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Randomization to a low-carbohydrate diet advice transiently improves glycaemic control compared with a low-fat diet at similar weight-loss in type 2 diabetes

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Abstract

Aims To compare the effects of a 2-year intervention with a low-fat diet (LFD) or a low-carbohydrate diet (LCD) based on four group-meetings to achieve compliance.

Methods Prospective, randomized trial of 61 adults with type 2 diabetes. Primary outcomes were weight and HbA1c. Patients on LFD aimed for 55-60 energy percent (E%) and those on LCD for 20E% from carbohydrates.

Results Mean body-mass-index and HbA1c of the participants were 32.7 ± 5.4 kg/m² and 57.0 ± 9.2 mmol/mol, respectively. Weight-loss did not differ between groups and was maximal at 6 months, LFD: -3.99 ± 4.1 kg, LCD: -4.31 ± 3.6 kg, ($p < 0.001$ within groups). At 24 months patients on LFD had lost -2.97 ± 4.9 kg and those on LCD -2.34 ± 5.1 kg compared with baseline ($p = 0.002$ and $p = 0.020$ within groups, respectively). HbA1c fell in the LCD-group only (LCD: 6 months -4.8 ± 8.3 mmol/mol, $p = 0.004$, 12 months: -2.2 ± 7.7 mmol/mol, $p = 0.12$, LFD: 6 months: -0.9 ± 8.8 mmol/mol, $p = 0.56$). At 6 months HDL-cholesterol had increased on LCD (from 1.13 ± 0.33 mmol/l to 1.25 ± 0.47 mmol/l, $p = 0.018$) while LDL-cholesterol did not differ between groups. Insulin doses were reduced in the LCD group (0 months: LCD: 42 ± 65 E, LFD: 39 ± 51 E, 6 months: LCD: 30 ± 47 E, LFD: 38 ± 48 E, $p = 0.046$ for between-group change).

Conclusions/interpretations Weight-changes did not differ between the diet groups while insulin doses were reduced significantly more on LCD at 6 months when compliance was good. Thus, aiming for 20% of energy from carbohydrates is safe from a cardiovascular risk factor view compared with a traditional LFD and it could thus constitute a treatment-alternative.

Keywords

Type 2 diabetes. Dietary intervention. Low-carbohydrate diet. Blood glucose. LDL. HDL.

Trial registry number: NCT01005498 at ClinicalTrials.gov.

Abbreviations

LCD Low-carbohydrate diet

LFD Low-fat diet

Introduction

The prevalence of type 2 diabetes is increasing world-wide and this is likely a consequence of the increasing prevalence of obesity. Weight-loss in obesity generally leads to improvement of cardiovascular risk factors and glycaemic control [1, 2] but few randomized studies have specifically targeted type 2 diabetes to compare the effect of different diets in this respect. Traditionally, a low-fat diet has been recommended [3] to patients with type 2 diabetes as a means to lose weight, and in particular a low intake of saturated fat has been advocated [4, 5]. Interestingly, in a randomized two-year study from Israel that achieved good compliance, a high-fat diet was shown to induce better weight-reduction and improved blood lipid levels than a traditional low-fat diet in obese subjects, while the subgroup of patients with diabetes that was randomized to the high-fat diet exhibited the largest reduction in HbA1c levels [6].

From a physiological point of view it could be argued that to achieve a good glycaemic control in type 2 diabetes carbohydrates should be avoided since a typical feature of type 2 diabetes is the combination of reduced insulin sensitivity and beta-cell failure to provide adequate amounts of insulin to handle glucose that is derived from the carbohydrates in the diet. However, when the macronutrient composition is changed in a diet by reducing carbohydrates, the energy from this source are primarily replaced by that from fat, since a high energy intake from protein is hard to achieve in the long-term. Thus a low-carbohydrate diet is quite similar to one with a high intake of fat, which has traditionally been regarded as linked with increased risk for arteriosclerosis, in particular if large amounts of saturated fat are consumed. However, recent data have challenged this concept of the risks with a high fat diet. In a Swedish observational study in 28 000 middle aged individuals neither a high fat intake or an intake of large amounts of saturated fat (22 E%) was linked with an increased risk for cardiovascular disease [7, 8].

Most earlier studies examining high-fat diets in patients with type 2 diabetes have had limitations such as a large drop-out frequency [9-12], lack of randomization [13-15], or a maximal duration of 12 months [11, 12, 16]. Another problem for the clinical feasibility of the study results for patients with type 2 diabetes has been a large amount of resources used to achieve compliance with the tested diets, typically incorporating numerous individual meetings with trained dieticians during the study [11, 16, 17] which requires large amount of resources for the medical provider in such a common disease if these measures were to become routine health care.

We performed a randomized study in patients with type 2 diabetes to compare glycaemic control and also of weight-loss and cardiovascular risk factors of a low-carbohydrate diet with that of a traditional low-fat diet. In contrast to most previous studies, the patients randomized to the low-carbohydrate diet were not advised to avoid saturated fat. The interventions were based on four group meetings with a duration of 60 minutes each for the first year and no further group meetings during the remaining 12 months were given. Our hypothesis was that the high-fat diet would improve glycaemic control more efficiently than the traditional low-fat diet in a study in which such little resources were allocated for achieving compliance so that clinical use of the protocol would be realistic for many providers of care.

Methods

The study was conducted in two primary health care centres in the cities of Motala and Borensberg located in southeast Sweden. Patients who fulfilled the criteria for participation

were contacted individually by one out of the total of three study nurses. The nurses had also been responsible for the care of these potential participants ahead of the study start. The inclusion criteria were a diagnosis of type 2 diabetes treated with diet with or without additional oral anti-diabetic medication, incretin-based therapy or insulin. There were no weight or age exclusion criteria but patients who had difficulties in understanding the Swedish language, suffering from severe mental disease, malignant disease or who were abusing drugs could not participate in the study.

The patients were randomized either to a low-carbohydrate diet or to a traditional low-fat diet, both with a caloric content of 1600 kcal for women or 1800 kcal for men. Randomization was not stratified and was based on drawing blinded ballots. The low-carbohydrate diet had an energy content where 50 E % were from fat, 20 E% from carbohydrates and 30 E% from protein. The low-fat diet had a nutrient composition that was similar to what is traditionally recommended for treatment of type 2 diabetes in Sweden with 30 E% from fat (less than 10 E% from saturated fat), 55-60 E% from carbohydrates and 10-15 E% from protein.

