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The Adoption of Mediterranean Diet Attenuates the Development of Acute Coronary Syndromes in People with the Metabolic Syndrome

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Abstract

Objectives: In this work we investigated the effect of the consumption of the Mediterranean diet on coronary risk, in subjects with the metabolic syndrome.

Methods: During 2000–2002, we randomly selected, from all Greek regions, 848 hospitalised patients (695 males, 58 ± 10 & 153 females, 65 ± 9 years old) with a first event of acute coronary syndrome and 1078 frequency matched, by sex, age, region controls, without any suspicious for cardiovascular disease. Nutritional habits were evaluated through a validated questionnaire, while the metabolic syndrome was defined according to the NCEP ATP III criteria. Mediterranean diet was defined according to the guidelines of the Division of Nutrition/Epidemiology, of Athens Medical School.

Results: Of the 1926 participants, 307 (36.2%) of the patients and 198 (18.4%) of the controls ($P < 0.001$) met the ATP III criteria. This was related with 2fold adjusted coronary risk (odds ratio = 2.35, 95% 1.87 – 2.84) in subjects with the metabolic syndrome as compared with the rest of them. No differences were observed concerning the prevalence of the metabolic syndrome and sex of subjects, after adjustment for group of study ($P > 0.1$). Eighty (26%) of the patients and 70 (35%) of the controls ($P < 0.01$) with the metabolic syndrome were "closer" to the Mediterranean diet. Multivariate analysis revealed that the adoption of this diet is associated with a 35% (odds ratio = 0.65, 95% 0.44 – 0.95) reduction of the coronary risk in subjects with the metabolic syndrome, after adjusting for age, sex, educational and financial level and the conventional cardiovascular risk factors.

Conclusion: Consequently, the adoption of Mediterranean diet seems to attenuate the coronary risk in subjects with the metabolic syndrome.

Background

The metabolic syndrome is a condition that promotes atherosclerosis and increases the risk of cardiovascular events [1–3]. According to the Centers for Disease Control and Prevention, at least 47 million Americans, or about one in five people, have this condition [1]. Contributors to the development of the metabolic syndrome may include genetics, a sedentary lifestyle, a Western diet (high in refined carbohydrates, low in fiber, and high in saturated fat), cigarette smoking, and progressive weight gain [2]. The characteristics of the metabolic syndrome include atherogenic dyslipidemia, a prothrombotic state, insulin resistance, hypertension, and abdominal obesity [3,4]. Each abnormality promotes atherosclerosis independently, but when clustered together, these metabolic disorders are increasingly atherogenic and enhance the risk of cardiovascular morbidity and mortality [1]. Based on observational studies there is evidence to support that several factors related to lifestyle habits may influence cardiovascular risk [5–7]. Among these factors the beneficial effect of several dietary patterns on human health, have already been underlined [8–10]. One of these diets, the Mediterranean diet, has received much attention during the past decades. It is reach in non-refined cereals, fruits and vegetables, and it has a high monounsaturated: saturated fat ratio. Although the benefits from the adoption of this diet on all cause survival have long been recognized, little is known about its association with the development of acute coronary events, in people with the metabolic syndrome. In this work, we evaluated the effect of the adoption of Mediterranean diet on the risk of developing non-fatal acute coronary events, in subjects with metabolic syndrome.

Materials and Methods

Study's population

The CARDIO2000 is a multicentre case-control study that investigates the association between several demographic, nutritional, lifestyle and medical risk factors with the risk of developing non-fatal acute coronary syndromes. From January 2000 to August 2001, 848 individuals who had just entered to the hospital for a first event of coronary heart disease (stable angina was excluded from the analysis) agreed to participate into the study (response rate 89%). Six hundred fifty-eight (77%) of them were males (59.0 ± 10 years old) and 190 (23%) were females (65.3 ± 9 years old). The inclusion criteria for cardiac patients are:

• First event of acute myocardial infarction diagnosed by two or more of the following features: typical electrocardiographic changes, compatible clinical symptoms, specific diagnostic enzyme elevations, or

• First diagnosed unstable angina corresponding to class III of the Braunwald classification.

