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Comparison of the effect of the Dietary Approaches to Stop Hypertension diet with usual dietary advice on expression of peroxisome proliferators-activated receptor gamma gene in women: A randomized controlled clinical trial

Mohammad Hasan Entezari[(1)], Rasol Salehi[(2)], Mohammad Kazemi[(3)], Mohsen Janghorbani[(4)], Marzieh Kafeshani[(5)]

Original Article

Abstract

BACKGROUND: Peroxisome proliferator-activated receptor gamma (PPAR-γ) which controls body weight, glucose homeostasis, and adipocyte differentiation is a valuable candidate gene for insulin resistance (IR). The present study aimed to compare the effects of the Dietary Approaches to Stop Hypertension (DASH) diet and usual dietary advice (UDA) on PPAR-γ gene expression in women at risk for cardiovascular disease (CVD).

METHODS: This randomized controlled trial was performed on 44 women aged 20-50 years at risk for CVD (BMI > 25 kg/m² and low physical activity). Participants were randomly assigned to the UDA (n = 22) or DASH (n = 22) diets for 12 weeks. 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/day sodium. The UDA diet was a regular diet with healthy dietary advice. Anthropometric indices and PPAR-γ gene expression were measured and compared between the two groups at the end of the study.

RESULTS: After the intervention, body mass index (BMI) and waist circumference (WC) significantly decreased in the DASH group (P < 0.050) but the results showed no significant differences between the two groups. At the end of the trial, PPAR-γ gene expression was significantly different between the UDA and the DASH diet groups (P = 0.040) and this difference remained significant after adjustment for BMI, and physical activity (P = 0.030).

CONCLUSION: The result of the study showed that the DASH diet significantly decreased the expression of PPAR-γ. This finding was unexpected and future studies on the current topic are therefore recommended.

Keywords: Peroxisome Proliferator-Activated Receptor Gamma, DASH Diet, Gene Expression

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Introduction

Insulin resistance (IR), which is described as decreased physiological response of the peripheral tissues to the action of the normal levels of insulin, is the main sign in some metabolic illnesses, such as metabolic syndrome and type two diabetes mellitus (DM).[1] IR aggregates in families and up to 30–70% of type two DM risks can be associated with genetics.[2] Nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR-γ) which is mostly expressed in adipose tissue and controls body weight, glucose homeostasis, and adipocyte differentiation is a valuable candidate gene for IR. Thus, mutations in this gene might affect IR and lipid metabolism.[3,4] Moreover, dietary factors are the most important environmental components in the pathogenesis and development of the general polygenic, food-related diseases; therefore, diet controlling is a crucial factor in the long-term wellbeing and quality of life (QOL) of individuals

1- Associate Professor, School of Nutrition and Food Sciences AND Food Security and Nutrition Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
2- Associate Professor, Department of Genetics and Molecular Biology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
3- Assistant Professor, Department of Genetics and Molecular Biology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
4- Professor, Department of Epidemiology and Biostatistics, School of Public Health, Isfahan University of Medical Sciences, Isfahan, Iran
5- School of Nutrition and Food Sciences AND Food Security and Nutrition Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
Correspondence to: Marzieh Kafeshani, Email: marzikafeshani@hlth.mui.ac.ir

with IR.[5,6] One of these regimes is the Dietary Approaches to Stop Hypertension (DASH) the impact of which on IR is a controversial topic. As regarding the composition of the DASH dietary pattern that contains high levels of calcium, potassium, magnesium, fiber and antioxidants, it is expected to improve insulin action in humans.[7]

The effect of dietary interventions on insulin action might be modified by genetic factors, so identifying the nutrient-sensitive genotypes seems necessary for optimizing nutrition recommendations based on an individual's genetic profile to reduce disorder.[8] To our knowledge, there were no interventional investigations in humans in the field of the effects of special dietary patterns on gene expression. Therefore, the objective of this study was to evaluate the impacts of the DASH diet versus usual dietary advices (UDA) on PPAR-γ gene expression.

