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The association between adherence to the Mediterranean diet and adiponectin levels among healthy adults: the ATTICA study ☆

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Abstract

Adiponectin is thought to exert anti-inflammatory actions. The aim of the present work was to evaluate the association of long-term adherence to the Mediterranean diet with adiponectin levels, in a sample of cardiovascular disease-free adults. In a random sub-sample of "ATTICA" study, 532 men and women, serum adiponectin was measured. Among several sociodemographic, clinical and biological factors, adherence to the Mediterranean diet was assessed by a special diet score (MedDietSCore) that incorporated the inherent characteristics of this traditional diet. Unadjusted analysis revealed that participants who were in the highest tertile of the diet score had an average 41% higher adiponectin levels, as compared to those who were in the lowest tertile ($P<.001$). Multiadjusted data analysis showed that compared to the highest tertile of diet score, participants in the middle or the lowest one had an average 0.99 ± 0.22 ($P=.001$) and 1.05 ± 0.27 μg/ml ($P=.001$) lower adiponectin levels after adjusting for age, sex and various bioclinical factors. Adherence to the Mediterranean diet was associated with an increase on adiponectin levels. This finding may partially explain beneficial effects of this traditional healthy diet on the cardiovascular system.

Keywords: Diet; Inflammation; Cardiovascular diseases; Epidemiology

1. Introduction

During the last few decades, a great effort has been made to examine the relationship between health and overall diet. The original Mediterranean diet can be defined as the dietary pattern found in the olive-growing areas of the Mediterranean region in the late 1950s and early 1960s [1]. Numerous epidemiological studies indicate that the consumption of Mediterranean diet is associated with a decrease in the incidence of cardiovascular disease (CVD) and stroke [2–4]. Its effects include improvement of lipid metabolism [3], blood pressure levels [5], body mass index [6], anti-inflammatory and anti-thrombotic markers [7,8] as well as of the antioxidant capacity of plasma [9].

Adipose tissue is an important endocrine organ secreting multiple, metabolically active proteins termed *adipokines* [10]. Among them, adiponectin is secreted exclusively by adipocytes, and paradoxically, its levels are decreased in obese subjects compared with lean ones [10,11]. Low levels of adiponectin are associated with adverse metabolic states such as diabetes [12], metabolic syndrome [13], dyslipidemia [14], lipodystrophy [15] and CVD [13,14,16]. A series of experiments have shown that adiponectin lowers plasma glucose levels through stimulation of glucose uptake, glycolysis, fatty acid oxidation and suppression of hepatic gluconeogenesis. Despite its role in insulin resistance, adiponectin also exerts anti-inflammatory actions since it exerts beneficial actions on endothelial homeostasis, reduces monocytes adhesion on endothelium and inhibits macrophage-to-foam cell differentiation by reducing intracellular cholesteryl ester content in human macrophages [10–11].

The identification therefore of possible interventions that could increase adiponectin levels is of great interest. Several drugs including renin-angiotensin system blocking agents, peroxisome proliferator activated receptor (PPAR) α and PPARγ agonists, hypoglycemic drugs and beta-blockers increase adiponectin levels [16]. Moreover, lifestyle modifications like weight loss, combined hypocaloric diet and moderate physical activity seem to improve plasma adiponectin levels, although exercise training without significant weight loss does not appear to increase its levels [17,18]. Although Mediterranean diet is thought to protect against cardiovascular disease and diabetes, little is known about its association with serum adiponectin levels. Adherence to Mediterranean diet is positively associated with adiponectin levels in diabetic women [19], but there is no data about this correlation in healthy population.

Therefore, in this study, the hypothesis that the protection of Mediterranean diet against cardiovascular diseases could be partly explained by its effect on adiponectin levels is under investigation

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in a sample of apparently healthy men and women from the "ATTICA" study.

2. Methods and materials

2.1. Study population

The study sample consisted of 3042 CVD-free men and women from the Attica region, Greece. Details of the study design and the data collection used in the ATTICA epidemiological study have been previously published [20]. From the design of the study, all participants had no history of CVD or any other atherosclerotic disease, as well as chronic viral infections. Moreover, participants did not have cold or flu, acute respiratory infection, dental problems or any type of surgery in the past week. For the purposes of this work, a random subsample from the ATTICA study's database consisted of 310 males (age, 40±11 years) and 222 females (age, 38±12 years), was selected. No differences were observed between the selected subsample and the total study population regarding the distributions of age (P=.4), gender (P=.3), physical activity status (P=.6), smoking habits (P=.5) and dietary characteristics (P=.4).

