The relation between compliance to the Mediterranean diet and the extensiveness of coronary artery disease

Akdeniz diyetine uyum ile koroner arter hastalığının yaygınlığı arasındaki ilişki

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ABSTRACT

Objective: There are various studies showing the cardiovascular benefits of the Mediterranean diet (MD), but, to the best of our knowledge, this is the first study which aimed to investigate the relation between adherence to the MD and severity of coronary artery disease (CAD).

Methods: The study was a single centre, cross-sectional prospective study which included 200 consecutive patients (131 men [65.5%] and 69 women [34.5%], mean age 57±9) who were diagnosed with CAD by coronary angiography between January 2012 and April 2013. A food frequency questionnaire was administered to the patients. Compliance to the MD was evaluated by the MD score (MDS), which collects prominent diet characteristics under 10 main titles. Each patient's angiographic data was examined by a cardiologist, and Gensini scores (GS) were then calculated to evaluate the extensiveness of coronary atherosclerosis.

Results: Forty-four percent of patients were in the third category of body mass index (BMI) (≥30 kg/m^2) and 17.5% were in the first category (BMI <25 kg/m^2). Education levels were markedly low, with 78% of the patients having fewer than six years in education. Most patients had low physical activity levels (55.5%). Frequency of metabolic syndrome was prominent (79%). The median (25–75 percentiles) of GS was found to be 21.25 (7–44.75) and the MD score was 4 (3–5). A negative correlation was found between compliance to the MD and GS (r=-0.380, p<0.001).

Conclusion: This study found that in patients with CAD, compliance with the traditional MD is related to decreased severity of coronary atherosclerosis.

ÖZET

Amaç: Akdeniz diyetinin (AD) kardiyovasküler faydalarını ortaya koyan çeşitli araştırmalar bulunsa da, bu çalışma bildiğimiz kadarıyla AD'ye uyum ile koroner arter hastalığı (KAH) yaygınlığı arasındaki ilişkinin araştırılmasını amaçlayan ilk çalışmadır.

Yöntemler: Çalışma kesitsel ve ileriye dönük bir tasarım ile tek merkezde gerçekleştirildi. Ocak 2012 ve Nisan 2013 tarihleri arasında koroner anjiyografi yapılarak KAH tanısı konulan 200 ardışık hastaya (131 erkek [%65.5], 69 kadın [%34.5], ortalama yaş 57±9) beslenme tüketim sıklığı anketi uygulandı. Akdeniz diyetine uyum, diyete ait belirgin özellikleri 10 ana başlık altında toplayan AD skalası ile değerlendirildi. Bir kardiyolog tarafından her bir hastanın anjiyografik verileri incelenerek koroner aterosklerozunun yaygınlığını değerlendirmek üzere Gensini skorları (GS) hesaplandı.

Bulgular: Hastaların %44'ünün beden kütle indeksi (BKİ) üçüncü kategoride (≥30 kg/m^2), yalnızca %17.5'ininki ise ilk kategorideydi (BKİ <25 kg/m^2). Eğitim seviyesi belirgin olarak düşüktü, popülasyonun %78'i altı yıldan daha az eğitim almıştı. Birçok hastanın fiziksel aktivite seviyeleri düşüktü (%55.5). Metabolik sendrom sıklığı belirgindi (%79). Gensini skorlarının mediyanı 21.25 (7–44.75) (25–75 persentil), AD skorununki ise 4 (3–5) olarak saptandı. Akdeniz diyetine uyum ile GS arasında negatif yönde korelasyon saptandı (r=-0.380, p<0.001).

Sonuç: Bu çalışmada, KAH olan hastalarda geleneksel AD'ye uyum koroner ateroskleroz ciddiyetinde azalma ile ilişkili olduğu saptanmıştır.

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Mortality related to cardiovascular (CV) disease is generally ranked among the first three orders of causes of mortality, although its ranking changes depending on geographic distribution in the world.[1] Although mortality related to cardiovascular diseases is higher in developed countries, it is found to be lower in those developed countries bordering the Mediterranean Sea such as Italy, Greece and Spain when compared to the United States.[2] In Turkey, mortality related to coronary events is in the first order with a rate of 39% according to the TEKHARF study.[3] However, the same study shows that the mortality rate related to coronary causes is lower in Turkey's Mediterranean region compared to other regions of the country.[3] The distribution of mortality related to CV causes in Turkey and internationally suggests that geographic location may have an important role.

