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High-energy breakfast based on whey protein reduces body weight, postprandial glycemia and HbA_{1C} in Type 2 diabetes

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Abstract

Acute studies show that addition of whey protein at breakfast has a glucose-lowering effect through increased incretin and insulin secretion. However, whether this is a long-term effect in Type 2 diabetes is unknown. Fifty-six Type 2 diabetes participants aged 58.9±4.5 years, BMI 32.1±0.9 kg/m^2 and HbA_{1C} 7.8±0.1% (61.6±0.79 mmol/mol) were randomized to one of 3 isocaloric diets with similar lunch and dinner, but different breakfast: 1) 42 g total protein, 28 g whey (WBdiet, n=19); 2) 42 g various protein sources (PBdiet, n=19); or 3) high-carbohydrate breakfast, 17 g protein from various sources (CBdiet, n=18). Body weight and HbA_{1C} were examined after 12 weeks. All participants underwent three all-day meal challenges for postprandial glycemia, insulin, C-peptide, intact glucagon-like peptide 1 (iGLP-1), ghrelin and hunger and satiety scores. Overall postprandial $AUC_{glucose}$ was reduced by 12% in PBdiet and by 19% in WBdiet, compared with CBdiet (P<.0001). Compared with PBdiet and CBdiet, WBdiet led to a greater postprandial overall AUC for insulin, C-peptide, iGLP-1 and satiety scores, while postprandial overall AUC for ghrelin and hunger scores were reduced (P<.0001). After 12 weeks, HbA_{1C} was reduced after WBdiet by 0.89±0.05% (11.5±0.6 mmol/mol), after PBdiet by 0.6±0.04% (7.1±0.31 mmol/mol) and after CBdiet by 0.36±0.04% (2.9±0.31 mmol/mol) (P<.0001). Furthermore, the participants on WBdiet lost 7.6±0.3 kg, PBdiet 6.1±0.3 kg and CBdiet 3.5±0.3 kg (P<.0001). Whey protein-based breakfast is an important adjuvant in the management of Type 2 diabetes.

Keywords: Whey; Breakfast; Protein; Weight; Diabetes

1. Introduction

Postprandial hyperglycemia and elevated glycemic excursions are associated with high HbA_{1C} and increased cardiovascular risk in Type 2 diabetes [1]. Therefore, for Type 2 diabetes individuals, diet should focus on the reduction of postprandial glycemia and the hyperglycemic peaks across the day. There is also evidence that postprandial glycaemia displays a diurnal variation with a more prolonged and higher glycemic response to an identical meal in the evening *vs.* the morning [2–4]. In addition, substantial evidence shows that high protein (>35 g) intake especially at breakfast, reduces overall daily postprandial glycemia and glycemic excursions [5–7].

We have recently reported that a diet with high-energy and high-protein content at breakfast (42 g protein) with medium-sized lunch and low-energy dinner reduces overall postprandial glycaemia in obese [3,8] and in Type 2 diabetes individuals [4]. Moreover, significant reduction in HbA_{1C} was achieved in Type 2 diabetes individuals that followed this schedule during three months [9]. Notably, the reduction in overall postprandial hyperglycemia was associated with a significant increase in insulin and glucagon-like peptide−1 (GLP-1) responses after breakfast, lunch and dinner, suggesting a daylong effect of the high-energy and protein breakfast [4,10]. High-energy, high-protein-based breakfast was more efficient in achieving weight loss, enhancing postprandial satiety and suppression of ghrelin and hunger after breakfast and subsequent meals [3,8].

Recently it has been suggested that in addition to the amount of protein, the quality and its source are important for reduction of postprandial glycemia and for other protein-stimulated metabolic effects. [11]. In fact, several acute studies have shown that whey protein exerts a greater postprandial glucose-lowering effect compared with other protein sources, such as soy, fish, gluten, eggs, casein, in healthy [12–16] and Type 2 diabetes individuals [17,18]. However, the long-term effect of whey protein consumption on overall daily postprandial glycemia has not been explored and, furthermore, only few studies addressed the long-term effect of whey on HbA_{1C} levels in

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Type 2 diabetes [19]. We, therefore, examined whether a high-energy, protein breakfast containing whey leads to a greater weight loss and reduction of overall postprandial glycemia and HbA_{1C} compared to isocaloric diet with a different source of protein or carbohydrates at breakfast for 12 weeks in Type 2 diabetes subjects.

