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Original Article

The effect of a low carbohydrate energy-unrestricted diet on weight loss in obese type 2 diabetes patients – A randomized controlled trial

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SUMMARY

Background & aims: Trials assessing the effectiveness and safety of the Atkins diet for weight loss in obese diabetic patients are limited and adherence is problematic. The current trial compared an Atkins-like diet to a conventional ADA-recommended diet over a one year period.
Methods: 52 type 2 diabetes patients, aged 35–75, BMI 30–39.9 kg/m^2, HbA1c > 7%, treated by diet or oral medication, were initially placed on a DASH diet for one month, then randomly assigned to a modified Atkins diet (ATK) with unrestricted calorie intake or a standard American Diabetes Association (ADA) calorie-restricted diet. Weight, fasting blood glucose, lipid profile, blood pressure, and microalbuminuria were measured at baseline and after 1.5, 3, 6 and 12 months, and compliance with the diets was assessed.
Results: Similar weight loss and decrease in HbA1c were observed in both groups. Improvement in glycemic control and cardiovascular risk factor levels accompanied the modest weight reduction, with no significant between-group differences. ATK was not associated with untoward renal effects. Substantial drop-out in both groups was noted.
Conclusion: There was no statistically significant advantage in terms of weight loss or glucose control for the Atkins-like diet. Adherence to a very low carbohydrate diet in a population accustomed to a Mediterranean-type diet rich in fruits and vegetables was modest, thus restricting its applicability to selected obese diabetes patients.

1. Introduction

Type 2 diabetes patients tend to suffer from obesity. Present treatment geared to weight reduction has generally met with little or modest success, with satisfactory maintenance of weight reduction usually posing an insurmountable hurdle.[1] Blood glucose control often does not remain stable over time, necessitating the administration of oral hypoglycemic drugs, some of which cause patients to regain weight.[2] Thus the need arises to identify efficacious alternatives to the currently prevailing dietary recommendations. Carbohydrate restriction has been shown to be effective in weight reduction and in decreasing hyperinsulinemia, hypertriglycerinemia and blood glucose, both in healthy and obese individuals.[3–5] The Atkins diet[6] advocates a high percentage of fats, no restriction on proteins, but very low carbohydrate intake. This leads to the use of fat for energy, thus resulting in hepatic production of ketone bodies via the metabolism of fatty acids. The results of randomized clinical trial testing of the Atkins diet and other low carbohydrate, high-fat diets in type 2 diabetic patients was summarized in 2009 as being limited in extent and suggesting "that low carbohydrate diets can be a viable option for achieving weight loss and may have beneficial effects on glycemic control, triglyceride levels, and high-density lipoprotein cholesterol levels in some patients".[7] Another meta-analysis demonstrated the benefits of the diet on fasting insulin.[8]

We tested the hypothesis that in obese type 2 diabetes patients under realistic outpatient clinic conditions, a very low-carbohydrate diet would achieve substantial weight loss and stabilize glucose metabolism, and be more acceptable over a 1-year period than the currently-employed low calorie diets.

2. Research design and methods

2.1. Patients

Patients with type 2 diabetes were selected from a university hospital clinic on the basis of the following criteria: aged 35–75

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years, body mass index (BMI) 30–39.9 kg/m^2, glycosylated hemoglobin (HbA1C) > 7%, not receiving insulin, and microalbumin excretion < 60 mg/day. Exclusion criteria were a serum creatinine level >1.4 mg/dl, diastolic blood pressure >100 mmHg or systolic blood pressure >180 mmHg, evidence of liver disease, LDL cholesterol >160 mg/dl despite lipid-lowering treatment, use of psychiatric medications, osteoporosis, cancer, food allergies, and consumption of a low carbohydrate diet in the past 6 months.

2.2. Study design

This study followed a concurrent randomized controlled clinical trial design. The protocol was approved by the university hospital ethics committee. All participants provided written informed consent. The study is registered with the Clinical Trials Protocol Registration System (NIH – FDA), ID #NCT00552890.

Stage 1 (during 4 weeks before randomization)

Patients were placed on a 4-week personalized diet containing 80% of their caloric requirements based on their recommended weights as determined by DASH (The Dietary Approach to Stop Hypertension).[9] The DASH diet was intended to neutralize the effect of fluid loss, typical in the first stages of many diets. All patients were advised to engage in physical aerobic activities (walking, swimming, running on a treadmill, etc.) three times a week for at least 30 min throughout the trial, as commonly recommended for people treated in community clinics.

