Comparative effects of carbohydrate versus fat restriction on metabolic profiles, biomarkers of inflammation and oxidative stress in overweight patients with Type 2 diabetic and coronary heart disease: A randomized clinical trial

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Abstract

BACKGROUND: This study was conducted to establish the comparative effects of carbohydrate versus fat restriction on metabolic indices in Type 2 diabetic (T2D) patients with coronary heart disease (CHD).

METHODS: This randomized, clinical trial was done among 56 overweight persons with T2D and CHD aged 40-85 years old. The patients were randomly allocated to take either a high-carbohydrate (HC) diet (60-65% carbohydrates and 20-25% fats) (n = 28) or a restricted carbohydrate (RC) diet (43-49% carbohydrate and 36-40% fats) (n = 28) for 8 weeks to determine metabolic status.

RESULTS: After 8 weeks of treatment, RC diet decreased fasting plasma glucose (FPG) (−11.5 ± 28.3 vs. +7.0 ± 26.9 mg/dl, P = 0.010) and high-sensitivity C-reactive protein (hs-CRP) (−564.3 ± 1280.1 vs. +286.1 ± 1789.2 ng/ml, P = 0.040) compared with a HC diet. Moreover, compared with a HC diet, RC diet increased total antioxidant capacity (TAC) (+274.8 ± 111.5 vs. +20.2 ± 82.5 mmol/l, P < 0.001) and glutathione (GSH) levels (+51.6 ± 111.5 vs. −32.6 ± 88.5 µmol/l, P = 0.003). No significant alterations between the two groups were found in terms of their effect on other metabolic profiles.

CONCLUSION: RC diet in overweight T2D with CHD had beneficial effects on FPG, hs-CRP, TAC, and GSH values.

Keywords: Carbohydrate Restriction, Metabolic Status, Type 2 Diabetes Mellitus, Coronary Heart Disease, Obesity

Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic disease and is estimated to reach 439 million persons worldwide in 2030.1 Prior studies have exhibited that the prevalence of obesity and T2DM in people with coronary heart disease (CHD) exceeds that of the general population.2 Different factors have been involved in the progression of T2DM and CHD such as little glycemic control and dyslipidemia.3,4 In addition, low-grade inflammation resulting from free radicals and reactive oxygen species (ROS) may help to the expansion of metabolic complexity in diabetic vascular disease.5-7

However, it remains unknown whether favorable effects of restricted carbohydrate (RC) diets are mediated through changes in metabolic profiles, the inflammatory process, and endothelial dysfunction. Some studies have revealed that carbohydrate limitation has a more favorable effect on aspects of the metabolic syndrome (MeTs) than a low-fat diet.8,9 In a study by Parillo et al.10 was observed that high-monounsaturated-fat/low-carbohydrate diet compared with low-monounsaturated-fat/high-carbohydrate (HC) diet decreased postprandial glucose, insulin and triglycerides values among patients with T2DM for 15 days, but unchanged other lipid profiles. Likewise, low-carbohydrate (20%) than low-fat diet significantly improved the inflammatory state in T2DM after 6 months.11 However, in a study, a HC diet significantly increased insulin and triglycerides concentrations by 8% and 13%, respectively, and lowered high-density lipoprotein (HDL)-cholesterol
by 6% compared with the low-carbohydrate diet.\textsuperscript{12} In addition, few studies have also shown that acute ingestion of carbohydrate clearly induces ROS, inflammation and oxidative stress.\textsuperscript{13,14}

To our knowledge, information on the effects of RC versus HC intake on metabolic status in overweight T2DM persons with CHD is limited. This research, therefore, was done to establish the effects of RC intake and its replacement with unsaturated fats on metabolic parameters in these persons.

