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The Dietary Approaches to Stop Hypertension Eating Plan Affects C-Reactive Protein, Coagulation Abnormalities, and Hepatic Function Tests among Type 2 Diabetic Patients[1–4]

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Abstract

Few studies exist regarding the effects of the Dietary Approaches to Stop Hypertension (DASH) diet on novel cardiovascular risk factors among type 2 diabetic patients. We evaluated the effects of the DASH eating pattern on C-reactive protein (CRP) level, coagulation abnormalities, and hepatic function tests in type 2 diabetic patients. In this randomized, crossover clinical trial, 31 type 2 diabetic patients consumed a control diet or the DASH diet for 8 wk. The DASH diet was rich in fruits, vegetables, whole grains, and low-fat dairy products and low in saturated fat, total fat, cholesterol, refined grains, and sweets, with a total of 2400 mg/d sodium. The control diet was a standard diet for diabetic patients. There was a 4-wk washout between the 2 trial phases. The main outcome measures were CRP level, coagulation indices, and hepatic function tests. The mean percent change for plasma CRP level was $-26.9 \pm 3.5\%$ after the DASH diet period and $-5.1 \pm 3.8\%$ after the control diet period ($P = 0.02$). Decreases in both alanine aminotransferase and aspartate aminotransferase levels were greater after consuming the DASH diet compared with the control diet ($-14.8 \pm 3.0\%$ vs $-6.6 \pm 3.4\%$; $P = 0.001$; $-29.4 \pm 3.7\%$ vs $-5.9 \pm 1.4\%$; $P = 0.001$, respectively). The decrease in the plasma fibrinogen level during the DASH diet period ($-11.4 \pm 3.6\%$) was greater than that during the control diet ($0.5 \pm 3.4\%$) ($P = 0.03$). Among diabetic patients, the DASH diet can play an important role in reducing inflammation, plasma levels of fibrinogen, and liver aminotransferases. Future longer term studies are recommended. J. Nutr. 141: 1083–1088, 2011.

Introduction

As many as 80% of patients with type 2 diabetes mellitus will develop and possibly die of macrovascular disease (1,2). Dyslipidemia and fibrinolytic and coagulation abnormalities play a leading role in increased cardiovascular risk among diabetics (3–5). Serum levels of aminotransferases also are elevated in type 2 diabetic patients and are associated with the development of cardiovascular risk and glycemic control abnormalities (6). There is also a major role for inflammation in the pathogenesis of type 2 diabetes. Furthermore, current evidence suggests that local C-reactive protein (CRP)[10] concentrations in diabetic atherosclerotic plaques could be higher than in nondiabetic ones (7).

Therefore, a therapeutic approach that can reduce inflammation and control cardiometabolic risk might be beneficial for diabetic patients (8). Evidence suggests that adherence to a healthy diet has beneficial effects on the management of obesity, type 2 diabetes, and cardiovascular events (9).

The Dietary Approaches to Stop Hypertension (DASH) diet, which encourages the intake of fruits, vegetables, and low-fat dairy products combined with sodium restriction, was developed for hypertensive patients (10). Actually, it is a well-balanced diet that is currently recommended for all adults (11). This diet is high

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[3] This trail was registered at clinicaltrials.gov as NCT01049321.
[4] Supplemental Fig. 1 is available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at jn.nutrition.org.
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[10] Abbreviations used: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; DASH, Dietary Approaches to Stop Hypertension; hs-CRP, high sensitivity C-reactive protein; MET, metabolic equivalent.

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in fiber, antioxidant components, unsaturated fatty acids, and low-fat dairy, which may be important for improved insulin resistance, decreasing the levels of inflammation and metabolic disturbance (12,13). Previous epidemiological studies found that the DASH eating pattern was associated with lower risk of type 2 diabetes (14), hypertension (15,16), and coronary heart disease (17,18). Prior research has also revealed that the DASH diet is beneficial for features of metabolic syndrome (12). Although there are existing trials on the diet's effects on hypertensive patients (19–21) and we previously assessed the effect of the DASH eating pattern on traditional cardiovascular risk factors among type 2 diabetics (22), we are unaware of studies that have examined the effect of the DASH eating pattern on novel cardiovascular risk factors in type 2 diabetic patients. In the present paper, we assess the effects of DASH on novel cardiovascular risk factors such as CRP, coagulation abnormalities, and tests of hepatic function among type 2 diabetic patients.