The Mediterranean region shows a marked difference in terms of dietary habits compared to other geographic areas. The traditional Mediterranean diet (MD) pattern is characterized by high consumption of plant foods (vegetables, fruits, cereals-preferably whole grain-fruit, nuts, legumes and olives). Olive oil as the principal source of added fat, moderate consuption of eggs, poultry and dairy products (mainly cheese and yoghurt), moderate to high intake of fish and seafood, low consumption of red meat and moderate intake of wine constitute the essentials of the MD. The index of adherence with the traditional MD was first defined by Trichopoulou.[4] In studies conducted subsequently using this index and modified indices, it has been shown that compliance with the MD might have a cardioprotective effect.[4–6] It is thought that this effect is achieved by modification of the risk factors for CV diseases, which include hyperlipidemia, hypertension, obesity and insulin resistance.[7–10]

Recent studies have found evidence that compliance with the MD might prevent inflammation, which plays an important role in the physiopathologies of atherosclerosis and cardiovascular disease.[11–13] In recent studies, it was shown that increased compliance with the MD might, over time, downgrade atherosclerosis in the coronary arteries.[14,15]

This study aimed to investigate the relation between MD compliance and the angiographic severity and extensiveness of atherosclerosis in patients with coronary artery disease (CAD). Despite findings indicating that foods consumed may have a role in the severity of CAD, this study may be the first to investigate the relation between MD compliance and extensiveness of CAD. Hence, it is important in that it will provide a direct evaluation of the effects of diet and lifestyle changes on the extensiveness of CAD using a visual quantitative method.

Abbreviations:

BMI	*Body mass index*
C&RT	*Classification and Regression Tree*
CAD	*Coronary artery disease*
CV	*Cardiovascular*
EF	*Ejection fraction*
FFQ	*Food Frequency Questionnaire*
GS	*Gensini score*
MD	*Mediterranean diet*
MDS	*MD score*
TPFI	*Tissue factor pathway inhibitor*

METHODS

Two hundred consecutive patients, aged between 35 and 80 years and resident in Aydın province in Turkey's Aegean region, who were found to have atherosclerotic lesions in the coronary arteries following coronary angiography between January 2012 and April 2013 were included in the study. All patients provided written informed consent. The study protocol was approved by the local Ethics Committee and conducted in accordance with the principles of the Helsinki Declaration.

Data including age, education status and sociodemographic characteristics of 200 consecutive patients were obtained by standard interview method between January 2012 and April 2013. The anthropometric measurements of the patients were obtained using standard procedures. Body weight was measured with the patients in light clothing and barefoot. The body weights measured were rounded to the nearest 100 g and the heights were rounded to the nearest 0.1 cm. body mass index (BMI) was calculated by dividing weight (kg) to the square of height (m^2). Generally, BMI was examined in three categories: ≤25, 25–29.9 and ≥30.0 kg/m^2.

In order to assess physical activity levels, the validated Turkish version of the International Physical Activity Questionnaire (IPAQ)-short was administered to the patients face-to-face after the coronary angiography process.[16] This questionnaire allowed for observation of physical activity levels and expression of physical activity frequencies and times. The physical acitvity levels of the patients were examined in three categories:[17]

1. Low: if physical activity levels were low enough

not to be included in the second and third levels;

2. Moderate:

2.1. Excessive physical activity: physical activity: >3 days/week and >20 min/day or

2.2. Moderate exercise or walking: >5 days/week and >30 min/day, or

2.3. The sum of any physical activities: 5 day/week or more; combination of walking corresponding to 600 meters-min/week and moderate or excessive exercise

3. High level:

3.1. Excessive physical activity: 3 days a week or more, 500 meters-min/week in total; or

3.2. Any cumulative physical activity: 7 days a week, walking reaching 3000 meters-min/week in total and moderate and advanced level exercise.