The study was approved by the Medical Research Ethics Committee of First Cardiology Clinic, School of Medicine, University of Athens and was carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association.

2.2. Dietary assessment

The evaluation of the nutritional habits was based on a validated food frequency questionnaire (i.e., the EPIC-Greek questionnaire) that was kindly provided from the Nutrition Unit of Athens Medical School [21]. All participants were asked to report the daily or weekly average intake of several food items that they have consumed (during the last year). Then, the frequency of consumption was quantified approximately in terms of the number of times per month a food was consumed. Alcohol consumption was measured in wineglasses (100 ml) and quantified by ethanol intake (grams per drink). One wineglass was equal to 12 g of ethanol concentration. Based on the Mediterranean diet pyramid, a diet score has been developed to describe a traditional dietary pattern [22] in order to evaluate overall dietary habits of the participants. In brief, the Mediterranean pattern consists of daily consumption of nonrefined cereals and products, fruits and vegetables, olive oil (as the main added lipid) and nonfat or low-fat dairy products; weekly consumption of fish, poultry, potatoes, olives, pulses and nuts and rarely eggs and sweets and monthly consumption of red meat and products. It is also characterized by moderate consumption of wine (one to two wineglasses a day). Thus, according to the previous dietary pattern and the reported monthly frequency consumption of the above food groups, a special diet score for each participant was calculated assessing adherence to the Mediterranean diet (range 0–55). In particular, for the consumption of items presumed to be close to this pattern (i.e., those suggested on daily basis or more than 4 servings per week), a score of 0 was assigned when a participant reported no consumption, 1 when reported consumption of 1–4 times a month, 2 for 5–8 times, 3 for 9–12 times, 4 for 13–18 times and 5 for more than 18 times. On the other hand, for the consumption of foods presumed to be away from this diet (like meat and meat products), the opposite scores were assigned (i.e., 0 when a participant reported almost daily consumption to 5 for rare or no consumption). Especially, for alcohol intake, a score of 5 was assigned for consumption of less than three wineglasses per day, 0 for consumption of more than seven and 4–1 for consumption of three, four to five, six and seven. Higher values of this diet score indicates greater adherence to the Mediterranean diet [23]. The tertiles of this score were also calculated.

2.3. Sociodemographic and lifestyle variables

Current smokers were defined as those who smoked at least one cigarette per day, former smokers were defined as those who had stopped smoking for at least 1 year and the rest of the participants were defined as non-current smokers. For the ascertainment of physical activity status, an index of weekly energy expenditure was developed using frequency, duration and intensity of sports-related physical activity. Participants who did not report any physical activities were defined as sedentary. Height and weight were recorded, and body mass index [weight (kg)/height (m^2)] was calculated.

2.4. Clinical and biochemical characteristics

Resting arterial blood pressure was measured three times in the right arm at the end of the physical examination with subject in sitting position. Fasting blood samples were collected from 8 to 10 a.m. C-reactive protein (CRP) was assayed by particle-enhanced immunonephelometry. Interleukin 6 (IL-6) was measured by sensitivity enzyme-linked immunosorbent assay (ELISA). The intra-assay and interassay coefficient of variation was <5% for CRP and <10% for IL-6. Tumor necrosis factor-α (TNF-α) was measured by Quantikine HS/immunoassay kit. Adiponectin was measured by ELISA (R&D Systems, Minneapolis, MN, USA). The intra-assay coefficient of variation was <10% for adiponectin. All samples were measured in duplicate.

Blood lipid examinations [serum total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides] were measured using chromatographic enzymic method in an automatic analyzer RA-1000. Low density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula. The intra-assay and interassay coefficients of variation of cholesterol levels did not exceed 3%; triglycerides, 4% and HDL cholesterol, 4%. Patients whose average blood pressure levels were greater than or equal to 140/90 mmHg or were under antihypertensive medication were classified as hypertensives. Hypercholesterolemia was defined as total serum cholesterol levels greater than 5.17 mmol/L or the use of lipid-lowering agents. Diabetes mellitus was defined as a fasting blood glucose >6.94 mmol/L or the use of antidiabetic medication.

2.5. Statistical analysis

Power analysis showed that the number of enrolled participants is adequate to evaluate two-sided hypotheses between diet score tertiles regarding standardised differences greater than 0.5, achieving statistical power greater than 0.75 at 5% probability level (P value).