Materials and Methods

This randomized controlled clinical trial (RCT) was performed on healthy women volunteers (20-50 years of age) who were at risk of cardiovascular disease (CVD) and referred to Isfahan Endocrine & Metabolism Research Center, Isfahan, Iran, in January 2015. At risk of CVD was defined as BMI > 25 kg/m^2 and low physical activity. Health was evaluated using a questionnaire on personal health, medical history and biochemical experiments. The inclusion criteria consisted of lack of pregnancy or lactation, lack of history of occurrence of hepatic, cardiovascular, gastrointestinal, renal, and thyroid diseases, and rheumatoid arthritis, DM, lupus, trauma, severe infection, and allergy. Moreover, they could not utilize omega-3 fatty acids supplements, multi-vitamins and minerals, antacid comprising magnesium and calcium, aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs) and anti-inflammatory and anti-depressant drugs. Participants were excluded if they had increased physical activity or weight changes during the study or poor adherence to the study protocol.

The research was conducted based on the standards of the Declaration of Helsinki; the design and purpose of the study were described for the participants, and written informed consent was obtained from all subjects. The study was approved by the ethical committee of Isfahan University of Medical Sciences, Iran. This trial was recorded at the Iranian Registry of Clinical Trials (IRCT) with the registered number of IRCT2014090719072N1.

The participants were randomly allocated to a UDA diet or the DASH diet for 12 weeks after a 2-week run-in period. The run-in period was performed to homogenize the groups in terms of the intake of macronutrients and basis of diets. The UDA diet was prescribed for patients in this stage. Group allocations were performed using random sequencing. The individual who prescribed the diets was aware of the group allocation, but laboratory members were blinded. The participants' socio-economic status was assessed using a validated questionnaire for Iranians.[9] The participants were evaluated every 2 weeks, and anthropometric and physical activity measurements were recorded. The diet was prescribed for patients. They were asked to record their physical activity 3 days every month and not change their activity level record, then, reported activities were scored and coded based on the Compendium of Physical Activities and expressed as the metabolic equivalent (MET). MET is the ratio of work metabolic rate to a standard resting metabolic rate and scored from 0.9 (sleeping) to 18 METs (running at 10.9 mph).[10]

Individuals were randomly allocated to one of two diets; UDA diet and the DASH diet. The UDA group was only recommended to "eat as regular" and received healthy dietary advices. The DASH diet was prescribed for the intervention group. The DASH diet is rich in fruits, whole grains, vegetables, low-fat dairy products, and low in saturated fat, cholesterol, total fat, sweets, refined grains and red meat. Moreover, it comprises 2,400 mg sodium per day, which was based on the Iranian Food Composition (Table 1).[11]

Table 1. Dietary goals of the Dietary Approaches to Stop Hypertension intervention vs. usual dietary advice

DASH	Usual dietary advice
at least eight servings/day of fruits and vegetables	Try to have a variety of foods in your daily diet.
two to three servings/day of low-fat dairy products	Do not skip any meals.
1/2 to 1 serving of nuts, seeds, and legumes daily	Minimize the intake of sugar, sweets, and sweetened drinks.
< 2400 mg/d of Na	Before cooking, remove fats and skin of the chicken and meat.
	Try to use whole-wheat and barley breads instead of rice.

DASH: Dietary Approaches to Stop Hypertension

A Mifflin-St Jeor equation was used to estimate the energy requirement for each person.[12] The participants were met every 2 weeks; each session lasted 45–60 minutes. They were contacted by the nutritionist every week by phone. The calorie count system was used to prescribe the diets, and the participants were taught to use the exchange list for modifying food items and calculating calories. Participants had to deliver their 3-day diet records (2 work days and 1 holiday) every month and their diet was evaluated by analyzing the food record diaries using the Nutritionist IV software (version 7.0; N-Squared Computing, Salem, OR, USA) that was adapted for Iranian food items.

Participants were weighed with minimal clothing and without shoes using digital scales (SECA, Hamburg, Germany) with an accuracy of approximately 0.1 kg. Height was measured in a standing position using a tape measure without shoes. Waist circumference was measured where the waist was narrowest over light clothing, using an unstretched tape measure, without pressure on the surface of the body and amounts were recorded with an accuracy of approximately 0.1 cm.