**Materials and Methods**

This treatment was a randomized clinical trial, which was done at the Cardiology Clinic of KUMS, Kashan, Iran, between November 2015 and January 2016. At baseline, people were matched according to age, body mass index (BMI), gender, and the dosage and kind of drugs. Since all people were overweight, both diets were designed to be calorie limited (350-700 kcal less than the computed energy). The macronutrient composition of the HC diet was equal with Iranian usual diets.\textsuperscript{15} Indeed, in the RC diet, 15-20% of the energy from carbohydrates was replaced by nonhydrogenated vegetable oils. The protein content of both diets was 14-17% of the total energy. To increase compliance, persons were given a portion list of food groups and solely educated about the goals of each phase as well as the portion list. To take nutrient intakes of people according to 3-day food records, we applied Nutritionist IV software (First Databank, San Bruno, CA). Physical activity was described as metabolic equivalents (METs).\textsuperscript{16}

In total, 56 patients were randomly divided into two groups: Group A (HC diet; 15 females and 13 males; n = 28) received 60-65% carbohydrates and 20-25% fats and Group B (RC diet; 15 females and 13 males; n = 28) received 43-49% carbohydrate and 36-40% fats for 8 weeks. Inclusion criteria were overweight patients aged 40-85 years old, BMI ≥ 25, having T2DM and CHD. Diagnosis of T2DM and CHD was done based on the American Diabetes Association\textsuperscript{17} and the American Heart Association,\textsuperscript{18} respectively. Exclusion criteria were consuming antiobesity medications within the last 3 months, having an acute myocardial infarction and/or a cardiac surgery within the last 3 months and a major renal or liver failure.

This intervention was confirmed by the Research Ethics Committee of KUMS (reference number IR.Kaums.REC.1394.96) and was registered in the Iranian registry of clinical trials (http://www.irtct.ir: IRCT20160102S523N61).

Weight and height were quantified at week 0 and week 8 at the cardiology clinic.

About 10 ml fasting blood samples were collected at week 0 and week 8. Fasting plasma glucose (FPG) and lipid parameters were established with enzymatic kits (Pars Azmun, Tehran, Iran). Insulin values were quantified using enzyme-linked immunosorbent assay (ELISA) kit (DiaMetra, Milano, Italy). Indices of insulin metabolism were calculated according to the existing formulas.\textsuperscript{19} High-sensitivity C-reactive protein (hs-CRP) was assessed by the commercial ELISA kit. The nitric oxide (NO) using Griess method,\textsuperscript{20} total antioxidant capacity (TAC) by Benzie and Strain\textsuperscript{21} method, total glutathione (GSH) using the method of Beutler and Gelbart\textsuperscript{22} and malondialdehyde (MDA) were determined by spectrophotometric method.\textsuperscript{23}

Based on a prior study,\textsuperscript{24} we used 2.5 as standard deviation (SD) and 2.1 as the change in mean (d) of homeostatic model assessment insulin resistance (HOMA-IR). Therefore, we needed 24 persons in each group and assuming 4 dropouts in each group; the final sample size was reached to be 28 people.

To establish the normal distribution of indices, the Kolmogorov–Smirnov was utilized. Results of normally distributed markers as mean ± SDs and non-normally distributed markers as median (Q1, Q3) were reported. The intention-to-treat (ITT) analysis of the primary study endpoint was applied for all of the randomly allocated participants with method of the last-observation-carried-forward method.\textsuperscript{25} To establish within-group differences (pre- and post-treatment), we used paired-samples t-tests. Pearson chi-square test was used for comparison of categorical markers. To determine the effects of RC diet intake on metabolic parameters, we applied independent samples Student’s t-test. To assess the effects of some confounders, we adjusted all analyses using ANCOVA test.

**Results**

In the RC group, 4 people and in the HC group, 4 people were withdrawn (Figure 1). However, all 56 people were contained in the final analysis using ITT principle.

Mean age, familial history, height, and weight, BMI, and METs at week 0 and week 8 were not alteration between the two groups (Table 1).
Based on the 3-day records, no significant alteration was seen between the two groups in terms of macro- and micronutrients (Table 2).