Research Design and Methods

Participants. According to medical records, a total of 60 patients diagnosed with type 2 diabetes at the Shaheed Motahari Hospital of Fooladshahr in Isfahan who had health insurance from the Isfahan Steel Company were eligible for the study. Of the patients invited in 2009, 15 refused and 1 patient no longer met the criteria for type 2 diabetes. In total, 44 patients enrolled. The sample size was calculated based on the formula suggested for cross-over trials (23): $n = [(Z_{1-\alpha/2}+Z_{1-\beta})^2 \cdot S^2]/2\Delta^2$, where α (type 1 error) was 0.05, β (type 2 error) was 0.20, S (the variance of CRP) was 2, and Δ (the difference in mean CRP) was 1. We considered CRP as our principal outcome variable and calculated the mean and variance of CRP: $n = [(1.96+1.28)^2 \cdot (2)^2]/2\,(1)^2 = 21$ (13). According to the formula, 21 patients were needed for adequate power.

A diagnosis of type 2 diabetes was confirmed if a patient either had fasting plasma glucose ≥ 126 mg/dL (6.3 mmol/L) or was taking oral glucose-lowering agents or insulin (24). Exclusion criteria are provided elsewhere (22). All participants provided informed written consent. This study was approved by the research council and ethics committee of the Isfahan University of Medical Sciences. The facilities for conducting research and biochemical experiments were provided by the Shahid Motahari Hospital of Fooladshahr.

Study procedures. We used a randomized cross-over design. After a 3-wk run-in, patients were randomly assigned to 8 wk of a control diet or the DASH diet. Group assignments were made using random sequencing generated in SPSS. Because this was a dietary intervention, patients were not blinded.

Measurements were obtained before and after each diet period (baseline and follow-up). During the study period, patients were prescribed the diet and prepared their own meals while living independently but were asked to not change their usual physical activity level. Every month, patients recorded their physical activity for 3 d.

Diets. We prescribed 2 diets for each patient: a control diet and the DASH diet. The control diet included macronutrient composition of 50–60% carbohydrates, 15–20% protein, <30% total fat, and <5% of energy intake from simple sugars (25). The DASH diet was rich in fruits, vegetables, whole grains, and low-fat dairy products, and low in saturated fat, total fat, cholesterol, refined grains, and sweets. Sodium intake was 2400 mg/d (8), which was based on the Iranian Food Composition Table. We prescribed adding minimal salt [only 1 teaspoon/d (4.6 g/d)] while cooking and insisted on removing table salt. Macronutrient composition did not differ between the DASH and control diets. However, the amount of PUFA was higher in the DASH diet ($P < 0.05$).

To calculate the energy requirement for each participant, we used equations suggested by the Institute of Medicine, Food and Nutrition Board (26). Diets were individually tailored using an energy count system and an exchange list was given to each patient to suggest substitutions for particular food items and to calculate energy.

Patient adherence was assessed in terms of attendance at monthly visits and by analysis of the 3-d food diaries. We found no significant difference between the prescribed amount and the amount consumed from each of the 5 food groups, as derived from the food record.

Measurements. Participants were weighed wearing minimal clothing and without shoes. Height was measured in a standing position, without shoes. Waist circumference was measured where the waist was narrowest over light clothing.