Group information was used to inform the randomized patients about which food items to choose from, and this was given at baseline, at 2, 6 and 12 months by two different physicians. One dedicated dietician provided the participants from both groups with suitable recipes at each group meeting, and was also available consecutively during the trial for questions from the participants. However, all the information necessary was provided at the group information occasions, and thus no individual meetings with the dietician were scheduled as part of the general protocol. Menus for one week were provided to the participants as meal suggestions by the dietician. Each patient had the same dedicated nurse during the whole study period and the nurses could also provide information about food to the patients during regular consultations. The patients were recommended to check plasma-glucose levels before and after meals after initiation of the study to allow for proper adjustment of medication to avoid hypoglycaemia. No information was given to change the level of physical activity of the participants. Since the duration of the trial was two years and also due to recruitment of patients with high risk for cardiovascular events, it was judged to be unethical not to be allowed to adjust medication to avoid cardiovascular disease in the study. The responsible physician for each patient at the primary health care centres was thus allowed to adjust hypo-lipidaemic and anti-hypertensive medications consecutively in the trial.

Investigations of anthropometrics and laboratory tests were performed at baseline and at 6, 12 and 24 months, and patients were also asked to fill-out questionnaires of well-being at these time-points. Diet records were also performed at these 4 visits with one additional recording at 3 months. The diet records were conducted during three consecutive days out of which one day was a Saturday or a Sunday and the participants were provided with dedicated scales and note-books from the organizers to weigh and record all food items that were consumed during these periods (there were no use of food frequency questionnaires). Sagittal abdominal diameter was measured with a sliding beam set square as the highest abdominal level above the upper surface of the corresponding bed. The laboratory tests were analyzed at the department of Clinical Chemistry at the University Hospital of Linköping as part of clinical routine and fasting LDL-cholesterol was thus calculated by the formula of Friedewald.

Statistics

Statistical calculations were done with PASW 18.0 software (SPSS Inc. Chicago, IL, USA). Linear correlations were calculated, as stated in the text. Comparisons within and between groups were done with Student's paired and unpaired 2-tailed t-test or as stated in the results

section. Mean (SD) is given unless otherwise stated. Statistical significance was considered to be present at the 5% level ($p \leq 0.05$). ANOVA with repeated measures was used for calculations of the changes during the total study duration.

The size of the study was based on an earlier 6 month pilot study of 28 participants with type 2 diabetes that were randomized to the same diets as in the study presented in this paper. Twenty subjects completed the pilot study and both diet-groups achieved similar weight-reductions while HbA1c levels tended to be lowered in the low-carbohydrate group only, without taking change in medication into account (low-carbohydrate: $p = 0.068$, low-fat group: $p = 0.8$). Based on these results the study sample was increased to at least 30 subjects in each group in the present study. None of the participants in the pilot study participated in the trial presented in this paper. The study duration of 24 months was requested by the the Regional Ethics Committee of Linköping.

Ethics

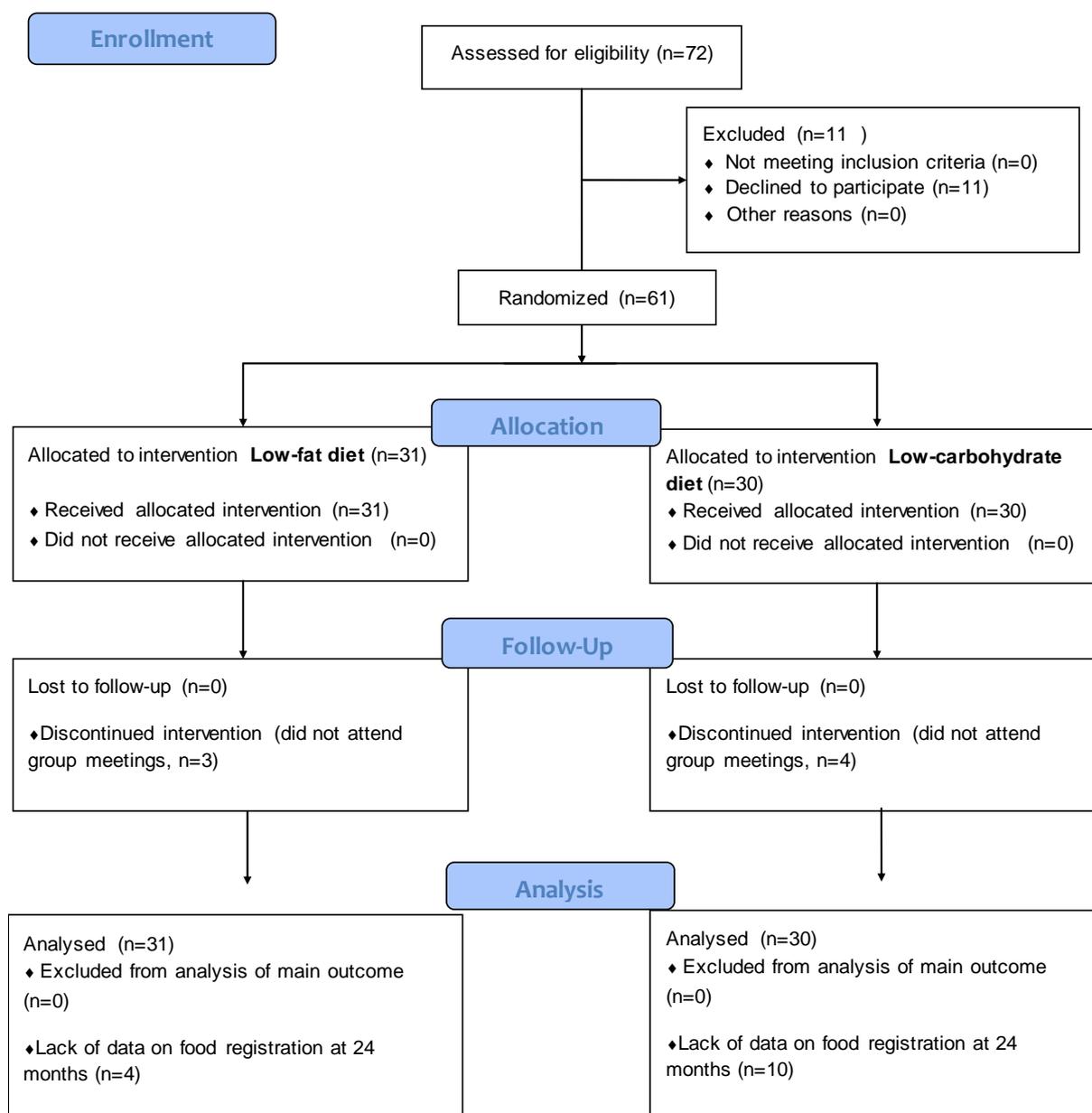
The study was approved by the Regional Ethics Committee of Linköping and performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participating subjects. The study was registered with trial number NCT01005498 at ClinicalTrials.gov.