Moreover, 1078 randomly selected cardiovascular disease free subjects (controls), frequency matched to the patients by age (± 3 years), sex, and region agreed to participate (response rate 83%). Eight hundred and thirty (77%) of them were males (58.0 ± 10 years old) and 248 (23%) were females (64.8 ± 9 years old). Controls were individuals who visited the outpatients departments of the same hospital and at the same period with the coronary patients for minor surgical operations. All the controls were subjects without any clinical symptoms, signs or any suspicion of cardiovascular disease in their medical history, as a physician evaluated it. We used this type of controls in order to have more accurate medical information, to eliminate the potential adverse effect of several, unknown, confounders and to increase the likelihood that cases and controls share the same study base [11]. The number of the participants was decided through power analysis, in order to evaluate differences in the coronary relative risk greater than 7% (statistical power > 0.80, significant level < 0.05).

Stratification

According to the population distribution provided by the National Statistical Services (census 2000), we stratified our sampling into all the Greek regions, in order to include various socio-economical levels and cultural particularities of the investigated population. The enrolled subjects are from, approximately, the one half of the clinics, public or private, of the two biggest metropolitan cities (Athens and Thessalonica), and from, almost, all the major clinics of the other regions (3 from Sterea Ellada, 3 from Thessalia, 2 from Hpeiros, 5 from Macedonia, 2 from Thrace, 5 from Peloponnese, 2 from Crete, 5 from Aegean and 3 from Ionian islands).

Randomised procedure

In order to reduce the unbalanced distribution of several measured or unmeasured confounders, both patients and controls were randomly selected. Thus, a sequence of random numbers (1...0) was applied in the hospitals' admission listings. The coronary patients who assigned to the number 1 were entered into the study and interviewed (i.e. approximately the one half of the cardiac patients that visited each cardiology clinic). The same procedure was applied for the controls, after taking into account the matching criteria.

Investigated parameters

A specialist retrieved the information regarding the investigated medical factors from the subjects' medical records, and the information regarding the life style characteristics through a confidential questionnaire during a specific

interview after the 2nd day of the hospitalisation, for the cases and at entry for the controls. The evaluation of the nutritional habits was based on a nutrient questionnaire according to the guidelines from the Department of Nutrition of the National School of Public Health [12]. The Mediterranean dietary pattern consists of: (a) daily consumption: of non refined cereals and products (whole grain bread, pasta, brown rice, etc), vegetables (2 – 3 servings/day), fruits (6 servings/day), olive oil (as the main added lipid) and dairy products (1 – 2 servings/day), (b) weekly consumption: of fish (4–5 servings/week), poultry (3 – 4 servings/week), olives, pulses, and nuts (3 servings/week), potatoes, eggs and sweets (3 – 4 servings/week) and monthly consumption: of red meat and meat products (4 – 5 servings/month). It is, also, characterized by moderate consumption of wine (1 – 2 wineglasses/day) and high monounsaturated: saturated fat ratio (> 2). This dietary pyramid was suggested by a Harvard-led group with substantial input from Greek scientists [13]. Thus, we measured the consumption of these food items as an average per week, during the past year. Then, the frequency of consumption was quantified approximately in terms of the number of times a month the food was consumed. The weekly consumption multiplied by 4 and a value of 0 was assigned to food items rarely or never consumed. In order to describe total diet we used composite scores, which are necessary for the evaluation of epidemiological associations [12]. We defined subjects who are "closer" to the Mediterranean type of diet using as cut-off points the median values of the monthly food consumption score as done by several investigators in the past [12]. Finally, alcohol consumption was measured by daily ethanol intake, in wineglasses (100 ml of 12% ethanol concentration).