Blood samples were collected after 12 h of overnight fasting. Separate tubes of sodium citrate buffers for plasma and serum were centrifuged at 4°C and 500 × *g* for 10 min. Tests that could be performed immediately were conducted the same day; otherwise, serum and plasma samples were promptly frozen (−20 C). Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) were measured by commercially available enzymatic reagents (Pars Azmoon) on a BT-3000 (Biotechinica) autoanalyzer. High-sensitivity CRP (hs-CRP) ELISA was performed on serum (IBL International). Inter- and intra-assay CV were <5% for all measurements. We used standard and control solutions for all measurements and standard curves were plotted for all of these standardized measurements. The plasma fibrinogen level was measured by using the Clauss method, which quantitatively determines the concentration of fibrinogen by adding thrombin and recording the rate of fibrinogen conversion to fibrin. The plasma D-dimer level was determined by immunometric flow through, which uses a specific monoclonal antibody against D-dimer by using a Nycocord Instrument. The laboratory staff were unaware of the treatment status.

Statistical analysis. We used General Linear Models (paired *t* tests) to globally compare means of all variables at the end of the 2 different diet periods with and without adjustment for weight. We calculated the percent change for each variable using the formula (E − B/B)×100, where E was the end of treatment value and B was the baseline value. Groups were compared using the percent change in the General Linear Model (paired *t* test) analyses. We used ANCOVA to compare adjusted means of end values and percent changes while weight change was included as a covariate.

Results were considered significant if the 2-tailed *P*-value was <0.05. Values reported in the text are mean ± SEM. Statistical analyses were performed using the SPSS for Windows version 13.0.

Results

Of the 44 participants, 31 type 2 diabetic patients completed the entire cross-over study. During the study, 1 patient was diagnosed with cancer and another with anemia, so these 2 patients could not follow their diets. Eleven patients deviated from the study protocol and therefore, their data were not available. The study flow diagram is provided in **Supplemental**

Figure 1. The mean patient age was 55.0 ± 6.5 y and the mean time since diagnosis of diabetes was 4 ± 0.5 y. Forty-one percent (n = 13) were male and 59% (n = 18) were female. According to medical records, none had retinopathy or nephropathy. Eighty percent (n = 25) were using oral hypoglycemic agents, 16% (n = 5) were using blood lipid-lowering agents, 16% (n = 5) were taking antihypertensive medications, 25% (n = 8) were consuming multivitamin mineral pills, and 9.6% (n = 3) were using herbal treatments (e.g. fenugreek seeds, green tea, and nettle). No other medications were reported. Medication dosage stayed constant for all patients throughout the study period. No patients were smokers.

Nutrient content and servings per food group from the 3-d diet self-report are shown (**Table 1**). Both diets were well tolerated. None of patients had complications after adoption of either diet. Participants' activity levels remained the same during the entire study period [mean and SE of physical activity during the control diet: 2.47 ± 0.21 metabolic equivalent (MET)·h/d; during the DASH diet: 2.61 ± 0.26 MET·h/d; P = 0.13).

The change in weight differed between the control (−2.8 ± 0.4%) and DASH (−6.5 ± 1.2%) diet periods (P = 0.007). Compared with the control diet, the fasting blood glucose level was −13.9 ± 4.5%, waist circumference was –5.6 ± 1.2%, and weight was –5.9 ± 1.1% lower following the DASH diet. With the DASH eating pattern, LDL cholesterol was reduced more than with the control diet (difference from the control diet, −7.7 ± 3.3%). Systolic and diastolic blood pressure were reduced by −9.6 ± 1.8% and −9.9 ± 3.6%, respectively. Compared with the control diet, the mean HDL cholesterol after the DASH diet period was 7.6 ± 1.7% lower. In summary, all these variables decreased significantly more during the DASH diet period than during the control diet period.

There were no significant differences in the baseline characteristics of the study participants except for the concentrations of direct bilirubin and ALT (**Table 2**). At the end of each diet period, concentrations of fibrinogen, AST, ALP, and hs-CRP differed and the differences remained significant in a separate, weight-adjusted model.

The percent change during the 2 diets differed for plasma fibrinogen, ALT, AST, and hs-CRP (Table 3). After adjusting for the effect of weight in a separate model, all significant changes remained.

