	246(59)	0.0	5.4	4.2	0	23
Milk (full-fat)	210	550(131)	10.4	6.0	7.1	31	24
Breakfast cereal	40	597(143)	23.9	5.4	2.4	30	23
Apple	200	469(112)	24.9	0.9	0.9	36	43
Total		**2079(497)**	**68.8**	**20.2**	**15.1**	**35**	**30**
LGI-HII							
Grain bread	18	157(38)	6.9	1.7	0.3	50	41
Cheddar cheese	22	373(89)	0.0	5.6	7.5	0	33
Yogurt (low-fat strawberry)	350	1383(330)	54.0	13.8	6.9	31	84
Banana	45	146(35)	8.0	0.3	0.1	52	59
Total		**2059(492)**	**68.8**	**21.4**	**14.8**	**35**	**70**

*AvCHO, available carbohydrate including sugars and starch, excluding fiber.

3.8.Laboratory measurements

Fasting blood glucose (FBG), insulin, total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride (TG), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured after a 12-h fast. Biochemical parameters were determined by using enzymatic kits from Roche Diagnostics with a Roche Cobas® 8000 modular analyzer series. On test days, approximately 2 mL of blood were drawn for each time points (0, 15, 30, 45, 60, 90, 120, 180 and 240 min) to determine serum glucose, insulin and C-peptide levels. Blood samples after collecting were immediately centrifuged and assayed. Serum glucose was measured by a spectrophotometric method (Roche Cobas® 8000 Modular Analyzer Series, c701 module), and serum insulin and C-peptide by a electrochemiluminescence immunoassay (ECLIA) method (Roche Cobas® 8000 Modular Analyzer Series, e602 module) using Roche kits (Roche Diagostics, Mannheim, Germany).

3.9.Assessment of appetite sensations

Subjective assessment of appetite sensations was performed by using a visual analogue scale (VAS) composed of lines (of 100 mm in length) with words anchored at each end, expressing the most positive and the most negative rating [34]. VAS was used to assess appetite scores (hunger, fullness, desire to eat, and prospective food consumption), desire for specific food types (sweet, salty, savoury, and fatty) and the palatability of test meals (visual appeal, smell, taste, aftertaste, and palatability). As shown in Figure 2, a series of VAS were administered using the paper-and-pen method at specific time-points (immediately before and after consuming test meal, and thereafter at 30, 45, 60, 90, 120, 180 and 240 min for 4 hours) during the examination period. Participants were asked to make a single vertical mark at the appropriate point between the 2 anchors on each scale corresponding to their feelings. A new VAS booklet was provided to participants for each rating time, and nobody could compare to his/her previous ratings when marking the VAS. Appetite scores were quantified by measuring the distance in millimeters between the left end of each line and the mark [8]. The questions on appetite, desire for specific food types and palatability of test meals, and anchored answers were as follows [34]:

- Hunger, "How hungry do you feel?" (not at all hungry – as hungry as I ever felt).
- Fullness, "How full do you feel?" (not at all full – totally full).
- Desire to eat, "How strong is your desire to eat?" (very weak – very strong).
- Prospective food consumption, "How much do you think you can eat?" (no food at all – a large amount of food).
- Desire for specific food types, "Would you like to eat something sweet/ salty/ savoury/ fatty?" (No, not at all – Yes, very much)
- Palatability of test meals, "How is the visual appeal/ smell/ taste/ palatability of test meal?" (Good – Bad), and "Is there any perceived taste in your mouth after test meal?" (Much – None)

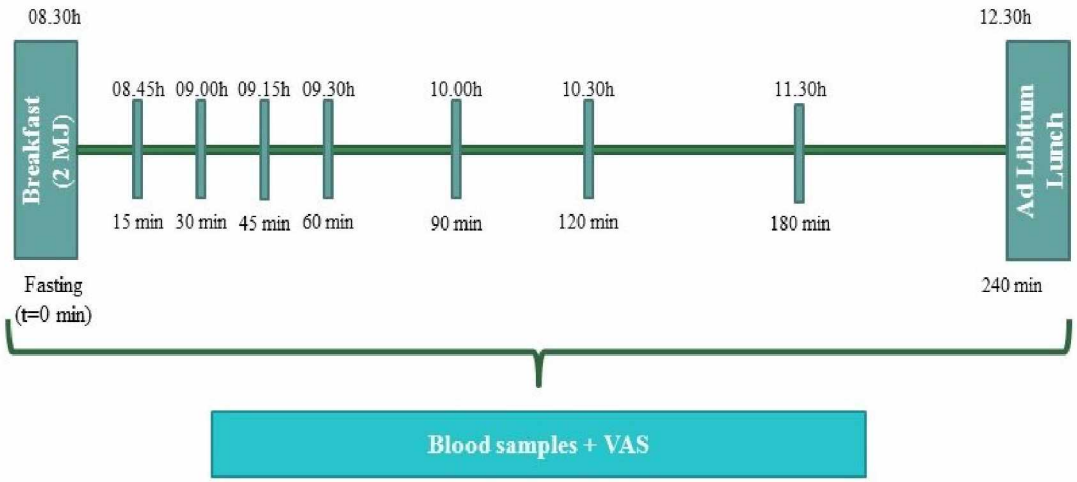

Figure 2. Study protocol on test days

4. Statistical Analysis Plan

4.1. Sample size and power analysis

Preliminary study was carried out to determine a sample size, and power analysis was conducted by using PASS 11 (power analysis statistical system). A power-based sample size calculation revealed that 16 participants were needed to provide 80% power to detect 5% difference between groups in areas under the curve (AUC) assessed after consumption test meals with similar GI and different FII amounts in obese adolescents with IR. It was decided to complete the study with 20 participants considering 25% losses. However, this study was concluded with 15 participants although 22 participants were recruited. Two enrolled participant declined to eat second test breakfast after consuming first test breakfast. One participant with the IPAQ score >1.2 was excluded from the study because of a decision about including only sedentary participants defined as scoring ≤1.2 on the IPAQ due to a possible effect of physical activity level on postprandial metabolic response [35]. Moreover, two participant at Tanner stage 3 or 4 were excluded due to a decision about including only participants completed pubertal maturation at Tanner stage 5 for the purpose of minimizing a possible effect of puberty on postprandial metabolic response since hormonal regulation may vary in each pubertal stages [7]. Finally, two participant were not included to the analysis of data because of hemolysis in their blood samples at some time points, leaving a total of 15 participants that were assessed for the main outcomes. When power analysis was repeated, that sample size had 81.2% power to detect differences in primary outcomes among the test meals at alpha level of 0.05.

4.2. Data 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 histogram and normal Q-Q plots, and also 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 [43]. Differences between groups were tested using t-tests. Categorical variables were compared by the chi-square tests. Wilcoxon signed rank tests were used for continuous variables without normal distributions. Postprandial responses for metabolic parameters and appetite sensations were quantified as area under the curve (AUC) calculated according to the trapezoidal rule [8,33]. As an estimate of glucose-adjusted insulin response, the index of insulin response to glucose was calculated as an insulin/glucose ratio by using serum glucose and insulin levels at time points [9]. A Student's 2-tailed t test for paired data was applied to determine statistical differences between AUCs. In addition, between-group comparisons were analyzed by using 2-factor (diet x time) repeated-measures analysis of variance (ANOVA), and Bonferroni post hoc tests were applied to significant group x time interactions. Baseline values for each variable were compared between groups by using paired t tests. In the event of a significant t statistic, baseline values were used as a covariate in the 2-factor repeated-measures ANOVA. For all statistical analyses, p values less than 0.05 were considered to have statistical significance [44].

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