RC diet decreased FPG (−11.5 ± 28.3 vs. +7.0 ± 26.9 mg/dl, P = 0.010) and hs-CRP (−564.3 ± 1280.1 vs. +286.1 ± 1789.2 ng/ml, P = 0.040) compared with a HC diet (Table 3). In addition, compared with a HC diet, RC diet increased TAC (+274.8 ± 111.5 vs. +20.2 ± 82.5 mmol/l, P < 0.001) and GSH levels (+51.6 ± 111.5 vs. −32.6 ± 88.5 µmol/l, P = 0.003). Within-group changes revealed a significant decrease of FPG (P = 0.040), serum hs-CRP (P = 0.020), and a significant increase of plasma TAC (P < 0.001), and GSH levels (P = 0.020) in the RC diet.

When we controlled the analysis for baseline values of biochemical indicators, age, BMI at week 0, METs change and familiar history, findings unaltered (Table 4).

**Discussion**

We illustrated that RC diet for 8 weeks among overweight diabetic persons with CHD had useful effects on FPG, hs-CRP, plasma TAC, and GSH values; however, it did not influence other metabolic profiles. We did not randomize participants based on their plasma MDA levels because all participants were T2DM and CHD. Random assignment to two groups was done after stratification according to age, BMI, gender, and the dosage and kind of medications and random assignment were done by the use of computergenerated random numbers.

T2DM patients are susceptible to metabolic complications. We found that RC diet compared with HC diet in overweight persons with T2DM and CHD for 8 weeks decreased FPG levels, but unaltered insulin metabolism and lipid profiles.
In a study by Ballard et al.,

Table 1. General characteristics of study participants

| Characteristics | HC diet | RC diet | P*** |
|----------------|---------|---------|------|
| (n = 28)       | (n = 28) |         |      |
| Familial history (%) | 10 (35.7) | 10 (35.7) | > 0.999† |
| Smoking (%)     | 2 (7.1) | 2 (7.1) | > 0.999† |
| Aspirin 80 mg (%) | 28 (100) | 28 (100) | > 0.999† |
| Statin (%)      | 28 (100) | 28 (100) | > 0.999† |
| Insulin therapy (%) | 6 (21.4) | 5 (17.9) | 0.730† |
| Antidiabetics (%) |         |         |      |
| Monotherapy     | 16 (72.7) | 16 (69.6) |      |
| Combination therapy | 6 (27.3) | 7 (30.4) | 0.810† |
| Hypertension (%) | 19 (67.9) | 20 (71.4) | 0.770† |
| ACEI/ARB drugs (%) | 28 (100) | 28 (100) | > 0.999† |
| Blocker drugs (%) |         |         |      |
| β-blocker       | 26 (92.9) | 27 (96.4) |      |
| Calcium channel blocker | 2 (7.1) | 1 (3.6) | 0.550† |
| Duration of DM (year) | 6.3 ± 5.0 | 6.6 ± 4.8 | 0.850 |
| Duration of CHD (year) | 8.2 ± 4.7 | 8.8 ± 4.0 | 0.620 |
| HbA1c (mmol/mol) | 56.5 ± 4.7 | 54.9 ± 6.9 | 0.300 |
| SBP at study baseline (mmHg) | 135.7 ± 7.5 | 133.2 ± 13.3 | 0.370 |
| SBP at end-of-trial (mmHg) | 136.2 ± 8.0 | 133.5 ± 13.8 | 0.360 |
| SBP change (mmHg) | 0.5 ± 1.4 | 0.3 ± 1.1 | 0.680 |
| DBP at study baseline (mmHg) | 84.1 ± 8.4 | 85.2 ± 8.0 | 0.620 |
| DBP at end-of-trial (mmHg) | 84.3 ± 8.5 | 85.1 ± 7.8 | 0.750 |
| DBP change (mmHg) | 0.2 ± 1.2 | 0.1 ± 1.1 | 0.200 |
| Age (year)       | 65.2 ± 11.6 | 61.1 ± 9.9 | 0.1500 |
| MET-h/day change | −0.3 ± 0.8 | −0.3 ± 0.9 | 0.850 |
| Height (cm)      | 156.8 ± 15.9 | 157.6 ± 11.2 | 0.820 |
| Weight at study baseline | 79.0 ± 14.8 | 77.6 ± 11.7 | 0.690 |
| Weight at end-of-trial | 76.8 ± 14.3 | 75.5 ± 11.9 | 0.700 |
| Weight change (kg) | −2.2 ± 2.1 | −2.1 ± 1.7 | 0.880 |
| BMI at study baseline | 32.2 ± 4.4 | 31.2 ± 3.5 | 0.360 |
| BMI at end-of-trial | 31.3 ± 4.4 | 30.4 ± 3.6 | 0.360 |
| BMI change (kg/m²) | −0.9 ± 0.8 | −0.9 ± 0.7 | 0.960 |
| MET-h/day at study baseline | 26.4 ± 2.0 | 27.0 ± 1.7 | 0.210 |
| MET-h/day at end-of-trial | 26.1 ± 2.1 | 26.7 ± 1.7 | 0.250 |