Plasma fibrinogen was −8.6 ± 4.2% lower during the DASH diet period than during the control diet period. AST and ALT were −19.9 ± 9.9% and −9.7 ± 4.8% lower, respectively, during the DASH diet period compared with the control diet period. During the DASH eating pattern, the CRP level was reduced more than during the control diet (difference from the control diet: −16.9 ± 7.4%).

Discussion

We found that the DASH eating pattern had beneficial effects on type 2 diabetic patients' novel cardiovascular risk factors, at least in the short term. After following the DASH diet for 8 wk, liver transferase enzymes, plasma fibrinogen level, and hs-CRP were reduced. Previous epidemiological studies have shown that adherence to the DASH dietary pattern may prevent type 2 diabetes (14), hypertension (14,15), and coronary heart disease (16). Clinical trials also indicated beneficial effects of DASH on lowering blood pressure (19–21,27). It is possible that even an educational program teaching the DASH diet via the internet could have beneficial effects on weight and blood pressure (28). To our knowledge, the present study is the first to examine the effects of the DASH eating pattern on novel cardiovascular risk factors among type 2 diabetic patients. Although previous studies have shown beneficial effects on patients with metabolic syndrome (12) and hypertension (19–21), they did not consider fibrinogen levels and hepatic functional tests.

In the present study, after assignment to the DASH diet, plasma fibrinogen levels were significantly reduced, which might be related to the higher vitamin C, fiber, and phytochemical

TABLE 1 Dietary intakes by type 2 diabetic patients who consumed DASH and control diets for 8 wk[1]

Daily dietary intakes	Control diet	DASH diet	P	Wash-out[2]
Nutrients				
Energy, *MJ*	9.06 ± 0.12	9.16 ± 0.14	0.62	8.82 ± 0.19
Protein, *% of energy*	15 ± 0.8	16 ± 0.9	0.71	15 ± 0.8
Total fat, *% of energy*	28 ± 0.9	29 ± 1.1	0.44	30 ± 1.6
Saturated fat, *% of energy*	7 ± 0.8	5 ± 0.5	0.61	10 ± 0.5
Polyunsaturated fat, *% of energy*	8 ± 0.6	13 ± 0.5	<0.05	9 ± 0.6
Monounsaturated fat, *% of energy*	11 ± 0.5	10 ± 0.6	0.73	9 ± 0.5
Cholesterol, *mg*	198 ± 10	194 ± 9	0.51	239 ± 13
Carbohydrate, *% of energy*	57 ± 1	55 ± 2	0.79	55 ± 2
Fiber, *g*	26 ± 1	30 ± 2	<0.05	18 ± 2
Potassium, *g*	3.22 ± 0.16	4.40 ± 0.18	<0.05	2.35 ± 0.13
Calcium, *mg*	912 ± 71	1299 ± 77	<0.05	723 ± 85
Food groups, *g*				
Fruits	311 ± 87	516 ± 113	<0.05	215 ± 79
Vegetables	114 ± 37	179 ± 69	<0.05	87 ± 21
Total grains	405 ± 126	270 ± 89	<0.05	330 ± 110
Whole grains	75 ± 22	135 ± 43	<0.05	30 ± 10
Low-fat dairy	360 ± 125	720 ± 234	<0.05	120 ± 32
Regular-fat dairy	129 ± 35	0	<0.05	120 ± 0.1
Red meat	30 ± 8	21 ± 7	0.26	48 ± 11
Poultry and fish	60 ± 24	60 ± 23	0.79	15 ± 7

[1] Values are mean ± SEM, n = 31.
[2] Wash-out period: patients returned to the diet used before the study.