According to the collected medical information, the majority of the controls (86%) and of the patients (83%) had at least one-laboratory measurement during the past 12 months. In addition, we measured, both in patients and controls, arterial blood pressure levels (average of 3 measurements with subject sited and calm for at least 30 minutes; using a standard sphygmomanometer. Fast total cholesterol as well as fast blood glucose levels were measured in serum. For the cardiac patients the measurements were collected during the first 12 hours of hospitalisation, and for the controls at the end of the interview. The previous information as well as the patients' and controls' reports assisted us to characterize the subjects as hypertensive, hypercholesterolemic and diabetics. In particular, in keeping with the long-standing classification criteria used in several epidemiological studies [2], patients who reported never having been told of having hypertension and were not currently taking any antihypertensive medication and whose blood pressure was less than 140 / 90 mmHg were classified as normotensives. Patients whose mean blood pressure levels were greater or equal to 140 / 90 mmHg or were under antihypertensive medication were classified as hypertensives. Hypercholesterolemia was defined, as cholesterol levels greater than 220 mg/dl or greater than 200 mg/dl when two other risk factors for coronary heart disease or use of special hypo-lipidemic treatment was present. Diabetics were those with fast blood glucose greater than 125 mg/dl or were under special diet or treatment. Finally, we measured the height and the weight both in patients and controls. In addition, we marked any significant changes in their body mass occurred during the past years. Thus, obesity was defined as body mass index (weight / {height} ^{2}) greater than 29.9 Kg/m^2. Current smokers were defined those who smoked at least one cigarette per day. Quantification of smoking status was based on the calculation of pack-years adjusted for nicotine containment equal to 0.8-mgr per cigarette. Former smokers were defined as the subjects who stopped smoking for over 1 year. Physical activity was defined as any type of leisure time exercise or occupational activity, at least 1/week during the past year, and was gradated in qualitative terms such as light (expended calories < 4 Kcal/ min, i.e. walking slowly, cycling stationary, light stretching etc.), moderate (expanded calories 4–7 Kcal/ min, i.e. walking briskly, cycling outdoor, swimming moderate effort etc.) and vigorous (expanded calories >7 Kcal/ min, i.e. walking briskly uphill, long distance running, cycling fast or racing, swimming fast crawl etc.) [20]. The rest of the subjects were defined as physically inactive. Also, the intension and the duration of physical exercise were taken into account. Subject's educational level was measured and classified into three groups: Group I, up to high school (or < 9 years of schooling); Group II, high school, technical school (or 9 – 14 years of eschooling) but not university and Group III, university. Mean annual income, during the past 5 years was, also, recorded. Further details regarding the design and methodology of the CARDIO2000 study have been previously presented [14,15].

As previously mentioned in this work we focused our interest in people with the metabolic syndrome. According to ATP III [2], the diagnosis of metabolic syndrome was established if 3 or more of the following risk factors were present:

• waist circumference >102 cm (40 in) for men or >88 cm (37 in) for women;

• triglyceride level >150 mg/dL;

• HDL cholesterol level <40 mg/dL for men or <50 mg/dL for women;

• blood pressure >130/85 mm Hg;

Table 1: Prevalence of the conventional cardiovascular risk factors in coronary patients and controls with the metabolic syndrome, stratified by the main factor of interest, i.e. adoption of the Mediterranean diet and physically active lifestyle or not

	Mediterranean diet		No Mediterranean diet		P-value
	Patients	Controls	Patients	Controls	
Current smoking	42 (53%)	29 (41%)	156 (69%)	51 (40%)	0.085
Physical inactivity	49 (61%)	33 (47%)	136 (60%)	64 (50%)	0.124
Hypertension	50 (63%)	23 (33%)	133 (59%)	51 (41%)	< 0.001
Hypercholesterolemia	47 (59%)	12 (17%)	145 (64%)	26 (20%)	< 0.001
Obesity	33 (41%)	15 (24%)	63 (28%)	31 (28%)	0.324
Diabetes mellitus	30 (38%)	10 (15%)	79 (35%)	23 (18%)	0.001

Last column represents the pooled probability value (p-value) that is derived from the cross – tabulated comparisons between group of the study (patients – controls) and the classical cardiovascular risk factors, stratified by the main factor of interest (i.e. combination of Mediterranean diet and physical activity or not).

• or fasting glucose >110 mg/dL.

Statistical analysis

Continuous variables are presented as mean ± one standard deviation while qualitative variables are presented as absolute and relative frequencies. In order to fit multivariate risk models an exploratory analysis was initially applied. Contingency tables with calculation of chi-squared test, as well as the calculation of Student's t-test were applied for the evaluation of the associations between the categorical and continuous variables with the outcome. Estimations of the relative risks of developing acute coronary syndromes, under several hypotheses, were performed by the calculation of the odds ratio (OR) and the corresponding confidence intervals through multiple logistic regression analysis, with stepwise elimination procedure. All reported P-values are based on two-sided tests and compared to a significant level of 5%. STATA 6 software was used for the calculations (STATA Corp. College Station, Texas, USA).