Data are means ± SDs. * HC diet: Energy-restricted diet that contained 60-65% of energy from carbohydrates, 20-25% from fats, and 14-18% from proteins. ** RC diet: Energy-restricted diet that contained 43-49% of energy from carbohydrates, 36-40% from fats, and 14-18% from proteins. *** Obtained from independent samples student’s t-test. † Obtained from Pearson chi-square test. BMI: Body mass index; ACEI: Angiotensin converting enzymes inhibitors; ARB: Aldosterone receptor blockers; CHD: Coronary heart disease; DBP: Diastolic blood pressure; METs: Metabolic equivalents; HbA1c: Hemoglobin A1c; DM: Diabetes mellitus; SBP: Systolic blood pressure; SD: Standard deviation; HC: High-carbohydrate; RC: Restricted carbohydrate.

In a study by Ballard et al., was seen that carbohydrate limited diets for 6 weeks decreased insulin, HOMA-IR and triglycerides values, but unchanged FPG and other lipid fractions. A meta-analysis study has shown that changes in values of hemoglobin A1c, FPG, total- and low-density lipoprotein-cholesterol did not differ significantly between the HC and low-carbohydrate groups. However, the HC diet significantly increased insulin and triglycerides concentrations by 8% and 13%, respectively, and lowered HDL-cholesterol by 6% compared with the low-carbohydrate diet. A significant improvement of lipid profiles was seen following the consumption of a carbohydrate-restricted diet among patients with MetS.

This study demonstrated that compared with an HC diet, adherence to RC diet for 8 weeks decreased serum hs-CRP and increased plasma TAC and GSH concentrations, while it did not affect plasma NO and MDA in overweight diabetic patients with CHD. In line with our study, in a parallel randomized clinical trial, Forsythe et al. demonstrated that a very-low-carbohydrate diet (12% of energy from carbohydrate) led to a greater reduction in some inflammatory markers compared to a low-fat diet among overweight men and women with atherogenic dyslipidemia. In addition, in another study among insulin-resistant patients, moderate carbohydrate restriction for 12 weeks resulted in lower inflammatory marker concentrations compared to fat restriction.
Table 2. Dietary intakes of study participants throughout the study

| Dietary intakes                  | HC diet (n = 28) | RC diet a (n = 28) | P*  |
|----------------------------------|------------------|-------------------|-----|
| Energy (kcal/day)                | 1679.0 ± 78.0    | 1652.0 ± 72.0     | 0.200 |
| Carbohydrates (g/day)            | 265.7 ± 16.9     | 200.0 ± 9.2       | < 0.001 |
| MUFA (g/day)                     | 15.9 ± 0.1       | 26.7 ± 1.3        | < 0.001 |
| Fat (g/day)                      | 46.5 (46.5, 46.9)| 73.0 (70.1, 74.6) | < 0.001 t |
| SFAs (g/day)                     | 16.6 (16.6, 16.9)| 23.1 (22.0, 23.5) | < 0.001 t |
| PUFAs (g/day)                    | 9.8 (9.7, 9.8)   | 18.6 (17.2, 18.7) | < 0.001 t |
| Protein (g/day)                  | 57.1 (57.1, 62.1)| 60.9 (57.2, 62.0) | 0.100 t  |
| Cholesterol (mg/day)             | 111.3 (0.8)      | 133.2 (8.5)       | < 0.001 t |