Continuous variables are presented as mean values±standard deviation. Categorical variables are presented as frequencies. Associations between categorical variables were tested by the calculation of chi-squared test, while associations between diet score categories and several biochemical, clinical and nutritional variables were tested by the use of the analysis of variance. However, due to multiple comparisons, the Bonferroni correction was used in order to account for the increase in Type I error. Correlations between food group intake and adiponectin levels were tested using the partial rho correlation coefficient. Multiple linear regression models were applied to test the association between the diet score and adiponectin levels, after controlling for several potential confounders. Adiponectin levels were log-transformed because of their skewed distribution. Standardized residuals were used to test model's goodness of fit. Normality was tested using the Kolmogorov–Smirnov criterion. All reported P values are based on two-sided tests and compared to a significance level of 5%. The SPSS 14 (SPSS, Chicago, IL, USA) software was used for all the statistical calculations.

3. Results

The distribution of several characteristics of the participants according to Mediterranean score is shown in Table 1. Participants in the highest tertile of the diet score tended to be younger and had lower body mass index and waist-to-hip ratio and appeared with lower percentage of obesity compared to those of the lowest tertile. These associations were confirmed even after adjusting for age, smoking, physical activity and body mass index of men and women. Furthermore, the participants who reported a greater adherence to the Mediterranean diet had higher physical activity levels; number of daily cigarettes smoked and lower presence of hypercholesterolemia, diabetes and hypertension.

Biochemical characteristics of the participants according to the Mediterranean diet score are shown in Table 2. Participants with the highest adherence in Mediterranean diet (i.e., highest tertile) have better lipidemic profile since they had lower total cholesterol, LDL cholesterol and triglycerides and higher HDL cholesterol levels

Table 1
Demographic, lifestyle and clinical characteristics by tertile of the Mediterranean diet score

	Mediterranean diet score (0–55)			P
	1st tertile (0–20)	2nd tertile (21–35)	3rd tertile (36–55)	
Age (yrs)	47±13	42±11 *	35±10 **	<.001
Male sex, %	76	58 *	16 **	<.001
Body Mass Index (kg/m²)	30±5	27±3 *	22±3 **	<.001
Obesity, %	41	15 **	1 **	<.001
Waist to hip ratio	0.94±0.92	0.87±0.1 *	0.79±0.85 **	<.001
Physical activity, %	29	38	44 *	.03
Smoking (current), %	54	46	38 **	.02
Hypertension, %	45	29 **	10 **	<.001
Diabetes, %	8	3 *	1 **	<.001
Hypercholesterolemia, %	45	40	21 **	<.001

Bonferronni-corrected values for the comparisons between second and third tertiles vs. first tertile of the Mediterranean diet score.
* P<.05.
** P<.01.

Table 2
Biochemical characteristics of the participants, by tertile of the Mediterranean diet score

	Mediterranean diet score (0–55)			P
	1st tertile (0–20)	2nd tertile (21–35)	3rd tertile (36–5)	
Total serum cholesterol (mmol/L)	5.28±1.09	5.15±1.06 *	4.47±0.98 **	<.001
HDL cholesterol (mmol/L)	1.14±0.31	1.19±0.41	1.37±0.36 **	<.001
LDL cholesterol (mmol/L)	3.41±1.01	3.26±0.93 *	2.74±0.91 **	<.001
Triglycerides (mmol/L)	1.58±1.12	1.32±0.77 *	0.96±0.38 **	<.001
C-reactive protein (mg/l)	2.0±2.7	2.1±2.3	1.4±2.1 **	<.001
Interleukin-6 (pg/ml)	1.6±0.6	1.5±0.6	1.2±0.4 **	<.001
Tumor necrosis factor-alpha (pg/ml)	7.8±4.8	7.3±4.2	4.6±4.6 **	<.001
Adiponectin (μg/ml)	3.4±1.9	3.6±1.8	4.8±2 **	<.001

Bonferronni-corrected values for the comparisons between second and third tertiles vs. first tertile of the Mediterranean diet score.
* $P<.05$.
** $P<.01$.

compared to those of the lowest tertile. In addition, this group of people had lower values of some inflammatory markers, such as CRP, IL-6 and TNF-α. Regarding the adiponectin levels, individuals in the highest tertile of the diet score had an average 41% higher level as compared to the ones in the lowest tertile. Moreover, diet score was positively correlated with adiponectin levels in both males (rho=0.130, $P=.02$) and females (rho=0.156, $P=.02$); however, it should be mentioned that the effect size (i.e., value of rho) was small. Additionally, 78 (14.7%) of the participants had metabolic syndrome (according to the NCEP ATPIII definition), and adiponectin levels were lower among those participants as compared to the participants without the syndrome (2.9±1.3 vs. 4.2±2.0 μg/mL, $P<.001$). Moreover, 25 (4.7%) women were on menopause, and adiponectin levels were lower among pre-menopausal as compared to post menopausal (4.7±1.9 vs. 5.9±2.5 μg/mL, $P=.009$).