Peripheral blood mononuclear cells isolation, RNA isolation, and real-time polymerase chain reaction: Human peripheral blood mononuclear cells isolation (PBMC) was conducted by centrifugation on a Ficoll-Paque Plus (Amersham Biosciences Corp., Little Chalfont, UK) density gradient. Total RNA was isolated from the PBMC using Trizol® reagent (Invitrogen) according to the manufacturer's instructions. Isolated RNA was dissolved in RNase-free water, and the amount of RNA was determined by measuring absorbance at 260 nm with a spectrophotometer. The RNA samples were treated with DNase I (Thermo Scientific, Waltham, MA, USA) in order to avoid potential contamination with genomic DNA. To synthesize double-stranded cDNA, 2 µg of total RNA was consumed using RevertAid First Strand cDNA Synthesis Kit (Thermo Scientific, Waltham, MA, USA) and oligodT primers. The primers for all assayed genes were designed using the Allele ID software (version 7.6; Primer Biosoft, Palo Alto, CA, USA) (Table 2). The real-time polymerase chain reaction (PCR) was performed using SYBR Green PCR Master Mix (Thermo Scientific, Waltham, MA, USA) and the StepOnePlus™ Real-Time PCR Detection System (Applied Biosystems, Foster City, CA, USA). Glyceraldehydes-3-phosphate dehydrogenase (GAPDH) was used as an endogenous control. The expression level of each target gene was calculated as $2^{-\Delta\Delta Ct}$, as previously described.[13]

Table 2. Primers used in real-time polymerase chain reaction

Gene	Primer sequences	Size (Base pair)
PPARG-F	GCCTTTTGGTGACTTTATGGA	21
PPARG-R	GTAGCAGGTTGTCTTGAATG	20
GAPDH-F	AAGCTCATTTCCTGGTATG	19
GAPDH-R	CTTCCTCTTGTGCTCTTG	18

PPARG: Peroxisome proliferator-activated receptor gamma; GAPDH: Glyceraldehydes-3- phosphate dehydrogenase

The normality of continuous variables, such as age, weight, BMI, waist circumference and physical activity, was evaluated by normal plots and one-sample Kolmogorov-Smirnov test. ANCOVA was used for assessing gene expression differences between the UDA and DASH diet after 12 weeks with changes in weight and waist circumference (WC) and physical activity as covariate. For each dependent variable, the changes from baseline were computed by subtracting the end-of-trial value from the baseline value. Within-group and between-group changes in anthropometric measures as well as biochemical indicators were compared using paired samples t-test and independent t-test, respectively. In addition, chi-square test was used to compare qualitative variables. The SPSS (version 16.0, SPSS Inc., Chicago, IL, USA) was used for statistical analyses and P values of less than 0.05 were considered as significant.

Results

Characteristics: Of the 51 participants, 44 individuals completed the study. During the study, 1 patient was diagnosed with polycystic syndrome and another with high weight change, so these 2 patients had to be excluded from the analyses. Moreover, 5 patients deviated from the study protocol, and therefore, their data were not available. The consort diagram is shown in figure 1. Differences in distribution of several characteristics among 22 individuals in the DASH group and 22 subjects in the UDA group are shown in table 3. The mean age of patients was 38 ± 8 years in the UDA group and 37 ± 9 years in the intervention group. There was no difference between the groups regarding age, socioeconomic status, weight, physical activity (PA) and gene expression at the baseline.