Values are means ± SDs for normally distributed variables and median (Q1,Q3) for non-normally distributed variables. HC diet: Energy-restricted diet that contained 60-65% of energy from carbohydrates, 20-25% from fats, and 14-18% from proteins. RC diet: Energy-restricted diet that contained 43-49% of energy from carbohydrates, 36-40% from fats, and 14-18% from proteins. Obtained from independent samples student’s t-test. MUFA: Monounsaturated fatty acids; PUFAs: Polyunsaturated fatty acids; SFAs: Saturated fatty acids; SD: Standard deviation; HDL: High-density; RC: Restricted carbohydrate

Barbosa et al. 32 also indicated that low energy and carbohydrate intake for 2 months were associated with higher TAC levels in apparently healthy adults. Moreover, the energy intake limitation by 2000 kJ among obese persons decreased oxidative stress. 33

Table 3. Effect of a restricted carbohydrate (RC) diet on metabolic profiles, biomarkers of inflammation and oxidative stress at baseline and 8 weeks after the intervention in patients with overweight type 2 diabetes mellitus (T2DM) and coronary heart disease (CHD)

| Variables                        | HC diet (n = 28) | RC diet (n = 28) | P*  |
|----------------------------------|------------------|------------------|-----|
| **FG (mg/dl)**                   | 124.1 ± 41.9     | 131.1 ± 48.9     | 0.170 |
| **Insulin (µIU/ml)**             | 151.5 ± 73       | 139.3 ± 59       | 0.160 |
| **HOMA-R**                       | 45.4 ± 21        | 42.4 ± 21        | 0.180 |
| **HOMA-B**                       | 45.1 ± 300       | 409.2 ± 241      | 0.180 |
| **QUICKI**                       | 0.31 ± 0.02      | 0.31 ± 0.02      | 0.370 |
| **Triglycerides** (mg/dl)        | 1305.4 ± 42.6    | 1447.8 ± 82      | 0.360 |
| **VLDL-cholesterol** (mg/dl)     | 26.1 ± 85        | 289.16 ± 16      | 0.360 |
| **Total cholesterol** (mg/dl)    | 1547.3 ± 32      | 1551.4 ± 429     | 0.920 |
| **LDL-cholesterol** (mg/dl)      | 77.5 ± 26.7      | 76.2 ± 36.4      | 0.810 |
| **HDL-cholesterol** (mg/dl)      | 51.0 ± 100       | 499.9 ± 93       | 0.440 |
| **Total-HDL-cholesterol** (mg/dl)| 3.1 ± 08         | 3.1 ± 07         | 0.760 |
| **hs-CRP (ng/ml)**               | 23480.2 ± 1925   | 2634.1 ± 1897    | 0.400 |
| **NO (µmol/l)**                  | 421.6 ± 99       | 450.8 ± 88       | 0.100 |
| **TAC (mmol/l)**                 | 802.0 ± 1694     | 882.2 ± 1784     | 0.200 |
| **GSH (µmol/l)**                 | 403.5 ± 100.6    | 370.9 ± 578      | 0.050 |
| **MDA(µmol/l)**                  | 3.1 ± 07         | 3.1 ± 05         | 0.920 |

