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Original article

Effects of 6 *vs* 3 eucaloric meal patterns on glycaemic control and satiety in people with impaired glucose tolerance or overt type 2 diabetes: A randomized trial☆

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A B S T R A C T

Background/objectives. – The study aimed to compare the effects of two eucaloric meal patterns (3 *vs* 6 meals/day) on glycaemic control and satiety in subjects with impaired glucose tolerance and plasma glucose (PG) levels 140–199 mg/dL at 120 min (IGT-A) or PG levels 140–199 mg/dL at 120 min and >200 mg/dL at 30/60/90 min post-oral glucose load on 75-g OGTT (IGT-B), or overt treatment-naïve type 2 diabetes (T2D).

Subjects/methods. – In this randomized crossover study, subjects with IGT-A ($n = 15$, BMI: 32.4 ± 5.2 kg/m^2), IGT-B ($n = 20$, BMI: 32.5 ± 5 kg/m^2) or T2D ($n = 12$, BMI: 32.2 ± 5.2 kg/m^2) followed a weight-maintenance diet (45% carbohydrates, 20% proteins, 35% fats) in 3 or 6 meals/day (each intervention lasting 12 weeks). Anthropometrics, diet compliance and subjective appetite were assessed every 2 weeks. OGTT and measurements of HbA1c and plasma lipids were performed at the beginning and end of each intervention period.

Results. – Body weight and physical activity levels remained stable throughout the study. In T2D, HbA1c and PG at 120 min post-OGTT decreased with 6 *vs* 3 meals ($P < 0.001$ *vs* $P = 0.02$, respectively). The 6-meal also intervention improved post-OGTT hyperinsulinaemia in IGT-A subjects and hyperglycaemia in IGT-B subjects. In all three groups, subjective hunger and desire to eat were reduced with 6 *vs* 3 meals/day ($P < 0.05$). There were no differences in HOMA-IR or plasma lipids between interventions.

Conclusion. – Although weight loss remains the key strategy in hyperglycaemia management, dietary measures such as more frequent and smaller meals may be helpful for those not sufficiently motivated to adhere to calorie-restricted diets. Our study shows that 6 *vs* 3 meals a day can increase glycaemic control in obese patients with early-stage T2D, and may perhaps improve and/or stabilize postprandial glucose regulation in prediabetes subjects.

1. Introduction

Type 2 diabetes (T2D) is one of the most important public-health concerns worldwide; according to the International Diabetes Federation (IDF), one in 10 adults will have T2D by 2040 [1]. Impaired glucose tolerance (IGT) represents the continuum between normal glucose tolerance and overt T2D. Interestingly, early lifestyle interventions can decrease the incidence of T2D by >70% and also the development of cardiovascular complications [1–3].

Medical nutrition therapy (MNT) is an integral component of diabetes prevention and management [3]. One of the nutritional strategies used in MNT is meal frequency, the number of daily meals consumed, and macronutrient distribution [3]. There are studies suggesting that more frequent meals increases weight gain due to fat deposition after meals [4,5], thereby increasing hyperglycaemia, hyperinsulinaemia, blood lipids and appetite [5–9]. In contrast, others support the idea that frequent meals could reduce body weight and normalize indices of glycaemic

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control (postprandial plasma glucose, insulin, lipid concentrations) [10].

Epidemiological [11,12] and clinical studies—both short-term with no caloric restriction [10,13–21] and long-term with caloric restriction [7,22]—have produced contradictory results regarding the association of meal frequency with indices of glycaemic control and T2D risk. From an epidemiological perspective, men consuming 1–2 meals *vs* 3 meals a day had a 25% greater risk of developing T2D in a 16-year follow-up [11], whereas meal frequency was not associated with T2D in women with a 6-year follow-up [12]. From a clinical perspective, two brief (2-day) crossover trials both showed that more frequent meals improved glucose metabolism in T2D [13,16]. In contrast, a short-term trial with no energy (calorie) restriction and lasting 8 weeks found no significant effects of consuming more meals per day on glucose metabolism [21]. Likewise, results from two long-term clinical trials with energy restriction and durations of 3–6 months were also contradictory: one study showed that fewer eucaloric meals/day (2 *vs* 6) decreased body weight, fasting plasma glucose (FPG), C-peptide and glucagon, with no differences in insulin, HbA1c, insulin sensitivity and blood lipids in patients with T2D taking antidiabetic drugs [7]; the other study showed that more eucaloric meals/day (6 *vs* 5) reduced body weight and HbA1c, with no differences in fasting and postprandial plasma glucose, insulin and blood lipids in treatment-naïve patients with T2D.

However, it is well known that antidiabetic agents have an impact on body weight and glucose/lipid metabolism [23], making it difficult to determine whether the beneficial (weight-loss) effects are due to the medications, energy deficits or meal frequency. In addition, no long-term studies have investigated the impact of meal frequency without caloric restriction on indices of glycaemic control in people with IGT or treatment-naïve T2D. Thus, our present study was designed to evaluate the effects of long-term 6- *vs* 3-meal eucaloric eating patterns on indices of glycaemic control and satiety in obese subjects with either IGT or T2D on a weight-maintenance diet. Our hypothesis was that the 6-meal pattern would improve glucose regulation in these subjects.