Results

Total study population

The study nurses consecutively asked 72 patients to participate in the study during the autumn of 2008 to the start of the clinical trial in March 2009. Ten patients declined participation because they judged the study to be too time-consuming and one patient believed that a high-fat diet might be hazardous. The remaining 61 patients entered the study but three in the low-fat diet group and four in the low-carbohydrate diet group expressed severe difficulties in following the prescribed diets and that they were not willing to participate in the group meetings. Data on main outcomes from these seven patients were used in statistical analyses according to intention to treat (Table 1, see also Figure 1 for flow diagram). The mean age in the low-fat group was 62.7 ± 11 years and there were 13 men and 18 women having a diabetes-duration of 8.8 ± 6.2 years. Corresponding figures for the low-carbohydrate group were 61.2 ± 9.5 years, 14 men and 16 women and a known diabetes-duration of 9.8 ± 5.5 years. Age, gender composition and known duration of diabetes did not differ between the groups (all $p > 0.5$). At baseline, two patients in the low-fat group and two in the low-carbohydrate group were treated with diet only, 13 in the low-fat group and 15 in the low-carbohydrate group were on oral anti-diabetic medication only and 11 in the low-fat group and 10 in the low-carbohydrate group were treated with a combination of insulin and oral medication. At 24 months 14 subjects (four in the low-fat diet group and 10 in the low-carbohydrate diet group) did not provide results on diet records, but data on main outcomes were used in calculations. The dietician had individual consultations with four patients in the low-carbohydrate group and with three patients in the low-fat group except for the information given during the group meetings. These individual contacts all took part during the first 12 months of the study. Table 1 shows anthropometrics, laboratory variables and medication from baseline throughout the study. The registered intake of energy from fat and carbohydrate differed between the groups (Table 2).

Figure 1, Flow Diagram



There was no difference in weight reduction between the groups at 6 months (low-fat diet group: -4.0 ± 4.1 kg, low-carbohydrate diet group: -4.3 ± 3.6 kg, $p = 0.75$ for difference in change between groups and $p < 0.001$ within either group, Table 1 and Figure 2). There were no statistically significant differences in weight reduction between groups also when baseline carbohydrate or fat intake was adjusted for (all $p > 0.5$).

A significant reduction in HbA1c was seen at 6 months in the low-carbohydrate group only (Table 1). However, HbA1c levels gradually returned to baseline levels after 6 months as shown in Figure 3 and Table 1. The change of HbA1c levels at 6 months compared with baseline was not statistically significant between the groups ($p = 0.089$). Reductions in oral medication and of insulin doses were done consecutively to avoid hypoglycaemia, and the

Table 1

Anthropometrics, metabolic outcomes and medication at 0, 6, 12 and 24 months after the initiation in patients with type 2 diabetes randomized to a low-fat (n= 31) or low-carbohydrate diet (n= 30).

| Variable | Diet | Time point | | | | | | | | | |
|----------------------------------|-----------|----------------------|------------------------------|----------------------|-------------------------------------|----------------------|-------------------------------------|----------------------|-------------------------------------|------------------------------|---|
| | | 0 months | | 6 months | | 12 months | | 24 months | | | |
| | | | P between groups at baseline | | P for change compared with baseline | | P for change compared with baseline | | P for change compared with baseline | P for change all time-points | P for change all time-points between groups |
| Weight (kg) | Low-fat | 98.8±21 | 0.15 | 94.2±21 | <0.001 | 94.9±21 | <0.001 | 95.9±21 | 0.002 | <0.001 | 0.33 |
| | Low-carb. | 91.4±19 | | 87.5±19 | <0.001 | 89.5±19 | <0.001 | 89.4±22 | 0.020 | <0.001 | |
| BMI (kg/m ²) | Low-fat | 33.8±5.7 | 0.11 | 32.3±5.5 | <0.001 | 32.6±5.3 | <0.001 | 32.8±5.5 | 0.002 | <0.001 | 0.20 |
| | Low-carb. | 31.6±5.0 | | 30.1±5.1 | <0.001 | 30.7±5.3 | <0.001 | 30.8±5.8 | 0.011 | <0.001 | |
| Waist (cm) | Low-fat | 110±13 | 0.29 | 106±15 | <0.001 | 106±14 | <0.001 | 108±16 | 0.035 | <0.001 | 0.42 |
| | Low-carb. | 106±15 | | 102±14 | <0.001 | 104±15 | 0.021 | 104±16 | 0.015 | 0.002 | |
| Sagittal abdominal diameter (cm) | Low-fat | 27±5 | 0.37 | 27±4 | 0.097 | 27±4 | 0.13 | 28±4 | 0.62 | 0.088 | 0.068 |
| | Low-carb. | 26±4 | | 25±4 | 0.006 | 25±4 | 0.006 | 25±4 | 0.014 | 0.002 | |
| HbA1c (% mmol/mol) | Low-fat | 7.2±2.9 55.6±8.0 | 0.23 | 7.2±3.0 54.7±9.7 | 0.56 | 7.3±3.2 56.4±11.4 | 0.66 | 7.4±3.1 57.6±10.8 | 0.29 | 0.40 | 0.76 |
| | Low-carb. | 7.5±3.1 58.5±10.2 | | 7.1±3.1 53.7±10.3 | 0.004 | 7.3±3.3 56.2±12.4 | 0.12 | 7.5±3.1 58.4±10.6 | 0.98 | 0.005 | |
| Systolic blood pressure (mmHg) | Low-fat | 136±13 | 0.73 | 128±12 | <0.001 | 126±12 | <0.001 | 125±13 | <0.001 | <0.001 | 0.74 |
| | Low-carb. | 135±15 | | 126±17 | 0.004 | 127±13 | 0.003 | 126±14 | 0.012 | 0.003 | |
| Diastolic blood pressure (mmHg) | Low-fat | 77±9 | 0.67 | 74±8 | 0.049 | 69±9 | <0.001 | 71±11 | 0.001 | <0.001 | 0.75 |
| | Low-carb. | 76±11 | | 72±8 | 0.019 | 70±10 | 0.002 | 71±8 | 0.004 | 0.002 | |