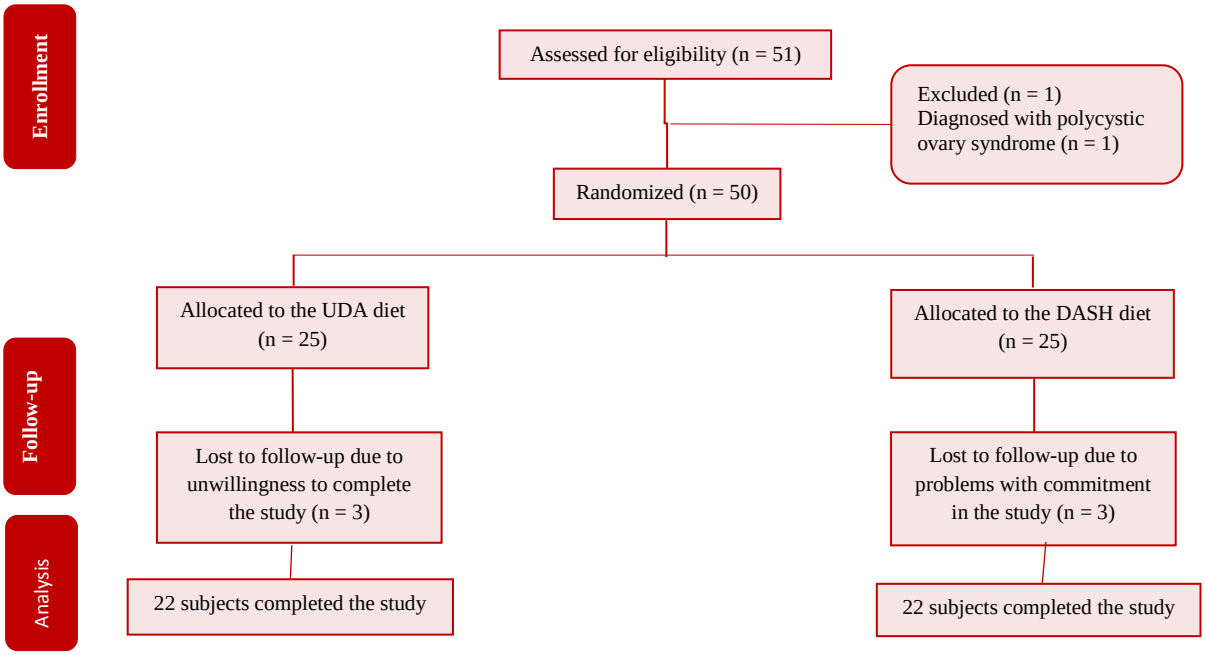

Figure 1. Flowchart of participants' recruitment and enrollment in the study
DASH: Dietary Approaches to Stop Hypertension; UDA: Usual dietary advice

Analysis of diet showed that calorie and protein intake of the two groups did not significantly differ, but these two diets were different in terms of total fat and fat composition intake, as well as the percentage of carbohydrate intake. These two diets were different in terms of sodium content. Although these differences were not statistically significant, they were nutritionally important. The DASH diet had a higher amount of calcium, potassium and fiber (Table 4).

Table 3. Baseline characteristics and effects of the Dietary Approaches to Stop Hypertension diet vs. usual dietary advice on anthropometric measures (mean values with their standard deviation)

Variable	UDA† (n = 22)	DASH* (n = 22)	P
Age (year)	38.9 (7.7)	37.3 (9)	0.530
Socio-economic status			
Low [n (%)]	6.0 (26.1)	9.0 (37.5)	
Medium [n (%)]	11.0 (47.8)	6.0 (25.0)	0.270
High [n (%)]	6.0 (26.1)	9.0 (37.5)	
Physical activity (MET-h/d)			
Baseline [n (%)]	42.0 (5.9)	40.0 (4.2)	0.200
End-of-trial [n (%)]	41.9 (6.3)	38.9 (3.5)	0.070
Difference (95%CI)	0.17 (-0.8,1.14)	1.04 (-0.62,2.70)	
BMI (kg.m^2)			
Baseline [n (%)]	32.8 (2.7)	33.46 (3.6)	0.300
End-of-trial [n (%)]	32.64 (2.6)	33.01 (3.8)	0.700
Difference (95%CI)	-0.28 (-0.98,0.42)	-0.39 (-0.69,-0.09)	
WC (cm)			
Baseline [n (%)]	99.8 (6.7)	102.3 (10.9)	0.020
End-of-trial [n (%)]	100 (6.7)	99.9 (8.7)	0.900
Difference (95%CI)	0.11 (-0.64,1.43)	-2.4 (0.09,4.60)	

* The DASH diet was high in fruits, vegetables, whole grains, and low-fat dairy products and low in saturated fats, total fats, cholesterol, refined grains, and sweets. † The usual dietary advice group received general oral and written information about healthy food choices. DASH: Dietary Approaches to Stop Hypertension; UDA: Usual dietary advice; MET: Metabolic equivalent; BMI: Body mass index; WC: Waist circumference; CI: Confidence interval
P < 0.050 is significant, Obtained from independent t-test.