2. Materials and methods

2.1. Subjects

Our study participants were recruited from the outpatients unit of Attikon University Hospital, and their initial assessment included a detailed history, and full clinical and biochemical examination (within the month prior to the study), as per the routine clinical practice. Study inclusion criteria were: (a) 2-h plasma glucose (PG) concentrations >140 mg/dL after a 75-g oral glucose tolerance test (OGTT); (b) body mass index (BMI) 30–45 kg/m^2; and (c) age 19–65 years. Exclusion criteria were: previous lifestyle-modification interventions (structured dietary plans and/or exercise weight-loss programmes); antidiabetic drug treatment; kidney, liver or cardiovascular disease; haematological abnormalities; hyper- or hypothyroidism; cancer; and mental disorders. Based on OGTT PG results, participants were divided into three groups: (i) IGT-A (PG levels 140–199 mg/dL at 120 min post-OGTT); (ii) IGT-B (PG levels 140–199 mg/dL at 120 min and >200 mg/dL at 30, 60 or 90 min post-OGTT); and (iii) newly diagnosed treatment-naïve T2D.

The study was registered on ClinicalTrials.gov as number NCT02248272. Its protocol and potential risks and benefits were fully explained to each participant before their written consent was obtained. The protocol was also approved by the Ethics Committee of Attikon University Hospital, and was carried out in accordance with the Declaration of Helsinki (1997).

2.2. Study design

The study had a randomized crossover design, and subjects were assigned to the interventions using computer-generated random number sequences. A researcher not involved in the collection or analysis of the scientific data was responsible for randomization of the participants to each meal-pattern intervention. Subjects followed a weight-maintenance diet (45% carbohydrates, 20% proteins, 35% fats) consumed as either 3 or 6 meals/day. Each meal pattern was adhered to for 12 weeks. Meals were defined as eating occasions providing >150 kcal in the morning ('breakfast'), at midday ('lunch') and in the evening ('dinner'). Snacks were defined as eating episodes of <150 kcal consumed at times other than specific meal times. Carbohydrate distribution was 20% at breakfast, 50% at lunch and 30% at dinner for the 3-meal intervention *vs* 20% at breakfast, 10% at morning snack, 30% at lunch, 10% at afternoon snack, 20% at dinner and 10% at bedtime snack for the 6-meal intervention [24].

Daily energy (calorie) requirements for each participant were calculated using the Schofield equation [25]. All participants then received dietary plans that were eucaloric in macronutrient composition, with guidance on which foods to consume and how to prepare meals. Table 1 presents an example of a 1900-kcal diet with 3- *vs* 6-meal patterns of food distribution. Changes were proposed, along with nutritional education sessions, to encourage compliance with the interventions, which was determined from food records and structured interviews. All volunteers were asked to be consistent with mealtimes throughout the intervention. Those reporting alcohol intakes were advised not to drink more than 1 unit/day of alcohol, defined as one small glass of wine, a half-pint of ordinary strength beer or a single measure of spirits, during the intervention. No participant was following a vigorous exercise programme at baseline, and all were asked to maintain their usual physical activity levels throughout the intervention.

2.3. Dietary and physical-activity assessments

At baseline, dietary habits were assessed through a semi-quantitative food frequency questionnaire (FFQ) to assess any likely nutritional differences prior to being assigned to a specific dietary regime. The FFQ evaluated each participant's dietary quality, using the MedDietScore, which assesses adherence to a Mediterranean-like dietary pattern, as previously defined elsewhere [26]. The score ranges from 0 to 55, with higher values indicating greater adherence to the Mediterranean diet.

All participants were asked to record the type and amount of all foods and beverages consumed daily during the intervention; these records were reviewed by dieticians every 2 weeks. For each 12-week intervention, five 7-day food diaries were used to check compliance with the dietary plan. Detailed instructions were given on how to record the quantity of food consumed, using standard household weights and measures. The dieticians also checked the food diaries for any misreporting and, when necessary, used food models and photographs to clarify discrepancies in portion sizes, with dietary adjustments made accordingly. Finally, these food records were analyzed using Diet Analysis Plus version 6.1 software (ESHA Research Inc, Salem, OR, USA), with extensive modifications to the database to include new foods and recipes.

At each clinical visit, subjects completed 10-point visual analogue scales (VAS) to record their subjective feelings of hunger, satiety and desire to eat over the previous 2-week period. During these evaluations, participants were not asked to be in a fasting state, but were instead advised to follow their meal patterns according to their assigned intervention arm. In addition, the participants' physical activity was assessed through a short validated questionnaire [the Athens Physical Activity Questionnaire (APAQ)]

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