| | | | | | | | | | | | |
|----------------------------|-----------|-----------|------|-----------------------|----------------|-----------|-------|-----------|--------|--------|------|
| Total cholesterol (mmol/l) | Low-fat | 4.3±1.0 | 0.40 | 4.2±1.1 | 0.91 | 4.3±1.1 | 0.96 | 4.0±0.9 | 0.11 | 0.23 | 0.33 |
| | Low-carb. | 4.5±1.0 | | 4.4±1.1 | 0.60 | 4.3±0.9 | 0.17 | 4.4±0.9 | 0.32 | 0.63 | |
| LDL-cholesterol (mmol/l) | Low-fat | 2.4±0.7 | 0.24 | 2.3±0.8 | 0.69 | 2.3±0.8 | 0.48 | 2.1±0.7 | 0.017 | 0.050 | 0.16 |
| | Low-carb. | 2.7±0.9 | | 2.5±0.7 | 0.37 | 2.5±0.8 | 0.12 | 2.4±0.7 | 0.020 | 0.13 | |
| HDL-cholesterol (mmol/l) | Low-fat | 1.09±0.29 | 0.57 | 1.10±0.30 | 0.36 | 1.17±0.24 | 0.004 | 1.20±0.32 | 0.002 | 0.001 | 0.15 |
| | Low-carb. | 1.13±0.33 | | 1.25±0.47 | 0.018 | 1.24±0.38 | 0.024 | 1.36±0.44 | <0.001 | <0.001 | |
| Triglycerides (mmol/l) | Low-fat | 1.8±0.8 | 0.89 | 1.8±1.3 | 0.79 | 1.7±0.9 | 0.88 | 1.7±0.9 | 0.81 | 0.98 | 0.35 |
| | Low-carb. | 1.7±1.4 | | 1.5±1.2 | 0.39 | 1.4±0.8 | 0.20 | 1.5±0.8 | 0.22 | 0.68 | |
| Total insulin dose (E) | Low-fat | 39±51 | 0.86 | 38±48 | 0.12 | 38±48 | 0.29 | 36±44 | 0.50 | 0.81 | 0.83 |
| | Low-carb. | 42±65 | | 30±47 ^a | 0.020 | 33±54 | 0.041 | 35±56 | 0.14 | 0.007 | |
| Metformin (mg) | Low-fat | 1435±946 | 0.80 | 1274±884 | 0.096 | 1371±875 | 0.40 | 1306±901 | 0.28 | 0.23 | 0.93 |
| | Low-carb. | 1375±950 | | 1442±872 ^a | 0.29 | 1358±915 | 0.86 | 1292±911 | 0.38 | 0.39 | |
| Glibenclamide (mg) | Low-fat | 0.4±1.9 | 0.26 | 0.3±1.3 | 0.33 | 0.3±1.3 | 0.66 | 0.3±1.3 | 0.66 | 0.69 | 0.56 |
| | Low-carb. | 1.1±2.6 | | 0.5±1.3 | 0.057 | 0.5±2.0 | 0.24 | 0.1±0.7 | 0.055 | 0.082 | |
| Simvastatin (mg) | Low-fat | 19±17 | 1.00 | 19±17 | - ^b | 24±17 | 0.032 | 24±17 | 0.032 | 0.003 | 0.54 |
| | Low-carb. | 19±18 | | 23±19 | 0.096 | 28±20 | 0.004 | 27±21 | 0.008 | 0.001 | |
| Atorvastatin (mg) | Low-fat | 2±5 | 0.97 | 2±6 | 0.33 | 3±9 | 0.18 | 3±9 | 0.18 | 0.24 | 0.88 |
| | Low-carb. | 2±5 | | 2±6 | 0.33 | 2±6 | 0.33 | 2±6 | 0.33 | 0.40 | |

Abbreviations: BMI, body-mass-index; Carb., carbohydrate.

^a Denotes statistically significant difference of change compared with baseline between the groups.

^b Since there were no changes in Simvastatin-doses, t-test is not applicable.

Table 2

Dietary outcomes at 0, 6, 12 and 24 months after the initiation in patients with type 2 diabetes randomized to a low-fat or low-carbohydrate diet. Data are given for all participants who provided complete diet records.

| | 0 months N=61 | 3-6 months N=55 | | 12 months N=42 | | 24 months N=47 | | P for change all time-points | P for change all time-points (between groups) |
|-------------------------------|-------------------------|---------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|------------------------------|---|
| | | | P compared with baseline | | P compared with baseline | | P compared with baseline | | |
| Energy intake (kJ) | | | | | | | | | |
| Low-fat diet | 7569±2063 | 6498±1787 | 0.005 | 6619±2075 | 0.075 | 6104±1891 | 0.002 | 0.010 | 0.065 |
| Low-carbohydrate diet | 7071±1782 | 5791±1531 | <0.001 | 6017±2075 | 0.037 | 5234±1799 | <0.001 | <0.001 | |
| Carbohydrate energy % | | | | | | | | | |
| Low-fat diet | 48±6 | 49±6 | 0.88 | 47±6 | 0.38 | 47±7 | 0.31 | 0.28 | <0.001 |
| Low-carbohydrate diet | 41±11 ^b | 25±8 ^a | <0.001 | 27±8 ^a | <0.001 | 31±6 ^a | <0.001 | <0.001 | |
| Fat energy % | | | | | | | | | |
| Low-fat diet | 32±5 | 29±5 | 0.12 | 31±6 | 0.96 | 31±7 | 0.87 | 0.28 | <0.001 |
| Low-carbohydrate diet | 39±7 ^b | 49±7 ^a | <0.001 | 47±6 ^a | <0.001 | 44±5 ^a | <0.001 | <0.001 | |
| Protein energy % | | | | | | | | | |
| Low-fat diet | 19±3 | 21±3 | 0.012 | 20±3 | 0.044 | 20±2 | 0.045 | 0.037 | 0.009 |
| Low-carbohydrate diet | 19±3 | 24±3 ^a | <0.001 | 23±5 ^a | 0.002 | 24±4 ^a | <0.001 | <0.001 | |
| Alcohol energy % | | | | | | | | | |
| Low-fat diet | 1±2 | 2±3 | 0.23 | 2±3 | 0.36 | 2±3 | 0.27 | 0.72 | 0.49 |
| Low-carbohydrate diet | 2±4 | 2±4 | 0.83 | 2±3 | 0.037 | 2±4 | 0.79 | 0.018 | |
| Total fat (g) | | | | | | | | | |
| Low-fat diet | 66±23 | 53±20 | 0.014 | 56±23 | 0.27 | 52±22 | 0.007 | 0.11 | 0.008 |
| Low-carbohydrate diet | 74±23 | 78±24 ^a | 0.081 | 77±29 | 0.22 | 63±24 | 0.17 | 0.10 | |
| Saturated fat energy % | | | | | | | | | |
| Low-fat diet | 13±3 | 11±2 | 0.090 | 12±3 | 0.96 | 13±3 | 0.61 | 0.20 | <0.001 |

| | | | | | | | | | |
|-------------------------------------|------|-------------------|--------|-------------------|--------|-------------------|--------|--------|--------|
| Low-carbohydrate diet | 16±4 | 20±4 ^a | <0.001 | 20±4 ^a | 0.008 | 19±2 ^a | <0.001 | <0.001 | |
| Unsaturated fat energy % | | | | | | | | | |
| Low-fat diet | 12±2 | 11±2 | 0.20 | 11±2 | 0.71 | 11±3 | 0.50 | 0.80 | <0.001 |
| Low-carbohydrate diet | 14±3 | 18±3 ^a | <0.001 | 17±3 ^a | <0.001 | 16±3 ^a | <0.001 | <0.001 | |
| Polyunsaturated fat energy % | | | | | | | | | |
| Low-fat diet | 5±2 | 5±2 | 0.92 | 5±2 | 0.97 | 5±2 | 0.58 | 0.76 | 0.001 |
| Low-carbohydrate diet | 6±3 | 8±2 ^a | <0.001 | 8±2 ^a | 0.006 | 6±2 | 0.044 | 0.002 | |

^a Denotes statistically significant difference between changes in the two groups.