Table 4. Daily energy and nutrient intakes in the Dietary approaches to stop hypertension and Usual Dietary Advice groups at baseline at the end of the study (Mean values with their standard deviation)

Intake	UDA group (n = 22)	DASH group (n = 22)	P
Energy (kcal)	1688.3 (799.7)	1633.4 (391.8)	0.770
Protein (g/day)	63.0 (34.5)	66.9 (24.0)	0.270
Total fat (g/day)	69.0 (35.0)	48.0 (21.0)	< 0.001
Carbohydrate (g/day)	211.0 (108.0)	239.0 (50.0)	< 0.001
Saturated fat (g/day)			
Crude†	15.2 (3.3)	13.4 (3.7)	0.200
Model I1‡	15.2 (4.9)	13.3 (5.0)	0.060
PUFA (g/day)			
Crude	26.5 (12.0)	16.3 (9.0)	< 0.001
Model I	26.0 (6.8)	16.7 (6.8)	< 0.001
MUFA (g/day)			
Crude	13.0 (6.0)	15.8 (6.0)	0.140
Model I	13.3 (4.4)	15.6 (2.9)	0.040
PUFA/SFA Ratio			
Crude	1.75 (0.6)	1.2 (0.8)	< 0.001
Model I	2.4 (2.1)	0.9 (3.5)	0.090
Fiber (g)			
Crude	14.6 (6.7)	14.8 (5.2)	0.940
Model I	11.2 (4.5)	14.3 (5.8)	0.050
Potassium (mg)			
Crude	2362.2 (1039.7)	2796.5 (1086.6)	0.190
Model I	2325.0 (542.0)	2831.0 (769.0)	0.010
Calcium (mg)			
Crude	674.1 (318.9)	875.1 (378.9)	0.060
Model 1	664.5 (260.0)	884.0 (287.0)	0.010
Magnesium (mg)			
Crude	249.3 (207.0)	255.3 (15.1)	0.910
Model I	246.0 (185.0)	259.0 (93.0)	0.800
Sodium (mg)			
Crude	1544.3 (151.2)	1613.7 (1625.4)	0.870
Model I	1682.0 (1242.0)	1645.0 (849.0)	0.700
Vitamin C (mg)			
Crude	104.6 (73.9)	138.2 (94.7)	0.200
Model I	102.9 (64.0)	140.0 (87.0)	0.120

Obtained from independent t-test; †crude model did not adjusted; ‡ Model 1 adjusted for energy intake (data are means ± SD); Data are means ± SD; P < 0.050 is significant.

DASH: Dietary Approaches to Stop Hypertension; MUFA: Monounsaturated fatty acids; PUFA: Polyunsaturated fatty acid; SFA: saturated fatty acid; SD: Standard deviation; UDA: Usual dietary advice

Nutrient intake and anthropometric measurements: The reported dietary intakes confirmed that participants modified their intake of nutrients in the direction of the intervention; however, the targets were not fully achieved. The estimated nutrient content of the 3-day food records consistent with the patients' reports is shown in table 4.

As shown in table 3, no significant differences were observed in body composition between the two groups. Nevertheless, after the trial, BMI significantly decreased (P < 0.050) and WC marginally decreased in the DASH group (P = 0.055).

Gene expression changes: The outcome of reverse transcription-PCR indicated that the DASH diet significantly decreased the expression of PPAR-γ compared to the UDA diet (P = 0.040), and after weight change and physical activity adjustment, the results did not noticeably alter (P = 0.030) (Table 5).