All values are means ± SDs. HC diet: Energy-restricted diet that contained 60-65% of energy from carbohydrates, 20-25% from fats, and 14-18% from proteins. RC diet: Energy-restricted diet that contained 43-49% of energy from carbohydrates, 36-40% from fats, and 14-18% from proteins. Obtained from independent samples student’s t-test. P values represent independent samples student’s t-test. CHD: Coronary heart disease; FPG: Fasting plasma glucose; GSH: Total glutathione; HOMA-R: Homeostasis model of assessment-estimated insulin resistance; HOMA-B: Homeostasis model of assessment-estimated B cell function; hs-CRP: High-sensitivity C-reactive protein; RC: Moderately restricted carbohydrate; MDA: Malondialdehyde; NO: Nitric oxide; QUICKI: Quantitative insulin sensitivity check index; TAC: Total antioxidant capacity; T2DM: Type 2 diabetes mellitus; SD: Standard deviation; HC: High-carbohydrate; RC: Restricted carbohydrate; VLDL: Very-low-density lipoprotein; LDL: Low-density lipoprotein; HDL: High-density lipoprotein

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Table 4. Adjusted changes in metabolic variables in patients with overweight type 2 diabetes mellitus (T2DM) and coronary heart disease (CHD)

| Variables                  | HC diet** (n = 28) | RC diet** (n = 28) | P***   |
|----------------------------|--------------------|--------------------|--------|
| FPG (mg/dl)                | 6.900 ± 3.100      | −11.300 ± 3.100    | 0.010  |
| Insulin (µIU/ml)           | −0.600 ± 0.700     | −1.700 ± 0.700     | 0.250  |
| HOMA-IR                    | −0.200 ± 0.200     | −0.500 ± 0.200     | 0.350  |
| HOMA-B                     | −2.100 ± 2.200     | −5.500 ± 2.200     | 0.310  |
| QUICKI                     | 0.004 ± 0.002      | 0.006 ± 0.002      | 0.060  |
| Triglycerides (mg/dl)      | 14.000 ± 11.400    | 6.900 ± 11.400     | 0.660  |
| VLDL-cholesterol (mg/dl)   | 2.800 ± 2.300      | 1.400 ± 2.300      | 0.660  |
| Total cholesterol (mg/dl)  | 2.800 ± 6.000      | 0.700 ± 6.000      | 0.800  |
| LDL-cholesterol (mg/dl)    | −1.300 ± 5.200     | 0.700 ± 5.200      | 0.770  |
| HDL-cholesterol (mg/dl)    | 1.600 ± 1.400      | −1.700 ± 1.400     | 0.150  |
| Total/HDL-cholesterol ratio| −0.100 ± 0.100     | 0.100 ± 0.100      | 0.210  |
| hs-CRP (ng/ml)             | 232.100 ± 260.000  | −514.300 ± 260.000 | 0.040  |
| NO (µmol/l)                | 0.300 ± 1.500      | 3.900 ± 1.500      | 0.140  |
| TAC (mmol/l)               | 9.400 ± 18.100     | 285.600 ± 18.100   | <0.001 |
| GSH (µmol/l)               | −41.300 ± 13.400   | 60.300 ± 13.400    | <0.001 |
| MDA (µmol/l)               | 0.200 ± 0.100      | 0.003 ± 0.100      | 0.130  |

All values are means ± standard error. Values are adjusted for baseline values, age, BMI at baseline, METs change and familial history. HC diet: Energy-restricted diet that contained 60-65% of energy from carbohydrates, 20-25% from fats, and 14-18% from proteins. RC diet: Energy-restricted diet that contained 43-49% of energy from carbohydrates, 36-40% from fats, and 14-18% from proteins. *** Obtained from ANCOVA. FPG: Fasting plasma glucose; GSH: Total glutathione; HOMA-IR: Homeostasis model of assessment estimated insulin resistance; HOMA-B: Homeostasis model of assessment estimated B-cell function; hs-CRP: High-sensitivity C-reactive protein; MDA: Malondialdehyde; METs: Metabolic equivalents; NO: Nitric oxide; QUICKI: Quantitative insulin sensitivity check index; TAC: Total antioxidant capacity; HC: High-carbohydrate; VLDL: Very-low-density lipoprotein; LDL: Low-density lipoprotein; HDL: High-density lipoprotein