Coronary angiography and assessment and severity of coronary artery disease

Coronary angiographies of the patients were performed using the transfemoral percutaneous technique and standard digital recordings were made. Right coronary and left coronary artery systems were visualized with multiple poses at different angles to assess vessel walls clearly. Estimations of coronary artery stenosis were done by computer-assisted analysis employing the edge detection method and cine-videodensitometry.

Presence of ≥50 luminal atheromatous stenosis in at least one coronary artery was considered CAD. Multiple plaque-like formations with regular borders or irregular depressions were considered atheromatous stenosis. Stenosis of a single lumen suggesting fibromuscular hyperplasia or a single stenosis not accompanied by any change in the same or different coronary artery was not considered lumen stenosis secondary to atherosclerosis.

The extensiveness of CAD was evaluated using angiographic Gensini score (GS).[18] Based on lumen stenosis, the following scoring was made: lumen stenosis 1–25%: 1 point, 26–50%: 2 points, 51–75%: 4 points, 76–90%: 8 points, 91–99%: 16 points, and complete stenosis: 32 points. Subsequently, these scores were multiplied by coefficients depending on the importance of the coronary vessel and the segment in which stenosis was present. For example, a coefficient of 5 was used for the left main coronary artery, a coefficient of 2.5 was used for the left anterior descending and proximal part of the circumflex coronary artery and a coefficient of 1 was used for the proximal right coronary artery. To obtain the total GS of the patient, the score for each luminal stenosis and the coefficients were added.

Assessment of food intake by food frequency questionnaire and MD compliance

Food frequency

The Food Frequency Questionnaire (FFQ) is widely used in large epidemiolgoical studies that include food and nutrient intakes. It is used to provide cheap and rapid quantitative information related to dietary pattern in long-term diets. In this study, the general food intake of the patients during the previous year was calculated using the Willett FFQs, which is of proven reliability and is administered in face-to-face interview by an experienced dietitian.[19] Information on nutrient components of the foods and beverages included in the FFQ were evaluated with the help of food composition database "Nutrition Information System 6.1" (BeBiS6.1) program.[20]

The subjects were asked to state their food and beverage intakes and their consumption in defined household measures, portion sizes or in known amounts for 6 main food groups. Standard portion sizes and household measures were used in the assessment of the amounts of consumed foods. The questionnaire did not include questions investigating portion, but the participants were asked to state the consumption frequencies of foods according to reference portion size given. The answers in the following 9 categories were used to determine the frequency of consumption of most foods: never or less than once a month, 1–3 times a month, once a week, 2–4 times a week, 5–6 times a week, once a day, 2–3 times a day, 4–5 times a day, 6 times a day or more.[19] In addition to beverage habits, the questionnaire also included questions related to parameters, including eating and cooking habits and preferance of oil during cooking. The 6 main food groups in the study were as follows: 1. Bread, cereal and cereal products (different bread types, rice, bulgur, oat, pasta, bakery products) 2. Meat, eggs and legumes 3. Milk and milk products

4. Vegetables (fresh and cooked vegetables excluding potato) and fruit (fresh and canned) 5. Beverages (fruit juices, alcoholic and non-alcoholic beverages, coffee, black tea, herbal teas) and 6. Fat, sweet and desserts.

For each subject, the daily intake of energy and nutrients and food groups in question was calculated. Food consumption frequency was calculated using the "Nutrition Information System6.1" (BeBiS 6.1) program.

Compliance with the Mediterranean diet

The score for compliance with the MD was evaluated using the 10-point MD scale. A value of 0 or 1 was assigned to each of nine indicated components with the use of the sex-specific median as the cutoff.[4] Thus, the total Mediterranean-diet score ranged from