Results

Descriptive analysis

Three hundred and seven (36.2%) of the patients and 198 (18.4%) of the controls (P < 0.001) met the ATP III criteria. The metabolic syndrome was more frequent in males' than in females' controls (22% vs. 10.4%, p < 0.001), while no statistically significant differences were found regarding the prevalence of the metabolic syndrome among male and female coronary patients (37% vs. 33%, p = 0.420). About the one half of the controls and 60% of the patients with the metabolic syndrome reported sedentary life (p = 0.240). Current smoking habits were highly associated with the prevalence of the metabolic syndrome, on both, patients and controls (p < 0.001). A consistent inverse association was observed between the prevalence of the metabolic syndrome and the financial status of patients (p for trend = 0.598) and controls (p for trend = 0.001). No associations were observed regarding the presence of the metabolic syndrome and the educational profile of the patients (p = 0.280) and the controls (p = 0.136). Focusing our interest on the consumption of Mediterranean diet we observed that 80 (26%) of the patients and 70 (35%) of the controls (p < 0.01) that fulfilled the criteria for the metabolic syndrome were "closer" to the Mediterranean diet. Table 1 presents the prevalence of hypertension, hypercholesterolemia, diabetes mellitus, physical inactivity, obesity and smoking habits, in patients and controls that adopted the Mediterranean diet compared to patients and controls that they did not adopt this diet. These associations raise the confounding effect of the adoption of the Mediterranean diet on obesity, physical activity and smoking habits. Moreover, both patients and controls that were defined "closer" to the Mediterranean diet had lower prevalence of the conventional cardiovascular risk factors compared to the rest of the subjects (Table 1).

Risk stratification

Multivariate analysis revealed that the metabolic syndrome 2fold the coronary risk (odds ratio = 2.35, 95% 1.87 – 2.84) after adjustment for age, sex, physical activity levels, smoking habits, financial status and presence of hypertension, hypercholesterolemia, and diabetes mellitus. However, the unadjusted odds ratio for developing an acute coronary event in people who adopted the Mediterranean diet was 0.64 (95% CI 0.44 – 0.95), indicating a 36% reduction of the coronary risk as compared with people that did not adopt this diet. After taking into account the effect of the aforementioned associations (descriptive analysis) as well as the effect of several potential confounders, like age and sex of the participants, systolic and diastolic blood pressures, total serum cholesterol and blood glucose levels, as well as premature family history

Table 2: Results from the multivariate analysis that was developed to evaluate the coronary risk (odds ratio; 95% confidence interval) in subjects with the metabolic syndrome

	Odds ratio	95% Confidence interval
Adoption of Mediterranean diet (yes vs. no)	0.77	0.645 – 0.918
Age of participants (1-year)	1.03	1.004 – 1.054
Male sex	2.02	1.079 – 3.787
Hypercholesterolemia (presence vs. absence)	6.00	3.720 – 9.686
Family history of CHD (yes vs. no)	5.16	3.016 – 8.837
Low vs. high income	1.69	1.166 – 2.392
Diabetes mellitus (presence vs. absence)	1.67	1.072 – 2.925
Current smoking habits (yes vs. no)	2.40	1.522 – 3.790
Physical activity vs. sedentary	0.89	0.839 – 0.945
Obesity (presence vs. absence)	1.05	0.641 – 1.312

of coronary heart disease, we found that effect of the consumption of Mediterranean diet on the coronary risk remains beneficial. In particular, the adoption of this diet is associated with a 23% (odds ratio = 0.77, Table 2) reduction of the coronary risk in subjects with the metabolic syndrome. The calculated attributable risk by the formula: attributable risk = (odds ratio – 1) / odds ratio [11], suggested that the one third (30%) of the acute coronary events could be prevented by the adoption of the Mediterranean diet, in subjects with the metabolic syndrome. Moreover, the adoption of Mediterranean diet by people who reported that they exercise at least once per week (> 4 kcal/min) seems to have an additive benefit, since it is associated with 47% (odds ratio = 0.53, $P < 0.01$) lower risk of developing acute coronary events, after adjusting for age, sex, and the levels of the common cardiovascular risk factors. This reduction of the coronary risk is much higher than Mediterranean diet or exercise (odds ratio = 0.89, $p < 0.05$) achieve alone in this group of people.