^b Denotes statistically significant difference between groups at baseline.

reduction of insulin was statistically significant only in the low-carbohydrate group at 6 months (Table 1). This change of the average insulin dose was statistically significant between the two groups at 6 months ($p= 0.046$).

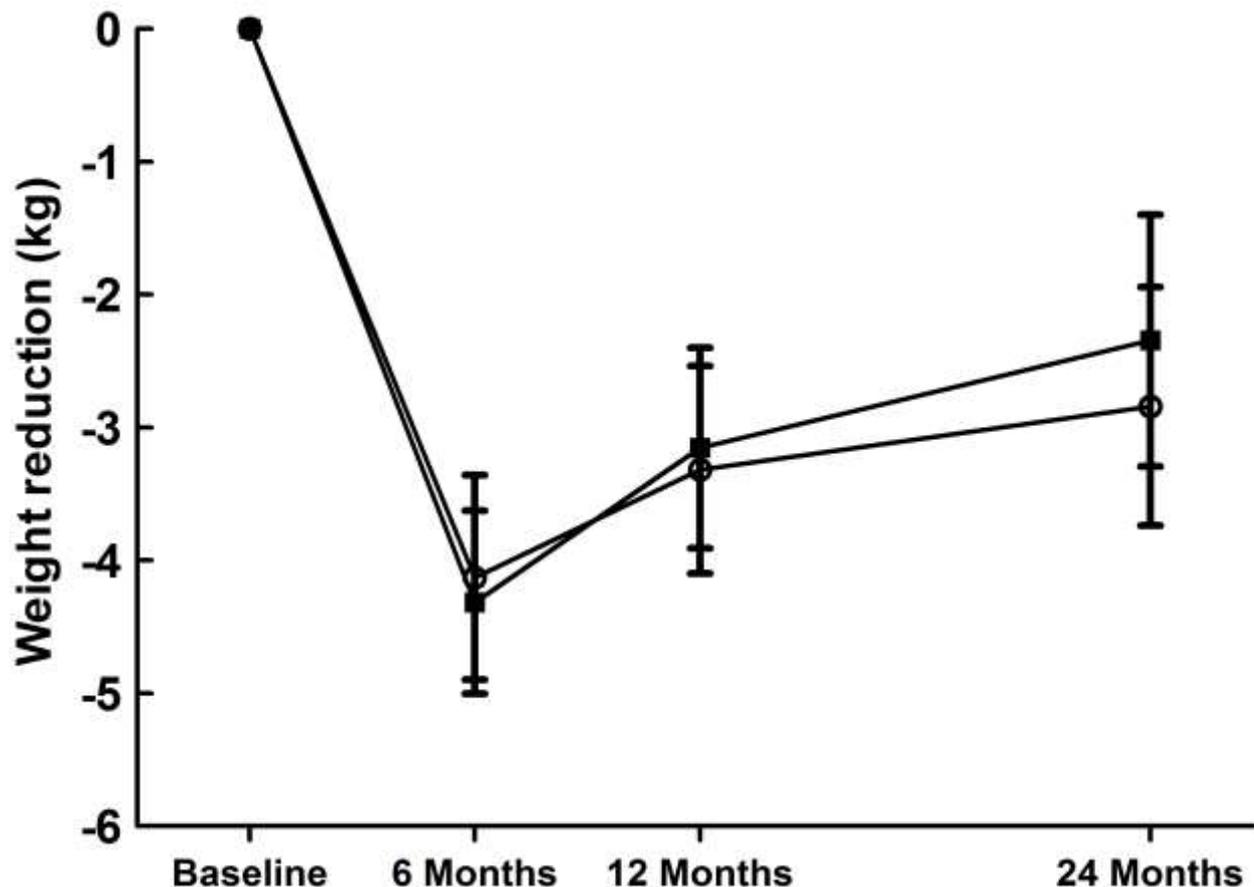


Figure 2: Comparison of the weight-reduction based on a low-carbohydrate diet with the aim to achieve 20 E% of calories from carbohydrates (filled squares) or on a low-fat diet (circles) aiming for 55-60 E% from carbohydrates, during two years in patients with type 2 diabetes. The weight-reduction did not differ between the groups ($p= 0.33$ for all time-points).

There were no significant differences between groups regarding office blood pressure levels in the study (Table 1). At 6 months, four patients in the low-carbohydrate diet group and one patient in the low-fat diet group had been started on statins or had their former dose increased (see also Table 1). Corresponding figures for such medical adjustments during the entire study period were nine patients in the low-carbohydrate diet group and seven patients on the low-fat diet. At the end of the trial 54 out of the total of 61 patients received lipid-lowering medication. At 6 months, the low-carbohydrate group showed significantly increased levels of HDL-cholesterol (Table 1, $p=0.018$ for change within group, $p= 0.077$ for change between groups). No patients suffered cardiovascular disease or other serious adverse events during the study.