Table 1. General characteristics of the subjects

	Variables			
	n	%	Mean±SD	Median
Age (years)			57±9	
Education (years)				
<6	156	78		
>6	44	22		
Income level				
Low	114	57		
Moderate-high	86	43		
Body mass index (kg/m^2)				
<25	35	17.5		
25–29.9	77	38.5		
≥30.0	88	44		
Waist circumference (cm)			99.2±15.9	
Physical activity				
Low	111	55.5		
Moderate	78	39		
Excessive	11	5.5		
Gensini score, median (25–75 percentiles)				21.25 (7–44.75)
Mediteranean diet score, median (25–75 percentiles)				4 (3–5)
Ejection fraction (%)			56.1±11.3	
Diabetes mellitus,	62	31		
Metabolic syndrome	158	79		
Hypertension	110	55		
Smoking	104	52		
Fasting blood glucose (mg/dl), median (25–75 percentiles)				101 (91–129)
Total cholesterol (mg/dl)			192.6±45	
Low density lipoprotein (mg/dl)			119.1±36.2	
High density lipoprotein (mg/dl)			39.3±9.3	
Triglyceride (mg/dl), median (25–75 percentiles)				144 (99.5–197.7)
Hemoglobin (g/dl)			13.5±1.7	
Serum creatinine (mg/dl)			0.86±0.48	
Uric acid (mg/dl)			5.9±1.5	

0 (minimal adherence to the traditional Mediterranean diet) to 9 (maximal adherence).[4]

In total, 14 all-inclusive food groups or nutrients were considered: potatoes, vegetables, legumes, fruits and nuts, dairy products, cereals, meat, fish, eggs, monounsaturated lipids (mainly olive oil), polyunsaturated lipids (vegetable-seed oils), saturated lipids and margarines, sugar and sweets, and nonalcoholic beverages. For each participant, intake of each of the indicated groups in grams per day and total energy intake were calculated.[4] For beneficial components (vegetables, legumes, fruits and nuts, cereal, and fish), individuals whose consumption was below the median were assigned a value of 0, and those whose consumption was at or above the median were assigned a value of 1. For components presumed to be detrimental (meat, poultry, and dairy products, which are rarely nonfat or low-fat), those whose consumption was below the median were assigned a value of 1, and those whose consumption was at or above the median were assigned a value of 0. For ethanol, a value of 1 was assigned to men who consumed between 10 and 50 g per day and to women who consumed between 5 and 25 g per day.[4]

For consumption of fat, the ratio of monounsaturated, rather than polyunsaturated, fats to saturated fats was used because due to the high ratio of olive and olive product utilization, the consumption of monounsaturated fats is considerably higher than that of monounsaturated fats in Turkey as well as in other Mediterranean countries.

Statistics

The Kolmogorov-Smirnov test was used to assess the normality of numeric variables. For the numeric variables that were normally distributed, comparison between two and three groups were analysed by the ANOVA or independent sample t-tests, and the results were expressed as mean±standard deviation. For the score and non-normally distributed variables, comparison of two groups was made using the Mann-Whitney U test, and the results were expressed as median. The Chi-square test was used for analysis of nominal data. Correlation analysis was performed with the Spearman correlation test. Significance was defined as $p<0.05$.

Classification and Regression Tree (C&RT). C&RT is a recursive partitioning method to be used both for regression and classification. C&RT is constructed by splitting subsets of the data set using all predictor variables to create two child nodes repeatedly, beginning with the entire data set. The best predictor is chosen using a variety of impurity or diversity measures. The goal is to produce subsets of the data which are as homogeneous as possible with respect to the target variable.[21] The C&RT method was used in this study in order to choose the best predictor for GS.

Table 2. Drug use distribution among the subjects

	Variables	
	n	%
Calcium channel blocker	27	13.5
Beta blocker	176	88
Angiotensin converting enzyme inhibitor	95	47.5
Angiotensin receptor inhibitor	27	13.5
Thiazide	49	24.5
Loop diuretic	18	9
Statin	139	69.5
Fibrate	5	2.5
Oral nitrate	41	20.5
Insulin	13	6.5
Oral anti-diabetic	37	18.5

RESULTS

The general distribution of the patients' characteristics are given in Table 1. Forty-four percent of patients were in the third category of BMI (≥30 kg/m^2) where only 17.5% were in the first category (BMI <25kg/m^2). Most of the patients had low physical activity levels (55.5%). Frequency of metabolic syndrome was prominent (79%). The distribution of drug usage among the participants is shown in Table 2. The median (25–75 percentiles) of GS was found to be 21.25 (7–44.75) and MD score was 4 (3–5). A negative significant correlation was found between MD score and GS ($r=-0.380$, $p<0.001$) (Figure 1).

Table 3 shows the median intakes of all nutrients by both genders. An examination of the correlation between each food group and GS showed no significance. However, a weak negative correlation was found between consumption of eggs and GS ($r=-0.165$, $p=0.02$). No correlation was found between consumption of olive and tea and GS ($p>0.05$).