2. Materials and methods

2.1. Study population

The study population initially included 56 individuals, 26 men and 30 women, with Type 2 diabetes<20 years and glycated hemoglobin (HbA_{1C}) levels of 7–9% (53–75 mmol/mol), aged 30–70 years, with a body mass index (BMI) of 26–34 kg/m^2, with negative urinary microalbumin test and estimated glomerular filtration rate (GFR) >60 ml/min. None had impaired thyroid, renal or liver function, anemia, pulmonary disease, psychiatric, immunological, neoplastic diseases or severe diabetes complications or underwent bariatric surgery. All participants were insulin-naive and patients taking oral hypoglycemic agents other than metformin were excluded. Anti-hypertensive, lipid-lowering medication and vitamins were allowed. Subjects treated with anorectic drugs, steroids and patients with known hypersensitivity to milk components were excluded as were individuals with >4.5 kg body weight change within the last 6 months. The study was approved by the institutional Helsinki Ethics Committee and written informed consent was obtained from each participant. The study start date for recruiting participants was November 2013 and continued until October 2014. The study was registered in ClinicalTrials.Gov (NCT01944449).

2.2. Study design

This was a randomized, open-label, parallel-arm clinical trial over 12 weeks (90 days) in Type 2 diabetes individuals comparing the effects of three isocaloric diet interventions with different composition, amount and source of protein at breakfast. Participants were recruited from the outpatient clinic at the Diabetes Unit in the Hospital de Clinicas Caracas, Venezuela, and were randomized to the three diet groups by a person not involved in the study using a raffle. The three diet interventions had the same meal-timing schedule and energy distribution consisting of high-energy and protein breakfast (660±25 kcal), medium-sized lunch (560±20 kcal) and low-energy dinner (280±15 kcal). Therefore, the only difference among the three diet groups was the source and amount of protein at breakfast: (1) whey protein breakfast diet (WBdiet) group (n=19, 8 males, 11 females) contained at breakfast 25% fat, 50% carbohydrates and 25% (42 g) protein of which 28 g are whey; (2) protein breakfast diet (PBdiet) group (n=19, 9 males, 10 females) contained at breakfast 25% fat, 50% carbohydrates and 25% (42 g) protein mainly from eggs (7 g), tuna (20 g), soy (7 g); (3) carbohydrate breakfast diet (CBdiet) group (n=18, 9 males, 9 females) contained at breakfast 25% fat, 64% carbohydrates and 11% (17 g) soy protein. The composition of lunch in the 3 diets was 29% fat, 48% carbohydrates and 23% protein. The composition of dinner in the 3 diets was 38% fat, 31% carbohydrates and 31% protein. The protein source for lunch and dinner was chicken, meat, fish or turkey. Lunch and dinner did not include dairy foods. The diet plan was calculated for a daily caloric intake of 1500 kcal. However, the daily caloric intake for each participant was obtained by subtracting 500 kcal from the calculated Harris Benedict Equation, in order to achieve progressive weight loss. In those cases that the recommended caloric intake was over 1500 kcal, the extra calories were added by 75% to the lunch and 25% to dinner. This was to avoid changing the experimental conditions of breakfast. The participants were provided with proper food replacement choices for each food item to allow variation, with the exception of whey protein that was consumed in WBdiet group every day at breakfast during all the diet period. The consumption of milk or milk products (i.e., yogurt, cheese) was allowed only in the WBdiet. Those assigned to WBdiet were provided every 2 weeks with bottles containing 35 g/bottle of whey protein. The whey protein was 80% non-hydrolyzed concentrate (Protein Food Products, La Victoria, Venezuela). The participants returned the empty bottles in the following visits for the assessment of compliance. The participants were asked to eat breakfast between 6:00 and 8:30, lunch between 12:30 and 14:30 and dinner between 18:30 and 20:30. A dietician assisted the participants before starting the diet and every 2 weeks. During the study, the participants recorded dietary intake 3 days during each week. Those participants with non-compliance of >3 days per week were withdrawn from the study. Participants were asked to avoid alcohol and maintain their usual physical activity. During 12 weeks of diet intervention, body weight was assessed bi-weekly in the clinic, together with the dietician consultation. HbA_{1C} was measured at the beginning and end of the diet intervention. The primary outcome was the overall postprandial hyperglycaemia during the three meal challenges. The secondary end-points were the change in body weight, waist circumference and HbA_{1C} after 12 weeks (90 days) and assessment of all-day postprandial plasma insulin, C-peptide, intact GLP-1 (iGLP-1), ghrelin, and satiety and hunger VAS scores in three test days.