TABLE 2 Differences in novel cardiovascular risk factors among type 2 diabetic patients following consumption of the DASH and control diets for 8 wk[1]

Serum measure	Control diet, $n = 31$	DASH diet, $n = 31$	P
D-dimer, *mg/L*			
Baseline	0.13 ± 0.01	0.12 ± 0.01	0.36
End	0.11 ± 0.007	0.11 ± 0.01	0.67
Adjusted[2]	0.12 ± 0.01	0.11 ± 0.01	0.84
Percent change	−3.8 ± 4.3	−1.0 ± 4.0	0.09
Adjusted[2]	−5.3 ± 4.4	0.1 ± 4.3	0.39
Fibrinogen, *g/L*			
Baseline	301.3 ± 5.6	304.4 ± 3.9	0.66
End	298.1 ± 5.7	268.0 ± 10.8	0.02
Adjusted[2]	161.3 ± 10.1	265.7 ± 10.0	0.001
Percent change	0.5 ± 3.4	−11.4 ± 3.6	0.03
Adjusted[2]	0.8 ± 3.7	−11.1 ± 3.7	0.03
hs-CRP, *mg/L*			
Baseline	3.11 ± 0.30	2.90 ± 0.31	0.85
End	2.91 ± 0.30	2.04 ± 0.20	0.02
Adjusted[2]	2.92 ± 0.2	2.03 ± 0.27	0.03
Percent change	−5.1 ± 3.8	−26.9 ± 3.5	0.001
Adjusted[2]	−0.2 ± 0.1	−0.9 ± 0.1	0.02
ALT, *IU/L*			
Baseline	12.3 ± 0.7	14.1 ± 0.6	0.01
End	11.4 ± 0.7	11.8 ± 0.5	0.60
Adjusted[2]	11.5 ± 0.6	11.8 ± 0.6	0.76
Percent change	−6.6 ± 3.4	−14.8 ± 3.0	0.001
Adjusted[2]	−5.7 ± 3.4	−15.7 ± 3.4	0.04
AST, *IU/L*			
Baseline	11.3 ± 1.0	10.0 ± 0.4	0.23
End	10.7 ± 1.0	6.3 ± 0.3	0.001
Adjusted[2]	10.8 ± 0.8	6.7 ± 0.8	0.001
Percent change	−5.9 ± 1.4	−29.4 ± 3.7	0.001
Adjusted[2]	−6.5 ± 2.9	−28.8 ± 2.9	0.001
ALP, *IU/L*			
Baseline	193.0 ± 6.6	187.0 ± 7.1	0.22
End	191.1 ± 6.6	178.2 ± 5.8	0.01
Adjusted[2]	190.2 ± 6.6	179.2 ± 6.5	0.25
Percent change	−0.7 ± 2.5	−3.5 ± 2.8	0.23
Adjusted[2]	−1.0 ± 1.8	−3.1 ± 1.8	0.44
Total bilirubin, *IU/L*			
Baseline	0.59 ± 0.02	0.59 ± 0.02	0.85
End	0.57 ± 0.02	0.55 ± 0.02	0.35
Adjusted[2]	0.56 ± 0.02	0.56 ± 0.02	0.83
Percent change	−10.8 ± 3.8	−5.8 ± 1.7	0.29
Adjusted[2]	−11.1 ± 3.1	−5.5 ± 3.1	0.22
Direct bilirubin, *IU/L*			
Baseline	0.16 ± 0.01	0.13 ± 0.01	0.04
End	0.13 ± 0.01	0.12 ± 0.01	0.19
Adjusted[2]	0.13 ± 0.01	0.12 ± 0.01	0.74
Percent change	−10.8 ± 3.8	−6.2 ± 2.4	0.28
Adjusted[2]	−10.4 ± 3.3	−6.6 ± 3.3	0.44

[1] Values are mean ± SEM, $n = 31$.
[2] Adjusted for weight reduction.

contents of this diet. Research has been inconsistent regarding the relationship between fiber intake and plasma fibrinogen level (29–33). Some cross-sectional studies have reported an inverse association (29,30), whereas some clinical trials and also observational studies have found no significant effect of fiber intake on fibrinolytic activity (31,32). Different methods used to measure fibrinogen levels might be responsible for these conflicting results. The DASH dietary pattern has higher soluble fiber. The favorable effect of soluble fiber intake on homeostatic risk factors for coronary heart disease might be explained by the production of SCFA, which may inhibit the hepatic synthesis of coagulating factors (33). Furthermore, these kind of fatty acids decrease serum fatty acids that result in an elevation of insulin sensitivity and in turn decrease the fibrinogen concentration (33). Current evidence also indicates that low-glycemic index diets could have a beneficial effect on serum fibrinogen levels (34).