Stage 2 (3 months following random allocation)

Patients were then randomly assigned to either a modified Atkins diet (ATK) or to a standard recommended American Diabetes Association (ADA) calorie-restricted diet.[10] The modified ATK diet was designed as a very low carbohydrate diet containing up to 25 g of carbohydrates daily for the first 6 weeks after randomization, thereafter increasing to a ceiling of 40 g daily. No restrictions were placed on intake of energy, proteins or fats. On the contrary, increased fat intake was encouraged, with patients being advised to consume fat rich in monounsaturated fatty acid (MUFA) and protein from poultry and fish rather than from saturated fatty acid (SFA)-rich red meat. Our modified Atkins diet also differed from the original Atkins diet in the amount of carbohydrates. The original Atkins diet restricts intake of carbohydrates to a maximum of 20 g/day during a first stage (2 weeks), while we allowed 25 g for a longer period in order to increase the probability that the patients would reach a state of ketosis. The ADA diet, which followed the recommendations of 2001,[10] included a calorie-restricted regime containing 10%–20% of the daily energy intake from protein and the other 80% divided between fats [which provided 18–20% of calories as MUFA, 8–10% as polyunsaturated fatty acids (PUFA) and 9–10% as SFA], carbohydrates and 35 g of fiber. Men were allowed up to 1500 kcal/day and women, 1200 kcal/day.

Patients were closely monitored weekly during the initial 12-week period following randomization and received weekly nutritional counseling with respect to the diet. Subsequently they were invited monthly, the latter inline with routine practice for consultation of obese diabetic patients under care of dietitians in the Israeli ambulatory health system. Table 1 summarizes the activities of the 25 sessions planned to be held by the dietitian with each participant through the duration of the trial.

Stage 3 (4–12 months following randomization)

After completion of stage 2, patients were asked to continue the same diet with monthly monitoring.

As in both the ATK and ADA groups the diet included fewer carbohydrates than the DASH diet, all participants were informed that they would be on a "low carbohydrate" diet. Participants and their treating physicians were masked as to patient allocation to the diets, whereas the trial dietitian was informed about the diet assigned to participants, and advised them accordingly.

2.3. Data collection and laboratory measurements

At enrollment patients were evaluated for weight, height, HbA1c, fasting blood glucose, lipid profile, blood pressure, urinary ketones and microalbuminuria. Body weight, blood pressure and urinary ketones (stick) were measured weekly in the hospital clinic during the first 3 months and patients were requested each week to rate themselves on a scale from 1 to 10 on their adherence to the diet. Subsequently they were measured monthly until the end of the one year follow-up.

Additional data, collected at enrollment, at 6 weeks, 3 months, 6 months and 12 months after randomization, included medical history (at enrollment), weight, waist and hip circumferences, a 3-day dietary recall, 3-day blood glucose profile measures, changes in medication, and a physical activity questionnaire. Weight was measured on a single calibrated scale. $HbA1_c$ was measured immunoturbidimetrically by a Cobas Integra in a central hospital laboratory. All other laboratory determinations were made in the patients' routine primary care clinic facilities.

2.4. Sample size

Assuming a two-sided type 1 error of 5%, we estimated that a sample size of 20 per group would provide >80% power to detect between-group differences in loss of ≥3 kg in body weight and reduction of ≥1% in $HbA1_c$ at any single time point in the trial. In fact smaller differences were detectable with use of the multilevel and repeated measures analyses described below. We recruited 56 patients to allow for expected drop-outs.

2.5. Statistical methods

Analyses were performed with SPSS for Windows, version 17 (Chicago, Illinois).

We used unpaired *t*-tests to assess the differences between the two groups at the beginning of the trial. Paired *t*-tests and the general linear model were used for analyses of the nutrient intake data, anthropometric measurements, blood pressure and biochemical data at predetermined points in the trial. Three analytic approaches were adopted to assess the trial results: (i) a repeated measures ANOVA in which we disregarded the drop-outs; (ii) a highly conservative intention-to-treat repeated measures ANOVA in which we imputed missing data at 6 weeks, 3 months, 6 months, and 12 months post-randomization by carrying forward the patients' time zero pre-randomization values for body weight and baseline values for clinical chemistries, except for the actual data of 11 withdrawals who returned at 12 months for interview and examination; and (iii) multilevel analysis implemented with MLwiN.[11] The multilevel modeling, which incorporated all trial participants, took account of repeated measures of weight (and the other dependent variables separately modeled), accounted for the missing data by modeling all the observations made without excluding participants with missing data points (assumed to be random) and accounted for between- and within-person variation in response to the diets over 6 and 12 months follow-up.

The main dependent variable was repeated measures of weight. The main independent variables in the multilevel models were trial group (i.e. type of diet), time in trial (linear and quadratic terms for time), their interaction term which modeled the treatment effect