2.3. Breakfast, lunch, and dinner meal challenge

During the diet intervention between the third and fifth week, all participants underwent three separate all-day meal challenge in the clinic, testing the WBdiet, PBdiet and CBdiet groups randomly, with 4–6 day wash-out period between test days. The test meals were provided in the clinic as breakfast at 08:00 h, lunch at 13:30 h and dinner at 19:00 h. The energy and content of all test meals had the same macronutrients, energy content and composition as the diets. Patients were asked not to take antidiabetic medication during the test days. Anthropometric data were collected in the morning. At 07:30, a catheter was placed in the antecubital vein of the non-dominant arm and remained in place until 22:00. Venous blood samples were collected just before breakfast at 8:00 (t=0 min) and at 30, 60, 120, and 180 min after eating commenced. The same procedure was repeated after lunch at 13:30 and dinner at 19:00.

2.4. Appetite questionnaires

Appetite scores for hunger and satiety were assessed during the three meal challenges, using 100-mm visual analogue scales (VAS) before and 30, 60, 120 and 180 min after breakfast, lunch and dinner. The participants by means of 2 visual analogue scale (VAS) questions that described hunger and satiety, were asked to make a single vertical mark on each scale somewhere between the 0 and 100 mm extremes (i.e., not at all hungry to very hungry) to indicate their feelings at that time-point.

2.5. Biochemical and hormonal blood analyses

Plasma glucose was immediately analyzed on Olympus AU 2700 analyzer (Beckman Coulter, Brea, CA, USA). Serum and plasma EDTA tubes for insulin and C-peptide were left on ice for 30 min. Blood samples for determining iGLP-1 were collected into chilled tubes containing EDTA, aprotinin and diprotin A (0.1 mmol/l). Samples were centrifuged at 3000 rpm at 4°C for 10 min and stored at −80°C. Insulin and C-peptide were determined by electrochemiluminescence using Cobas 601 Roche Diagnostics (Madison, WI, USA) analyzer according to the manufacturer's instructions. Plasma iGLP-1 was quantified using ELISA (Millipore, Billerica, MA, USA). Plasma ghrelin (total) was measured with an enzyme immunoassay kit (Phoenix Pharmaceuticals, Belmont, CA).

2.6. Sample size and power analysis

With a sample size of 45 participants (15 in each diet group), the present study provided 80% power to detect 5% difference between-group in overall postprandial plasma area under the curve (AUC) for iGLP-1, insulin, glucose, C-peptide and ghrelin. To allow discontinuation, 56 participants were recruited.

2.7. Statistical analyses

Fifty-six subjects were enrolled in the study. Eight subjects dropped out and were excluded from the analyses. The results are based on n=48 subjects. AUCs (0–180 min) were calculated by the trapezoidal rule and were used as an estimate of response to meal consumption. The results are expressed as mean±S.E.M. For time series, a 2-way analysis of variance (ANOVA) (time×diet) was performed and a least-significant difference t test post hoc analysis was used for comparison between the diets at each time-point. A student's t test was used for comparing AUC at different time intervals. In addition, a Multivariate ANOVA for repeated measurements was performed assessing between and within subjects effects for diet and time. P≤.05 was considered statistically significant. Statistical analysis was performed with JMP software (version 11, SAS Institute Inc. Cary, NC, USA).

3. Results

3.1. Participants

Fifty-six individuals with Type 2 diabetes were enrolled and randomized to WBdiet (n=19), PBdiet (n=19) and CBdiet (n=18). Eight individuals dropped out (2 of WBdiet, 3 of PBdiet and 3 of CBdiet) due to poor ability to follow meal timing and dietary instructions. Results were analyzed based on 48 completers (22 males, 26 females). These patients were 59.0±0.7 years old, had controlled Type 2 diabetes with mean duration of 10.5±0.4 years, HbA_{1C} of 7.8±0.05% (61±0.3 mmol/mol) and BMI of 32.11±0.1 kg/m^2 (Table 1). Twenty patients were treated with diet alone and 28 were treated with diet and metformin. Seventeen patients had a history of hypertension and were treated with angiotensin-converting-enzyme (ACE) inhibitors and/or calcium channel antagonists.

3.2. Effect of WBdiet, PBdiet and CBdiet on glucose

The mean fasting plasma glucose decreased over 12 weeks in all 3-diet groups. However, the greatest reduction by 11% (0.73±0.06 mmol/mol) was achieved in the WBdiet compared with PBdiet and CBdiet [−6.5% (−0.43±0.06 mmol/mol) and −1.8% (−0.12±0.04