Table 3. Daily food intakes by gender (median)

Foods	Men			Women		
	Median	n	%	Median	n	%
Vegetables (g/day)						
≥ Median	192.9	67	51.1	172	35	50.7
< Median		64	48.9		34	49.3
Legumes (g/day)						
≥ Median	14.3	66	50.4	5.025	35	50.7
< Median		65	49.6		34	49.3
Fruits and nuts (g/day)						
≥ Median	200	80	61.1	200	42	60.9
< Median		51	38.9		27	39.1
Dairy products (g/day)						
≥ Median	230	68	51.9	231.6	35	50.7
< Median		63	48.1		34	49.3
Cereals (g/day)						
≥ Median	335.25	66	50.4	177	35	50.7
< Median		65	49.6		34	49.3
Meat (g/day)						
≥ Median	2	66	50.4	2.01	37	53.6
< Median		65	49.6		32	46.4
Fish (g/day)						
≥ Median	4.02	70	53.4	1.98	46	66.7
< Median		61	46.6		23	33.3
Olive oil (g/day)						
≥ Median	30	85	64.9	35	36	52.2
< Median		46	35.1		33	47.8
Potatoes (g/day)						
≥ Median	32.2	69	52.7	25.74	38	55.1
< Median		62	47.3		31	44.9
Eggs (g/day)						
≥ Median	17.9	73	55.7	16.5	35	50.7
< Median		58	44.3		34	49.3
Ethanol (g/day)						
≥ Median	0	30	22.9	0	69	100
< Median		101	77.1		0	0
Saturated fatty acid (g/day)						
≥ Median	19.57	66	50.4	21.1	35	50.7
< Median		65	49.6		34	49.3
Monounsaturated fatty acid (g/day)						
≥ Median	34.29	66	50.4	36.93	35	50.7
< Median		65	49.6		34	49.3
Polyunsaturated fatty acid (g/day)						
≥ Median	9.01	66	50.4	9.54	35	50.7
< Median		65	49.6		34	49.3
Monounsaturated fatty acid: Saturated fatty acid						
≥ Median	1.75	66	50.4	1.63	35	50.7
< Median		65	49.6		34	49.3
Energy intake (kj/day)						
≥ Median	1123.26	66	50.4	1320.09	35	50.7
< Median		65	49.6		34	49.3
Sugar and sweets (g/day)						
≥ Median	6.6	69	52.7	0	69	100
< Median		62	47.3		0	0
Olive (g/day)						
≥ Median	21	69	52.7	15	45	65.2
< Median		62	47.3		24	24.8
Total fibre (g/day)						
≥ Median	114.07	66	50.4	123.51	35	50.7
< Median		65	49.6		34	49.3

C&RT was used to better define the risk factors which had an impact on Gensini scores. The decision rules of C&RT provide specific information about risk factors based on the rule induction. The variables included in the C&RT analyses and their significance of importance on GS are set out in Figure 2. The C&RT has 4 leaf nodes, of which 3 are terminal nodes. The variables were: ejection fraction (EF) (importance value=184.229) and MDS (importance value=56.664). EF was the most important determining factor for GS. This first-level split produced the two initial branches of the decision tree. For the EF (≤51) subgroup, there was no predicting variable so it was the terminal node. For the EF (>51) subgroup, MDS proved the best predicting variable; MDS (≤4.5) versus MDS (>4.5). For the MDS subgroup there was no predicting variable (Figure 3).

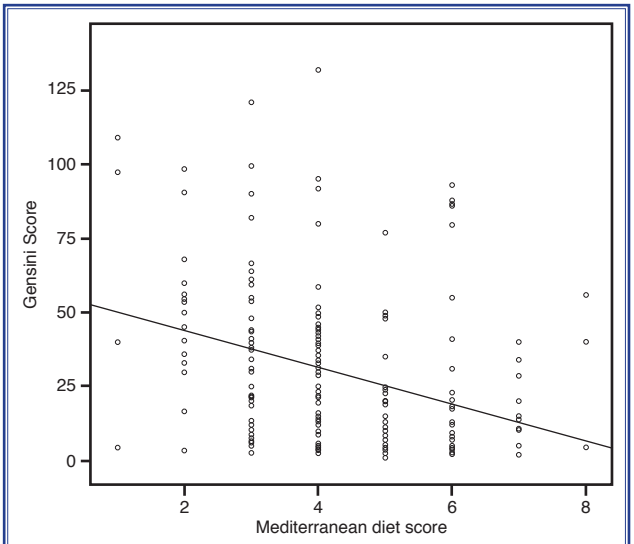

Figure 1. Graph of relation between GS and MDS.