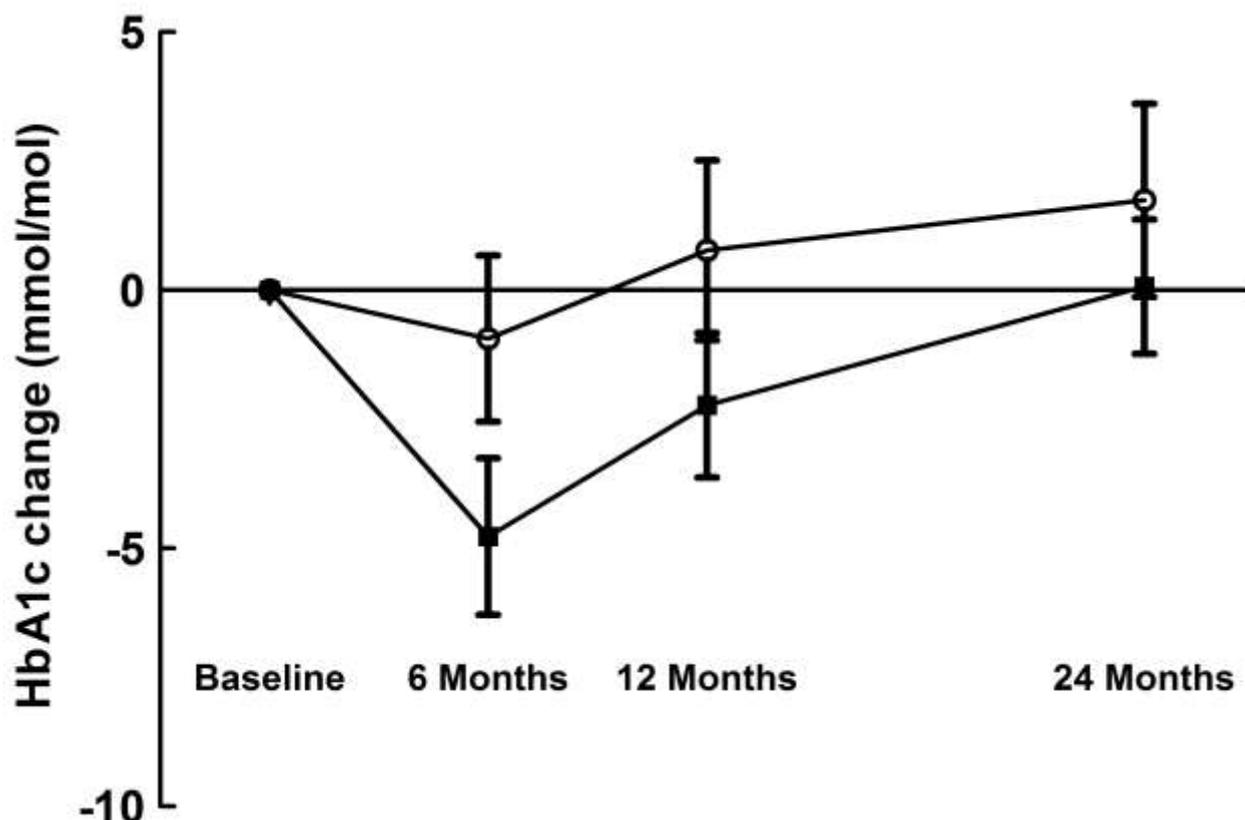


Figure 3: Comparison of the reductions in HbA1c levels following a low-carbohydrate diet with the aim to achieve 20 E% of calories from carbohydrates (filled squares) or on a low-fat diet (circles) aiming for 55-60 E% from carbohydrates, during two years in patients with type 2 diabetes. The reduction of HbA1c levels was statistically significant within the low-carbohydrate group ($p=0.005$ for all time-points) but did not differ between the groups when compared at all time-points ($p=0.76$).

The results of the dietary records are shown in table 2. During the first six months the adherence to the proposed diet was comparatively good in both groups as judged by mean values of macronutrient intake (Table 2). The low-fat group did not significantly change the macronutrient composition during the study while there was an increase of energy from fat in the low-carbohydrate diet (Table 2). Despite reduction of caloric intake, total intake of fat showed no reduction in the low-carbohydrate group, which was in contrast to the low-fat group (Table 2). The percentage of energy from saturated fat increased in the low-carbohydrate group throughout the whole study but there were no differences between the groups regarding caloric intake, according to the diet records (Table 2).

Completers analysis

Additional analyses were made according to compliance with caloric intake. Table 3 shows results when only those patients that consumed ≤ 1600 kcal/day for women or ≤ 1800 kcal/day for men according to the last diet record at 24 months and it includes 17 patients in the low-fat group and 18 patients in the low-carbohydrate group. At 24 months the patients randomized to low-fat diet weighed 3.1 ± 4.3 kg less than at baseline and corresponding figure for the low-carbohydrate group was 3.5 ± 4.0 kg, i.e. suggestive of that in particular the high-fat group had less compliance at this time point that affected weight gain in the total cohort (i.e. -3.5 ± 4.0 kg in completers compared with -2.3 ± 5.1 kg in the total cohort). While sagittal abdominal diameter was stable in the low-fat group, this was reduced 2 cm in the contrasting group. On

the other hand the low-fat group with caloric compliance reduced both systolic and diastolic blood pressures, effects there were lacking in those randomized to the high-fat diet (Table 3). A second completers analysis based on compliance with fat intake is available as electronic supplementary material (compliance defined as: ≤ 35 energy % from fat in low-fat group, $n=20$, or ≥ 45 energy % from fat for the low-carbohydrate group, $n=12$, chi-square between groups for compliance with intake of fat: $p=0.06$). Similar results as in completers analysis according to caloric intake was found in this post-hoc calculation regarding sagittal abdominal diameter and blood pressures. HDL-cholesterol increased from 1.11 ± 0.36 mmol/l to 1.46 ± 0.59 mmol/l ($p=0.001$ for all time points) in those compliant with eating the low-carbohydrate diet according to fat intake, while corresponding figures for the low-fat diet were 1.05 ± 0.26 mmol/l at baseline to 1.17 ± 0.25 mmol/l at 24 months ($p=0.006$ within group and $p=0.016$ for change between groups).

Table 3

Completers analysis of anthropometrics, metabolic outcomes and medication at in patients with type 2 diabetes randomized to a low-fat or low-carbohydrate diet who were compliant with energy-restriction (<1600 kcal for women or <1800 kcal for men) according to the diet records at the 24 month registration. Low-fat diet n= 17, low-carbohydrate diet, n= 18.