Despite the previous unadjusted associations, residual confounding may exists, thus multi-adjusted regression analysis was applied. The results from multiple linear regression analyses are presented in Table 3. Participants in the highest or middle tertile of the diet score have higher adiponectin values compared with the ones in the lowest tertile. In particular, participants in the middle or the highest tertile (i.e., greater adherence to the Mediterranean diet) had on average 0.98 ±0.24 ($P=.001$) and 1.07±0.30 μg/ml ($P=.001$) higher adiponectin levels compared to individuals in the lowest tertile (i.e., away from this traditional dietary pattern), even after adjusting for various potential confounders, such as age, gender, waist to hip ratio, smoking habits, physical activity status, presence and management of hypertension, diabetes, hypercholesterolemia and TNF-α levels (Table 3). Moreover, the aforementioned relationship exists even after adjustment for glucose or insulin levels, IL-6, CRP, HDL and total-cholesterol, since they have been suggested as potential cofactors of adiponectin levels.

Furthermore, food group analysis, controlled for age, body mass index, smoking habits and physical activity status revealed that adiponectin levels were positively correlated with green tea drinking (rho=0.108, $P=.04$), low-fat dairy products intake (rho=0.119, $P=.04$), spinach and cabbage consumption (rho=0.108, $P=.03$), and vegetables (rho=0.142, $P=.02$). However, these correlations, although significant, were weak in terms of the effect size measured. No other associations were found regarding adiponectin levels and various foods or food groups, as well as alcoholic beverages drinking.

4. Discussion

In this work, a strong positive association between the adherence to the Mediterranean diet and serum adiponectin levels among healthy individuals was revealed. This association was independent of various anthropometric, lifestyle and clinical characteristics, which were considered as potential confounders in our analyses. To the best of our knowledge, this is the first study that provides these evidences in a general population sample and expands the current scientific knowledge about the benefits of this traditional diet on atherosclerotic disease.

Several epidemiological studies have revealed that the consumption of a Mediterranean-type diet could be beneficial for metabolic diseases including coronary heart disease (CHD) and diabetes [2–5]. Several mechanisms have been proposed to mediate this protection, and their overall description includes the anti-inflammatory, antithrombotic and antioxidative effects of Mediterranean diet [24,25,26].

Low-grade systemic inflammation is considered to play a role in the future development of metabolic diseases. The imbalance between proinflammatory mediators such as IL-6 and TNF-α and anti-inflammatory mediators such as IL-10 and adiponectin could determine such a state. Lower adiponectin levels have been found in patients of Type 2 diabetes, obesity, metabolic syndrome and CHD [12–16], and proinflammatory markers such as CRP, IL-6 and TNF-α, have been negatively associated with its levels [15,18,30].

Therefore, the identification of possible interventions that could increase adiponectin levels is of great interest. Despite the drug treatment that could modify adiponectin levels, lifestyle modifications are an important issue for altering its levels. Long-term weight loss and hypocaloric diet combined with exercise have been reported to increase adiponectin levels in obese subjects [17]. Epidemiological and clinical studies have revealed that the consumption of fiber [27], omega-3 polyunsaturated fatty acids [28], monounsaturated fatty acids [29] and nuts [19] are correlated with increased adiponectin levels in obese or diabetic subjects. In addition, a significant difference in plasma adiponectin levels before and after intake of Oolong tea in coronary artery disease patients has been reported [30]. Several studies have also associated moderate alcohol consumption with higher adiponectin concentration [31–34] although some studies failed to find such association [35]. This study revealed that adiponectin levels were positively correlated with low-fat dairy products intake, spinach, cabbage and vegetables consumption as well as with green tea drinking. No other associations were found regarding adiponectin levels and various foods or food groups, as well as alcoholic beverages drinking.