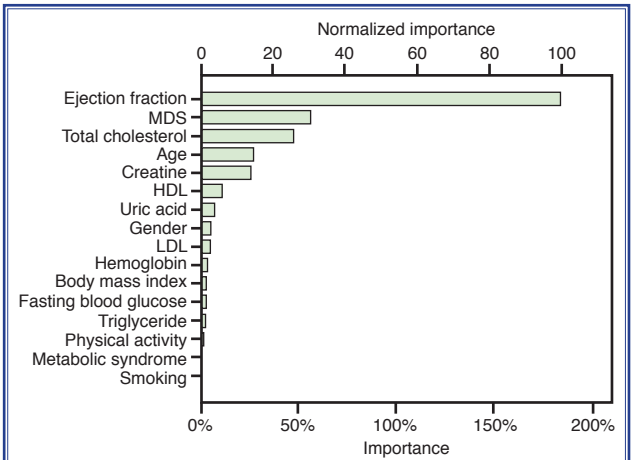

Figure 2. Variables included in the analysis of "Classification and Regression Tree", and their order according to the significance of importance on Gensini score. MDS: Mediterranean diet score; HDL: High density lipoprotein; LDL: Low density lipoprotein.

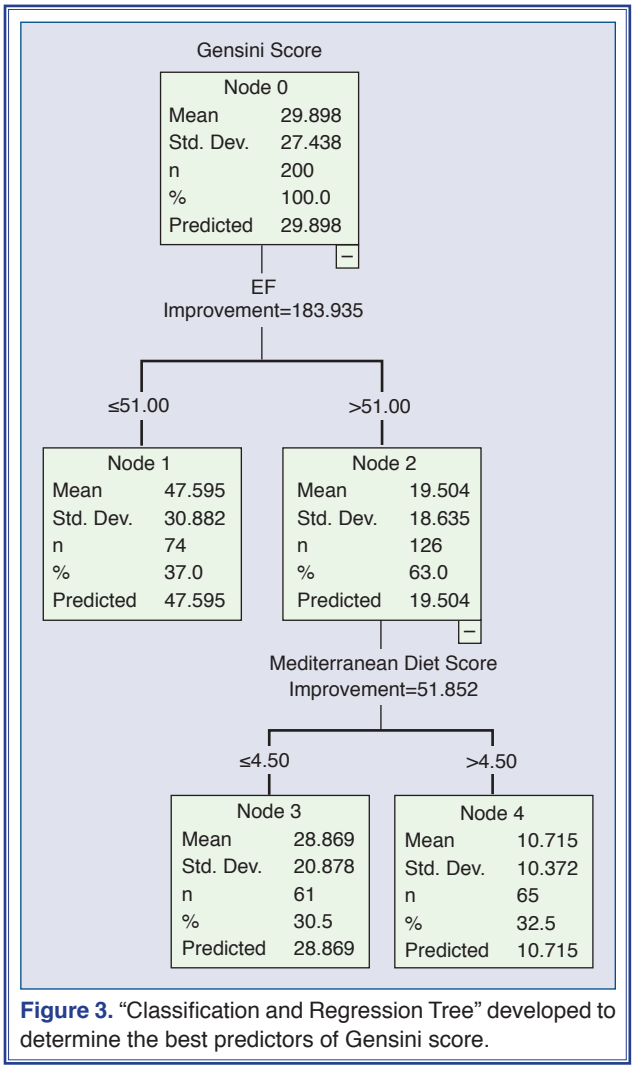

Figure 3. "Classification and Regression Tree" developed to determine the best predictors of Gensini score.

DISCUSSION

This study set out to demonstrate the relation between compliance with the MD and the severity and angiographic qualitative extensiveness of coronary artery disease.