However, consumption of an RC diet compared with an HC diet did not affect any significant effect on inflammatory biomarkers among women with MetS for 6 weeks. In another study by Rankin and Turpyn, low carbohydrate diet compared with HC diet increased CRP during weight loss among overweight women for 4 weeks. The previous studies have shown that acute ingestion of carbohydrate clearly induces ROS, inflammation and oxidative stress. Decreased total saturated fatty acids, palmitoleic acid levels, down-regulation of nuclear factor-kappa B and cyclooxygenase-2 expression following the consumption of an RC diet may result in its anti-inflammatory and anti-oxidative effects. It must be considered that consumption of the MRC diet significantly decreased serum hs-CRP (564.3 ng/ml), and increased plasma TAC (274.8 mmol/l), and GSH (51.6 µmol/l) concentrations in this study.

One strength of our study was an assessment of metabolic status and its randomized design. One of our limitations was no examine the compliance to the RC and HC eating plan. In addition, the current 8-week diet intervention in a group of among 56 overweight diabetic patients with CHD could be viewed as short in duration and small in sample size in comparison to larger clinical trials. In our study, persons were overweight patients with T2D and CHD aged 40-85 years old. We believe that adherence to the same diets in different age ranges may have different outcomes. Therefore, this should be taken into account in the explanation of our findings.

**Conclusion**

RC diet for 8 weeks among overweight diabetic patients with CHD had useful effects on some metabolic indices. This offers an RC diet with high unsaturated and low saturated fat may allow the advantageous remedial potential for overweight persons with T2DM and CHD handling.

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**Conflict of Interests**

Authors have no conflict of interests.

**References**

1. Zhang P, Zhang X, Brown J, Vistisen D, Sicree R, Shaw J, et al. Global healthcare expenditure on
Moderate carbohydrate restriction and T2DM

1. Carbohydrate restriction as a cornerstone in the management of type 2 diabetes: a meta-analysis. Diabetes Care 2009; 32(5): 959-65.

2. Ades PA, Savage PD. Potential benefits of weight loss in coronary heart disease. Prog Cardiovasc Dis 2014; 56(4): 448-56.

3. Garcia-Bailo B, El-Sohemy A, Haddad PS, Arora P, Benzaied F, Karmali M, et al. Vitamins D, C, and E in the prevention of type 2 diabetes mellitus: modulation of inflammation and oxidative stress. Biologies 2011; 5: 7-19.

4. Kotur-Stevuljevic J, Memon L, Stefanovic A, Spasic S, Spasojevic-Kalimanovska V, Bogavac-Stanojevic N, et al. Correlation of oxidative stress parameters and inflammatory markers in coronary artery disease patients. Clin Biochem 2007; 40(3-4): 181-7.

5. Paneni F, Beckman JA, Creager MA, Cosentino F. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part I. Eur Heart J 2013; 34(31): 2436-43.

6. von Bibra H, St John Sutton M, Schuster T, Ceriello A, Siegmund T, Schumm-Draeger PM. Oxidative stress after a carbohydrate meal contributes to the deterioration of diastolic diabetic function in nonhypertensive insulin-treated patients with moderately well controlled type 2 diabetes. Horm Metab Res 2013; 45(6): 449-55.

7. Zhang X, Yan SM, Zheng HL, Hu DH, Zhang YT, Guan QH, et al. A mechanism underlying hypertensive occurrence in the metabolic syndrome: cooperative effect of oxidative stress and calcium accumulation in vascular smooth muscle cells. Horm Metab Res 2014; 46(2): 126-32.

8. Feinman RD, Volek JS. Carbohydrate restriction as the default treatment for type 2 diabetes and metabolic syndrome. Scand Cardiovasc J 2008; 42(4): 256-63.