| Variable | Diet | Time point | | | | | | | | | |
|----------------------------------|-----------|---------------------|------------------------------|---------------------|-------------------------------------|----------------------|-------------------------------------|----------------------|-------------------------------------|------------------------------|---|
| | | 0 months | | 6 months | | 12 months | | 24 months | | | |
| | | | P between groups at baseline | | P for change compared with baseline | | P for change compared with baseline | | P for change compared with baseline | P for change all time-points | P for change all time-points between groups |
| Weight (kg) | Low-fat | 90.6±19 | 0.66 | 86.7±19 | <0.001 | 88.0±19 | <0.001 | 87.5±19 | 0.008 | <0.001 | 0.75 |
| | Low-carb. | 88.0±16 | | 83.4±15 | <0.001 | 85.6±15 | <0.001 | 84.4±16 | 0.002 | <0.001 | |
| BMI (kg/m ²) | Low-fat | 31.6±5 | 0.71 | 30.2±5 | <0.001 | 30.7±5 | <0.001 | 30.5±5 | 0.005 | <0.001 | 0.74 |
| | Low-carb. | 31.0±4.5 | | 29.4±4.1 | <0.001 | 30.0±4.5 | 0.001 | 29.8±4.5 | 0.002 | <0.001 | |
| Waist (cm) | Low-fat | 107±13 | 0.31 | 102±15 | <0.001 | 103±16 | <0.001 | 103±16 | 0.004 | <0.001 | 0.57 |
| | Low-carb. | 103±12 | | 100±10 | 0.004 | 100±10 | 0.072 | 100±12 | 0.003 | 0.023 | |
| Sagittal abdominal diameter (cm) | Low-fat | 26±5 | 0.97 | 25±3 | 0.58 | 26±3 | 0.68 | 26±4 | 0.49 | 0.46 | 0.40 |
| | Low-carb. | 26±4 | | 25±3 | 0.009 | 24±3 | 0.003 | 24±3 | 0.016 | 0.002 | |
| HbA1c (% , mmol/mol) | Low-fat | 7.4±2.8 57.9±7.6 | 0.83 | 7.3±3.1 55.9±9.9 | 0.23 | 7.2±2.9 55.5±8.0 | 0.021 | 7.5±3.1 58.5±10.4 | 0.69 | 0.19 | 0.73 |
| | Low-carb. | 7.5±2.8 58.4±7.5 | | 7.0±2.9 52.8±8.3 | 0.016 | 7.2±3.1 54.8±10.1 | 0.062 | 7.5±2.9 58.3±8.7 | 0.94 | 0.026 | |
| Systolic blood pressure (mmHg) | Low-fat | 134±11 | 0.73 | 129±13 | 0.078 | 127±12 | 0.022 | 123±10 | 0.005 | 0.007 | 0.73 |
| | Low-carb. | 133±13 | | 125±16 | 0.053 | 127±13 | 0.085 | 126±14 | 0.195 | 0.13 | |

| | | | | | | | | | | | |
|---------------------------------|-----------|-----------|-------|-----------|---------------|-----------|-------|-----------|--------|--------|------|
| Diastolic blood pressure (mmHg) | Low-fat | 74±10 | 0.91 | 74±8 | 0.84 | 68±9 | 0.035 | 70±8 | 0.032 | 0.012 | 0.80 |
| | Low-carb. | 74±11 | | 71±8 | 0.17 | 71±11 | 0.16 | 71±8 | 0.11 | 0.22 | |
| Total cholesterol (mmol/l) | Low-fat | 4.0±0.7 | 0.078 | 4.1±0.9 | 0.67 | 4.0±0.7 | 0.66 | 3.9±0.8 | 0.57 | 0.73 | 0.11 |
| | Low-carb. | 4.5±1.0 | | 4.4±1.3 | 0.65 | 4.4±0.9 | 0.34 | 4.4±1.0 | 0.67 | 0.90 | |
| LDL-cholesterol (mmol/l) | Low-fat | 2.2±0.4 | 0.043 | 2.2±0.7 | 0.84 | 2.2±0.6 | 0.91 | 2.0±0.7 | 0.16 | 0.43 | 0.13 |
| | Low-carb. | 2.7±0.9 | | 2.5±0.9 | 0.37 | 2.5±0.7 | 0.10 | 2.4±0.8 | 0.066 | 0.34 | |
| HDL-cholesterol (mmol/l) | Low-fat | 1.14±0.32 | 0.94 | 1.18±0.32 | 0.28 | 1.21±0.26 | 0.029 | 1.26±0.34 | 0.050 | 0.080 | 0.67 |
| | Low-carb. | 1.15±0.36 | | 1.26±0.48 | 0.034 | 1.23±0.38 | 0.017 | 1.37±0.46 | <0.001 | <0.001 | |
| Triglycerides (mmol/l) | Low-fat | 1.5±0.7 | 0.88 | 1.4±0.7 | 0.67 | 1.4±0.7 | 0.17 | 1.6±1.0 | 0.52 | 0.49 | 0.91 |
| | Low-carb. | 1.4±0.6 | | 1.4±1.1 | 0.97 | 1.4±0.5 | 0.84 | 1.5±0.8 | 0.56 | 0.96 | |
| Total insulin dose (E) | Low-fat | 32±41 | 0.73 | 30±37 | 0.34 | 31±38 | 0.73 | 30±40 | 0.68 | 0.92 | 0.38 |
| | Low-carb. | 26±54 | | 14±28 | 0.13 | 16±33 | 0.16 | 20±37 | 0.34 | 0.12 | |
| Metformin (mg) | Low-fat | 1353±981 | 0.81 | 1176±865 | 0.27 | 1324±847 | 0.79 | 1265±903 | 0.65 | 0.58 | 0.90 |
| | Low-carb. | 1278±844 | | 1444±784 | 0.055 | 1306±860 | 0.85 | 1222±826 | 0.71 | 0.37 | |
| Glibenclamide (mg) | Low-fat | 0.7±2.6 | 0.45 | 0.5±1.7 | 0.33 | 0.6±1.7 | 0.67 | 0.6±1.7 | 0.67 | 0.69 | 1.0 |
| | Low-carb. | 1.5±3.1 | | 0.5±1.2 | 0.056 | 0.3±0.9 | 0.083 | 0.2±0.8 | 0.099 | 0.039 | |
| Simvastatin (mg) | Low-fat | 21±17 | 0.64 | 21±17 | ^{-b} | 25±17 | 0.19 | 25±17 | 0.19 | 0.14 | 0.95 |
| | Low-carb. | 18±19 | | 23±19 | 0.16 | 26±23 | 0.049 | 26±23 | 0.049 | 0.025 | |
| Atorvastatin (mg) | Low-fat | 1±2 | 0.21 | 1±5 | 0.33 | 1±5 | 0.33 | 1±5 | 0.33 | 0.40 | 0.30 |
| | Low-carb. | 3±7 | | 3±8 | 0.33 | 3±8 | 0.33 | 3±8 | 0.33 | 0.40 | |

Abbreviations: BMI, body-mass-index; Carb., carbohydrate.

^a Denotes statistically significant difference of change compared with baseline between the groups (no significant differences in this table).

^b Since there were no changes in Simvastatin-doses, t-test is not applicable.