There are many published epidemiological and experimental studies which have reported the positive effects of the MD on the cardiovascular system. In recent years, close attention has been given to publications which demonstrate the close relation

between MD compliance and atherosclerosis both at the gene level and molecular level.[12,13,22–24] It is thought that the anti-inflammatory properties of the MD contribute particularly to the anti-atherogenic property. In one study, application of a 3-month MD was shown to inhibit the increase in the levels of lipoprotein receptor-related protein (LRP1), which is involved in the formation of inflammation-related cyclooxygenase-2 (COX-2) and foam cells in monocytes.[24] In the same study, nuts, which are a component of the MD, were found to increase the expression of tissue factor pathway inhibitor (TPFI).[24] Considering evidence suggesting that increasing the gene level related to TPFI decreases restenosis rates in atherosclerotic vessels, it may be thought that the MD has an important role in vascular remodeling.[25] According to PREDIMED study data, a significant decrease was found in the plasma concentrations of inflammatory biomarkers including CRP, IL-6, intercellular adhesion moecule (ICAM-1), and vascular cell adhesion molecule (VCAM-1) following a 3-month MD.[5] In a substudy of PREDIMED, it was shown that the MD decreased the levels of CD49d molecule in perpheral T lymphocytes related with atherosclerosis and CD11b, CD49d and CD40 in monocytes.[12]

It is thought that the antioxidants in the basic structure of the MD contibute especially to the cardioprotective effect. It is known that vegetative nutrients and olive oil, which are especially rich in antioxidants, are important components in this context. Fatty acids constituting olive oil are reserved by natural antioxidants including carotenes, tocopherols and phenolic compounds.[26,27] Approximately 36 different polyphenol groups have been identified in olive oil.[28] It is thought that the nitric oxide-rich structure of polyphenols play a role in preservation of endothelial function. The anti-inflammatory and anti-atherogenic effects of polyphenols in olive oil have been demonstrated in experimental studies.[29,30]

There is evidence suggesting that the MD shows its cardioprotective effect partially by way of lipid metabolism. There are data suggesting that nut and olive oil, important components of the MD, decrease LDL-cholesterol levels.[31,32] In a recent study, it has been found that the MD has an effect on lipoprotein subgroups and increases the particle size of LDL in a way that renders it less atherogenic.[23] In another study, it was shown that the MD also decreased lipid peroxidation.[33]

With the scoring system allowing evaluation of compliance with MD based on consumption of many food groups together, it has become easier to evaluate the effect of the MD on the cardiovascular system as a whole. This allows evaluation of the synergistic effects of combined use of foods. In this study, we observed that as MD compliance increased, the angiographic severity of CAD decreased. When we compared each food component of the MD with the GS which reflects the extensiveness of CAD, we generally found no significant relation. However, we found a very weak negative correlation between consumption of eggs and GS. There are controversial data about the relation between egg consumption and CAD in the literature. In a recent study, no correlation suggesting that consumption of eggs increases the risk of stroke or coronary artery disease has been found.[34] In another study, it was found that consumption of egg more than once a week decreased the severity of CAD.[35] Neither the number of our patients nor the design of our study was sufficient to make any clear analysis on this subject.

This study is the first study which shows the relation between the extensiveness of angiographic quantitative CAD and compliance with the MD. The findings suggest that increased compliance with the MD leads to lower extensiveness of CAD. Life-style change in patients with CAD has the potential to decrease the extensiveness of atherosclerosis.

Study limitations

There are some limitations to the study. Potential affections because of the cross-sectional design of the study are inevitable. In addition, the relatively advanced age of the study population does not allow for adaptation of the study results to the general population. The fact that the study was a regional study disallows generalization of the results to other races and regions. An angiographic scoring was used to evaluate the extensiveness of atherosclerosis. However, coronary angiography is not a test which can completely evaluate the extensiveness of atherosclerosis in the vessel wall. Despite all these limitations, the authors think this study provides significant data in terms of showing the potential positive effects of life-style changes on coronary atherosclerosis.

Conclusion

In patients with CAD, compliance with the traditional MD is related with decreased severity of coronary atherosclerosis.

Conflict-of-interest issues regarding the authorship or article: None declared

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