9. Muzio F, Mondazzi L, Harris WS, Sommariva D, Branchi A. Effects of moderate variations in the macronutrient content of the diet on cardiovascular disease risk factors in obese patients with the metabolic syndrome. Am J Clin Nutr 2007; 86(4): 946-51.

10. Parillo M, Rivellese AA, Ciardullo AV, Capaldo B, Giacco A, Genovese S, et al. A high-monounsaturated-fat/low-carbohydrate diet improves peripheral insulin sensitivity in non-insulin-dependent diabetic patients. Metabolism 1992; 41(12): 1373-8.

11. Jonasson L, Guldbrand H, Lundberg AK, Nyström FH. Advice to follow a low-carbohydrate diet has a favourable impact on low-grade inflammation in type 2 diabetes compared with advice to follow a low-fat diet. Ann Med 2014; 46(3): 182-7.

12. Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Sato M, et al. Influence of fat and carbohydrate proportions on the metabolic profile in patients with type 2 diabetes: a meta-analysis. Diabetes Care 2009; 32(5): 959-65.
25. Lachin JM. Fallacies of last observation carried forward analyses. Clin Trials 2016; 13(2): 161-8.
26. Mirhashemi SM, Najafi V, Raygan F, Asemi Z. The effects of coenzyme Q10 supplementation on cardiometabolic markers in overweight type 2 diabetic patients with stable myocardial infarction: A randomized, double-blind, placebo-controlled trial. ARYA Atheroscler 2016; 12(4): 158-65.
27. Zarei M, Farahnak Z, Hosseinzadeh-Attar MJ, Javanbakht MH, Hosseinzadeh P, Derakhshanian H, et al. Lipid peroxidation and antioxidant enzymes activity in controlled and uncontrolled Type 2 diabetic patients. ARYA Atheroscler 2016; 12(3): 118-23.
28. Ballard KD, Quann EE, Kupchak BR, Volk BM, Kawiecki DM, Fernandez ML, et al. Dietary carbohydrate restriction improves insulin sensitivity, blood pressure, microvascular function, and cellular adhesion markers in individuals taking statins. Nutr Res 2013; 33(11): 905-12.
29. Hickey JT, Hickey L, Yancy WS, Hepburn J, Westman EC. Clinical use of a carbohydrate-restricted diet to treat the dyslipidemia of the metabolic syndrome. Metab Syndr Relat Disord 2003; 1(3): 227-32.
30. Forsythe CE, Phinney SD, Fernandez ML, Quann EE, Wood RJ, Bibus DM, et al. Comparison of low fat and low carbohydrate diets on circulating fatty acid composition and markers of inflammation. Lipids 2008; 43(1): 65-77.
31. McLaughlin T, Carter S, Lamendola C, Abbasi F, Yee G, Schaaf P, et al. Effects of moderate variations in macronutrient composition on weight loss and reduction in cardiovascular disease risk in obese, insulin-resistant adults. Am J Clin Nutr 2006; 84(4): 813-21.
32. Barbosa KB, Volp AC, Marques-Rocha JL, Ribeiro SM, Navarro-Blasco I, Zulet MA, et al. Low energy and carbohydrate intake associated with higher total antioxidant capacity in apparently healthy adults. Nutrition 2014; 30(11-12): 1349-54.
33. Skalicky J, Muzakova V, Kandar R, Meloun M, Rousar T. Oxidative stress and metabolic syndrome in obese adults with and without controlled diet restriction. Bratisl Lek Listy 2009; 110(3): 152-7.
34. Rankin JW, Turpyn AD. Low carbohydrate, high fat diet increases C-reactive protein during weight loss. J Am Coll Nutr 2007; 26(2): 163-9.
35. Lee JY, Zhao L, Youn HS, Weatherill AR, Tapping R, Feng L, et al. Saturated fatty acid activates but polyunsaturated fatty acid inhibits Toll-like receptor 2 dimerized with Toll-like receptor 6 or 1. J Biol Chem 2004; 279(17): 16971-9.

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