However, people consume meals consisting of a variety of foods with complex combinations of macro- and microingredients. Pattern analysis examines the effects of a whole dietary profile rather than focusing on individual nutrients or foods. Conceptually,

Table 3
Results from multiadjusted linear regression model that evaluated the association between serum adiponectin levels (dependent variable) and adherence to Mediterranean diet (independent variable)

	β±S.E.	P
Mediterranean diet score		
1st compared with 3rd tertile	−1.05±0.27	.001
2nd compared with 3rd tertile	−0.99±0.22	.001
Age (per 1 year)	0.04±0.08	<.001
Male vs. female gender	−0.80±0.20	<.001
Waist-to-hip ratio	−1.05±0.75	.05
Physical activity (yes/no)	0.16±0.12	.15
Smoking (yes/no)	−0.32±0.15	.03
Hypertension (yes/no)	−0.46±0.20	.01
Diabetes mellitus (yes/no)	−0.88±0.32	.03
Hypercholesterolemia (yes/no)	−0.006±0.18	.97
Triglycerides (per 1 mg/dl)	−0.005±0.001	.001
Tumor necrosis factor-α (per 1 pg/ml)	−0.06±0.04	.10

dietary patterns represent a broader picture of food and nutrient consumption and may therefore be more predictive of disease risk. Dietary glycaemic index reflects overall eating patterns rather than the effects of individual foods and has been inversely associated with adiponectin concentrations [27]. Mediterranean diet, which refers to the eating pattern of the people in the Mediterranean countries, has already been associated with proinflammatory and prothrombotic markers. It is reported that greater adherence to the Mediterranean diet was independently associated with a reduction in CRP, IL-6 and fibrinogen levels, while concerning TNF-α levels, a borderline decreased was observed [7]. Although these data support that Mediterranean diet reduce the proinflammatory mediators and, therefore, protect from low-grade systemic inflammation, limited data exists about its influence in anti-inflammatory ones, especially adiponectin. A previous study has shown that the Mediterranean diet combined with exercise increases adiponectin levels in obese postmenopausal females even after adjustment for the decreased body weight [18]. Finally, adherence to Mediterranean diet is positively associated with plasma adiponectin levels in diabetic females [19].

The findings of the present work are in accordance with the aforementioned ones and widen the current knowledge by revealing that the adherence to Mediterranean diet is correlated with higher adiponectin concentrations in a random sample from the general population. Specifically, individuals in the highest tertile of the Mediterranean diet score had higher serum adiponectin levels, even after adjusting for age, gender, waist-to-hip ratio, physical activity, smoking as well as presence and management of hypertension, diabetes mellitus and hypercholesterolemia. This association seems to be independent by the reduction in proinflammatory markers and modulation in lipids since the association remained significant after control for TNF-α, IL-6, CRP, HDL cholesterol, LDL cholesterol, triglycerides, and total-cholesterol.

An inverse relation between body mass index and serum adiponectin levels has been established in several studies [35,36]. In this study, the above relationship as well as a negative relation with waist-to-hip ratio was also confirmed. It was also observed that adiponectin levels were lower among people with metabolic syndrome. It is reported that adiponectin levels are higher in women than men, independent of the fact that women usually have more overall adiposity than men [36,37]. The biological basis for this sex difference is unknown. One possible explanation is that estrogens increase or testosterone inhibits adiponectin production; however, evidence is limited and contradictory [38]. Although normal ageing in humans is associated with several hormonal and metabolic alterations is not clear yet, its influence is on adiponectin levels. Some studies demonstrate a positive relation with adiponectin levels [31,36,39], while others failed to find such correlation [37]. It is believed that gender plays a role in the relationship between age and adiponectin concentration. In this study a positive correlation in all subjects was also found. Smoking is known as one of the risk factors of atherosclerosis, and its relation with metabolic disorders has also been reported. Previous study has revealed that smoking is negatively associated with adiponectin levels in healthy Japanese population [40], although others did not [33,34]. In this study, smokers appear to have lower adiponectin levels compare with the nonsmokers. In addition, physical activity failed to reveal an association with adiponectin levels and this is in accordance with previous studies [33,35] although some studies found such association [41]. Previously, it was reported that adiponectin is independently correlated with the hypertension. Hypoadiponectinemia may cause endothelial dysfunction and/or activation of the renin-angiotensin system, which both are related to hypertension, or even hypertension may cause inhibition in adiponectin expression through an increase in sympathetic nerve activity [42]. In accordance with the above data, the present study confirms a negative correlation between adiponectin levels and hypertension.

5. Limitations

Because of the cross-sectional design of the study, it cannot establish causal relations but only generate a hypothesis for the association of a dietary pattern with adiponectin levels. Moreover, adherence to the Mediterranean diet was assessed through a valid diet score; although this specific score, as well as other similar indexes, have been entirely used in epidemiologic as well as clinical studies, this dietary assessment approach needs careful interpretation and generalization.

6. Conclusion

In conclusion, greater adherence to the Mediterranean-type diet enhances adiponectin levels in healthy population. Since adiponectin has established anti-inflammatory actions, its increased levels might head off low-grade inflammation state.

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