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Effect of a 90 g/day low-carbohydrate diet on glycemic control, small dense low density lipoprotein, and carotid intima-media thickness in type 2 diabetic patients: an 18month randomized controlled trial protocol

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1 Aim

This study explored the effect of a moderate (90 g/d) low-carbohydrate diet (LCD) in type 2 diabetes patients over 18 months.

2 Study site

The study was conducted at the Department of Family Medicine, National Taiwan University Hospital with recruitment going from February 2, 2016 to July 28, 2016 and the completion date from June 15, 2017 to January 4, 2018.

3 Study design

This was a single centre, parallel-designed, open-label randomised control trial for 18 months, which was allocated with Taves covariate-adaptive randomisation and stratified by sex and BMI (<24 and ≥24)

4 Inclusion criteria

Adults aged 20–80 years with type 2 DM

1. Diabetes for more than one year and had a poorly controlled HbA1c ≥ 58 mmol/mol (7.5%) in the previous three months, regardless of whether they received medications.

5 Exclusion criteria

1. Pregnant or lactating women
2. Impaired renal function with a serum creatinine ≥ 132.6μmol/L (1.5 mg/dL)
3. Abnormal liver function (alanine aminotransferase (ALT), aspartate aminotransferase ≥3 times the normal upper limit) or liver cirrhosis
4. Significant heart diseases (unstable angina, unstable heart failure)
5. Frequent gout attacks (≥3 times/year)
6. Participation in other weight-loss programmes or the use of weight-loss drugs, eating disorders and the inability to complete the questionnaire.

6 Intervention

The patients were assessed by the research physician, the research nurse and the dietitian at the first visit to record current medication use and compliance. Additionally, patients were instructed to keep a food diary for three days. Patients who complied with this requirement were evaluated and randomised by the research assistant. Individual dietary instruction was given by the research dietitian for each randomised group. Motivation group classes were arranged for both groups separately.

6.1 Dietary intervention and surveillance

For the LCD group, the daily carbohydrate intake was limited to less than 90 g without any restriction to the total energy. The concept of LCD with six servings of carbohydrates was introduced, and a list was provided to illustrate food items of 15 g of equivalent carbohydrates (one serving of carbohydrates). For those with good dietary compliance, sulfonylurea and insulin injections were reduced to half doses in advance to prevent hypoglycaemia.

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For the traditional diabetic diet(TDD) group, the target total calorie intake was calculated by multiplying the ideal weight by 25 kcal/kg for those with a BMI between 18.5 and 24, 20 kcal/kg for overweight/obese subjects (BMI > 24) and 30 kcal/d for underweight subjects with a BMI < 18.5. The macronutrient percentage was 50–60% for carbohydrates, 1.0–1.2 g/kg for protein and ≤ 30% for fat.

A three-day weighted food record was taken every six months. The calorie and nutrition intake of the three-day weighted food record were calculated using the E-Kitchen nutritional analysis software by a blind evaluator with enrolment numbers only.

All patients met with the research nurse every three months; these were arranged with the clinic visit, and reminders were given by phone calls.

6.2 Physical activity surveillance

Exercise was recommended for both groups and was not a part of the intervention. Physical activity was assessed every three months using the International Physical Activity Questionnaire, Taiwan (IPAQ-Taiwan).

6.3 Rules for medication adjustment

The medication for both groups was adjusted every six months if HbA1c was higher than 64 mmol/mol (8.0%) or lower than 48 mmol/mol (6.5%), with or without hypoglycaemic symptoms.

7 Primary outcomes

Glycaemic control status (HbA1c, fasting glucose and 2-h glucose) and the change in the medication effect score (MES)

7.1 Medication effect score (MES)

The percentage of the maximum daily dose for each medication was multiplied by an adjustment factor, and these products were summed up to produce the final MES value. The maximum daily dose of insulin was defined as 1 unit per kilogram of baseline weight, delineating insulin resistance. The adjustment factors were the reported median absolute reduction in HbA1c for each medication and are detailed as follows: 1.5 for metformin and sulfonylureas, 2.5 for insulin, 1.0 for thiazolidinedione, 0.65 for α-glucosidase inhibitor, 0.65 for dipeptidyl peptidase-4 inhibitors and 0.7 for sodium-glucose cotransporter 2 inhibitors.

For example, if a patient took 2 mg/d of glimepiride and 1500 mg/d metformin (the maximum doses for glimepiride and metformin were 8 mg/d and 3000 mg/d, respectively), the MES was calculated as 1.5×2 (mg) / 8 (mg) + 1.5 × 1500 (mg) / 3000 (mg) = 1.125, with higher values indicating a greater use of medication. The MES values were confirmed with the patients at every visit to determine their actual use.

8 Secondary outcomes

The lipid profile, sdLDL, serum creatinine, microalbuminuria and carotid intima-media thickness(IMT).

9 Outcome Measurement

1. Fasting blood samples were obtained to assess fasting glucose, HbA1c, serum lipids [total cholesterol, high-densitylipoprotein(HDL), LDL, triglyceride, sdLDL], serum creatinine and 2-h blood samples for 2-h glucose levels at every visit.
2. The antidiabetic agents were categorised according to their mechanism and reported as types (categories) of diabetic medications with the number of diabetic medications (the total number of tablets and the number of insulin shots per day) at every visit.
3. Blood pressure, weight, BMI, body composition (fat %) and waist, hip and thigh girths were measured by a research assistant every three months.
4. The sdLDL was checked at baseline and then at six, 12, and 18 months.

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5. The microalbumin/creatinine ratio was analysed from random urine samples collected at baseline and 18 months. 6. Complete blood cell count, uric acid, and ALT were checked at baseline and 18 months.
7. Carotid IMT was measured at baseline and 18 months.

10 **Statistical analysis**

The analysis was performed using an intention-to-treat analysis. The participants were called back if they missed the blood test before their visits. The blood samples were reserved with another tube and provided tests if the regular samples failed. Because the participants regularly followed up at family physicians, there were no missing data.

A paired t-test was conducted to compare the differences between baseline and completion of the study at 18 months within the TDD or LCD groups regarding nutrition, physical activity, glycaemic control, lipids, other blood chemistry, microalbumin/cre, carotid IMT, blood pressure, anthropometric measurements and diabetic medication.

An independent t-test was used to compare the differences or 18-month mean difference (18 months minus baseline) between the TDD and LCD groups regarding the above items.

The time trend of glycaemic control, MES, weight, blood pressure and lipid profile between the TDD group and the LCD group were estimated using the generalised estimating equations (GEE) method with an autoregressive (AR) covariance matrix.

All analyses were conducted using SAS statistic software package 9.4 version (TS1M3 DBCS3170). A p-value < 0.05 was deemed statistically significant.

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