Discussion

The results of this investigation indicated that the expression of PPAR-γ in the UDA group was higher than the DASH group. To the best of our knowledge, the effect of the DASH diet on PPAR-γ gene expression in humans has not been reported previously, but some studies have been performed on different polymorphisms of this gene.[14,15]

Table 5. The effects of the Dietary Approaches to Stop Hypertension diet vs. usual dietary advice on gene expression (Mean values with their standard deviation)

Gene expression	UDA			DASH			P	P‡
	Baseline	12th week	P*	Baseline	12th week	P		
	11.07 ± 3.90	12.34 ± 4.75	0.180	10.80 ± 0.70	9.28 ± 3.90	0.230	0.040	0.030

All values are mean ± SD
The UDA group had the usual diet.
The DASH diet was high in fruits, vegetables, whole grains, and low-fat dairy products and low in saturated fats, total fats, cholesterol, refined grains, and sweets.
The amount of sodium intake was 2400 mg/day
* Obtained from paired t-test through the comparison of between-group differences by ANCOVA; ‡ Adjusted for a change in weight, WC, and PA; P < 0.050 is significant. UDA: Usual dietary advice; DASH: Dietary Approaches to Stop Hypertension; SD: Standard deviation; WC: Waist circumference; PA: Physical activity

PPAR-γ activation improves insulin signaling, glucose transportation, glycogen synthesis, mitochondrial function and fat mobilization.[16-18] Some mechanisms have been suggested for these effects including activation of fatty acid transporters such as fatty acid transport protein 1 (FATP1), a cluster of differentiation 36 (CD36), glycerol kinase (GK) and phosphoenolpyruvate carboxykinase (PEPCK), and thus, the retaining of fatty acids in adipose tissue.[19,20] PPAR-γ modulates the endocrine activity of adipose tissue by regulating the synthesis of secreted adipocyte proteins (adipokines) that affect insulin signaling in hepatic and peripheral tissues.[21] Thus, adiponectin expression increases, whereas the production of plasminogen activator inhibitor-1 (PAI-1), leptin, tumor necrosis factor-a (TNF-a), resistin, and interleukin 6 (IL-6) reduces.[22] Furthermore, it directly increases adipocyte glucose disposal by induction of the glucose transporter type 4 (GLUT4).[23]

The characteristics of physiologically related activators of PPAR-γ are not clear, although PPAR-γ is activated by fatty acids.[16,24-26] As previously mentioned, fat intake was significantly higher in the UDA group, and its composition differed in the two groups. For example, the polyunsaturated fatty acid (PUFA): saturated fatty acid (SFA) ratio was significantly higher in the UDA group (P = 0.009). These results are in agreement with the findings of previous studies which have shown that PUFAs could act as ligands of PPAR-γ or could modify its expression.[27-30] It is also consistent with the findings of studies that have revealed that some n–3 and n–6 PUFAs activate PPAR-γ.[31] Moreover, they are in agreement with findings of studies which have reported the main interaction between usual dietary fat composition and the PPAR-γ Pro12Ala polymorphism.[32,33] Furthermore, after the intervention, weight and WC significantly decreased in the DASH group compared with the UDA group, which is acceptable regarding the DASH composition. This result is in agreement with one study which showed a 25% reduction in PPAR-γ mRNA expression after a 10% decrease in body weight.[27] These findings suggest that PPAR-γ is required in the maintenance of normal insulin sensitivity in mice, but also creates the fascinating idea that it may be required for the adversative effects of a high-fat diet on carbohydrate metabolism.[34]

Conclusion

The present study was proposed to determine the impact of the DASH diet on the PPAR-γ gene expression. This study indicated that BMI and WC decreased significantly in the DASH group in comparison with the UDA group. The second major finding was that the DASH diet significantly decreased the expression of PPAR-γ. This finding was unexpected, and future studies on the current topic are therefore recommended.

Limitations: A number of important limitations need to be considered. First, dietetic intake in the present investigation was self-reported, and participants were advised to follow a specific diet rather than delivering prepared foods, thus resulting in possible imperfect adherence to the recommended diets. The second limitation in this study was that the sample volume was relatively small, so further investigations and experimentations in different population are strongly recommended. Third, the findings cannot be generalized because the study participants were restricted to women.

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Conflict of Interests

Authors have no conflict of interests.

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