Given our results, the DASH eating pattern could reduce plasma CRP levels. The DASH diet has high amounts of fiber that might be correlated with lower levels of inflammatory markers. A randomized, cross-over intervention showed that a high-fiber (30 g/d) DASH diet or a fiber-supplemented diet (30 g/d) could reduce plasma levels of CRP (35). The DASH diet had higher amounts of fruits and vegetables, which have been inversely associated with plasma CRP level in Tehranian women (36). Furthermore, whole grain intake is inversely related to plasminogen activator inhibitor-1 and plasma CRP concentrations (37).

Sodium intake was restricted in the DASH diet. Higher sodium intake is associated with increased levels of inflammation (38) and this might be related to higher levels of coagulation (39). However, a recent clinical trial showed that a low-sodium diet had no effect on measures of inflammation or coagulation (40).

Although ALT concentrations did not differ at the end of the 2 diet periods, the percent decrease was significantly greater during the DASH diet period, perhaps due to the differences at baseline. Because of this significant difference at baseline, the percent change was more important for this variable compared with AST, for which there was no significant difference observed at baseline.

Recent studies have shown that these liver enzymes are correlated with diabetes and cardiovascular diseases (6). Because of serum liver enzyme's status as a novel cardiovascular risk factor and its association with glycemic control abnormalities, our study provides new evidence for the benefits of consuming a specific diet, like DASH, for type 2 diabetic patients.

In summary, the DASH eating pattern is a diet characterized by high quantities of whole grains, vegetables, fruits, and legumes and, therefore, high amounts of fiber, which may confer advantages on glycemic control and other cardiometabolic risk factors related to insulin status and cardiometabolic risks (41). A higher intake of legumes in the DASH eating pattern might also be responsible for its beneficial effects on metabolic parameters. Soy products, also consumed in higher quantities in the DASH diet, might be associated with better cardio-metabolic status and lower plasma levels of CRP (42,43). Red meat consumption was also lower during the DASH diet period. An Iranian study showed a relationship between red meat intake and plasma CRP level (44). However, consuming higher amounts of nonhydrogenated vegetable oil while on the DASH diet may provide an explanation (45,46). The effects of the DASH diet on other cardiometabolic risk factors assessed in the present trial show weight and waist circumference reduced to a significantly greater degree following the DASH diet compared with the control diet (22). Therefore, the extent to which the benefits of the DASH eating pattern on inflammation, coagulation, and liver enzyme levels are mediated by weight loss is not clear. However, because significant associations remained after adjustment for weight, it appears that the DASH diet exerts beneficial effects independent of weight reduction.

The rate of noncompliance in the DASH and control groups was the same, so compliance did not differ. Because our cross-over trial took place over a short time period, we had few patients

who dropped out or were excluded; the number of patients remaining in the study was higher than our calculated sample size of 31. Thus, noncompliance was not a major concern in regard to sample size.

In the current study, patients received only recommendations to follow a particular diet rather than receiving preprepared foods. This contrasts with previous reports, in which researchers controlled exactly what the participants consuming the DASH diet ate. In our study, dietary intake was assessed through patients' self-reported food records. Although the diets in our study were not followed exactly, our results suggest that even imperfect compliance with the DASH diet recommendations could have benefits. Our trial should have good external validity, because we conducted this study on type 2 diabetic patients without any specific disorder. During the study, the physician was requested not to change medication dosages to avoid any resulting bias. Therefore, when possible, medication regimens were changed only upon conclusion of the study.

The DASH eating pattern may play an important role in managing novel risk factors for cardiovascular diseases among type 2 diabetic patients. Longer term studies are needed to assess whether these effects are maintained over time.

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