Discussion

Our study did not confirm the finding that weight reduction is more efficient in individuals subjected to a low-carbohydrate diet than a low-fat diet as was found in some previous trials [6, 9, 12, 18-20]. An important difference in our study compared to these earlier studies [6, 9, 12, 18-20] was that we spent comparatively less resources to achieve compliance. In our study only four group meetings were offered during the first 12 months of the trial. The rationale for this design was to make results applicable to regular clinic care in which educational activities such as group meeting can be offered as a means to improve glycaemic control. No patients were lost to follow up and data on glycaemic control was complete at 24 months while data on weight was lacking in only one participant at this time-point. This design and outcome of our study left minimal room for the selection of participants, that did indeed find any of the diets particularly suitable, to affect the main outcomes. Our findings indicate that if patients are randomized to a low-carbohydrate diet compared with a low-fat diet with resources used to achieve changes of diet composition that are readily available for many providers of care, both diets induce similar weight-reductions. This was also in line with the finding that both groups reported similar caloric intake during the study. Westman et al. have earlier reported more efficient weight reduction on a low-carbohydrate diet after 6 months when compared with a low-fat diet [9]. In that study diet information was facilitated, compared to our design, by lack of calorie restriction in the low-carbohydrate group. This could have affected the more beneficial findings compared with our study regarding weight-loss. Also Westman et al. incorporated a total of 18 group meetings during their 6-month study which could have been related to differences in outcome, and information on increased exercise was also part of their life-style change program, which was not included in ours. Specifically we aimed to study the effects of macro-nutrient composition on glycaemic control and on cardiovascular risk-factors, which was why we aimed for achieving no differences in caloric intake in the information that we gave to the participants. Interestingly, we did find an increase in HDL-cholesterol after 6 months and a specific reduction in HbA1c levels in the low-carbohydrate group only, which suggests that these effects are dependent on macro-nutrient composition *per se*, and this was in line with findings of Westman et al [9].

We also acknowledge that we might have achieved better weight reduction if a design similar to that used in “Weight Watcher’s” programs had been incorporated. For regular care provided by the Swedish tax-based system, incentives used in Weight Watcher’s such as public display of results of the body-weight of the participants, would not be feasible for general use in clinic care due to regulation of patient privacy. Also one should keep in mind that there is a selection and incentive at hand in such commercially run programs regarding participants who are willing to pay the fees for participation. However effective weight-loss in the “Weight Watcher’s” group was recently shown in a study even when the cost for the participation had been reimbursed by the study-organizers [21].

Although patients in our study that had been randomized to the low-carbohydrate group reported a lower intake of carbohydrates at baseline compared to the low-fat group, this was unrelated to weight-changes in statistical analyses. In retrospect this group difference in reported intake of macronutrients between the groups might have been a consequence of that the participants were informed of the results of the randomization before the diet record at baseline was performed. Consequently, some participants might have adjusted the diet to become similar to that which they had been allocated to, ahead of the first group-information. Unfortunately the baseline-difference was not elucidated until the end of the trial and it was

thus judged to be of little meaning to ask participants with little intake of energy from carbohydrates in the low-carbohydrate group at baseline whether this was a consequence of the randomization, more than two years earlier.

The largest changes in macronutrient intake were seen in patients randomized to the low-carbohydrate group. Indeed, patients in the low-fat group had the same macronutrient composition at baseline as during the study, suggestive of that this was indeed a traditional diet and that they, according to the diet-records, had been given similar diet-recommendations earlier.

The patients on the low-carbohydrate diet increased the percentage of energy intake from both total- and from saturated fat throughout the 24 months of the trial according to diet records, which was in line with the study protocol. At 6 months, when the weight reduction was most pronounced, only the low-carbohydrate diet group displayed changes in blood lipid levels in the form of increased levels of HDL-cholesterol. However, during the study there had been changes also in lipid-lowering therapy that makes these findings inconclusive, as whether they solely were dependent on changes of the diet. At the end of the trial, several patients had been newly started on lipid-lowering therapy. This is an obvious limitation of our trial from a mechanical point of view, but it was a consequence to focus the trial on the effects of a small use of extra resources for the diets to be implemented, in regular primary care, to allow for implications of potential findings to be incorporated in the same setting in a realistic manner. However, since HMG-CoA reductase inhibitors (statins) mainly affect LDL-cholesterol levels and since earlier trials have also found that diets high in fat elevate HDL-cholesterol to a greater extent than high-carbohydrate diets in type 2 diabetes [9, 11, 16], we find it likely that the increase in HDL-cholesterol in our trial was mainly an effect of the change of diet.

We acknowledge that general applicability of our study results might be limited due to the high participation rate that was accomplished. The study nurses had also taken care of the same patients ahead of the study start and when identifying potential participants according to inclusion and exclusion criteria it can not be excluded that they might have discharged patients who they on beforehand judged would not have been suitable participants for various reasons. Another potential explanation for the high participation rate was that the study protocol was not very time-consuming for the patients since it only encompassed four group meetings. We also acknowledge the problems that are at hand with diet records. Despite that diet records with note-books and scales can be more detailed and precise than standardized food frequency questionnaires, results from surveys of food intake have low reproducibility and in particular there are systematic errors in under-reporting caloric intake [22]. Thus total caloric intake might not be accurate in our study, but the lowering of HbA1c in only the low-carbohydrate group at 6 months and also differences in HDL-cholesterol changes at similar weight reduction suggest that the groups did indeed change their macro-nutrient intake differently in our trial.

The analyses of the outcome in the participants that were compliant with either caloric intake or with the energy % from fat implied better long term effects on weight loss than in the total cohort analysed on an intention to treat basis. Although this was a post-hoc analysis, and thus data should be interpreted with caution, it was of interest to note that HDL-cholesterol increased 33% in patients reasonably compliant with fat intake, which was in line with data from Westman et al. [9]. On the other hand, blood pressure levels were not reduced in patients on the low-carbohydrate diet at 24 months. It can not be excluded that salt intake increased in

parallel with ingestion of fat, as has been demonstrated in the general population [23], leading to less favourable blood pressure levels. Unfortunately we did not collect urine for determination of the amount of sodium in the study.

In conclusion our findings support the use of a low-carbohydrate diet with 20 E% of calories from carbohydrates as an alternative to a traditional low fat diet, if the aim primarily is to improve glycaemic control in type 2 diabetes. We achieved a weight loss of about 4 kg in both groups after 6 months based on group information on three occasions and there was only one more group meeting which took place at 12 months study duration. However, as in many earlier studies, compliance with the low-carbohydrate diet was reduced after 6 months, as judged by the increase in body-weight and according to food records, and it can not be ruled out that different results could have been obtained if more effort had been spent on achieving compliance with the diet composition and with the reduction of caloric intake.

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Contribution statement

Author contribution: HG did the pilot study and came up with the study idea, ran the study and wrote the manuscript. BD, BB and M B-L collected and researched data and reviewed the manuscript. TL and CJÖ participated in the design of the study, researched data and reviewed the manuscript. MF participated in the design of the study, and had a particular responsibility in statistical evaluations. FHN designed the study with HG, researched data and wrote/edited the manuscript.

Duality of interest

The authors declare that there is no duality of interest associated with this manuscript.

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