Discussion

In this work we evaluated the effect of the adoption of Mediterranean diet on the development of acute coronary syndromes, in subject with the metabolic syndrome. The data analysis revealed that the adoption of the Mediterranean diet is associated with a considerable reduction of the coronary risk, in these people, after adjustment for several potential confounders.

The metabolic syndrome is a condition well established in nowadays, and it is associated with the promotion of atherosclerosis and increase of the cardiovascular risk. Moreover, there is extensive scientific evidence, especially in countries with better and long lasting national health programs, that the prevalence of metabolic syndrome has increased in the last decade, which suggest that the disease burden (including type 2 diabetes) has increased as well [1]. Despite its multiple origins, obesity, sedentary life coupled with unhealthy diet and genetic factors interact to produce this syndrome. ATP III raised the significance of diagnosing and treating the metabolic syndrome, focusing on physical activity, lowering excess body fat and on specific dietary patterns. During the past years several epidemiological studies have underlined the relation between diet and incidence of coronary heart disease, and other diseases [16–18]. Dietary factors exert their influence largely through their effects on blood lipids and lipoproteins, as well as on the other established modifiable risk factors, with the exception of cigarette smoking. Our findings support the hypothesis that adoption of Mediterranean diet by subjects who met the criteria for the metabolic syndrome is associated with a significant reduction of the risk of developing acute coronary events. The investigated type of diet is low in saturated fat, high in monounsaturated fat, mainly from olive oil, high in complex carbohydrates, from legumes, and high in fibre, mostly from vegetables and fruits. Also, epidemiological studies suggest that the Mediterranean diet is associated with lower coronary heart disease risk, especially through the reduction of blood pressures, body mass index, and levels of several thrombogenic factors [12,13,18,19]. Recently, the findings from the Lyon Diet Heart study illustrate the potential importance of the Mediterranean dietary pattern, especially when compared to other recommended diets, like Step-I diet [19]. Also, results from a Spanish Study suggest that the monounsaturated fatty acids diets are associated with a significant reduction and a better control of both systolic and diastolic blood pressure [20]. However it still remains a matter of debate if the protective influence is primarily caused by single nutrients, e.g. dietary fatty acids, potassium or dietary fibre or if it can be attributed to the Mediterranean diet as a whole [12].

EUROASPIRE Study group investigators suggest to the cardiologists, physicians and public health policy makers to moderate the prevalence of the cardiovascular risk factors

in order to further reduce coronary heart disease morbidity and mortality and improve patient's chances of survival [21]. This reduction may be achieved through the adoption of a healthier lifestyle, including stopping smoking, initiation of physical activities and adoption of a healthy diet. Recently the NCEP ATP III recommended for *Therapeutic Lifestyle Changes* [2] in order to reduce the prevalence of the metabolic syndrome among populations. These changes underlined the importance of low-saturated diet consumption (<7% of total fat) and physical exercise. In our work we found that the adoption of Mediterranean diet seems to be associated with a considerable reduction of acute coronary events (i.e. 30%) in people with the metabolic syndrome. Interestingly, is that the adoption of Mediterranean diet by physically active people is associated with much higher reduction of the odds of developing acute coronary event, than diet or exercise achieve alone. A plausible explanation could be the low concentration of this type of diet in saturated fat and the non-lipid-lowering benefits that physical activities and Mediterranean diet have been reported to produce (including antithrombotic and anti-inflammatory effects) [22,23]. In accordance to that, several investigators have reported that non-pharmacological lifestyle interventions, like diet and exercise, could be useful in the management of hypertensive subjects [24,25].

This is the first study concerning the prevalence of the metabolic syndrome in Greece and the effect of the Mediterranean diet on the related coronary risk. The results of our study suggest that one third of the acute coronary events could be prevented by the adoption of the Mediterranean diet in subjects with the metabolic syndrome. Education and training will be critical to ensure that physicians have knowledge to diagnose and treat patients with the metabolic syndrome. So the early identification, treatment (with non pharmacological interventions) and prevention of the metabolic syndrome seems to be extremely challenging and provoking for the health policy makers, in order to reduce the epidemic of overweight, improper nutrition and sedentary lifestyle. However, even the observed association is independent from several potential confounders it is hard to claim that our findings suggest causal evidence and much remains to be learned about this "ecological" effect on coronary risk in people with the metabolic syndrome.

Limitations of the study

In retrospective case-control studies, two main sources of systematic errors may exist, the selection and the recall bias. In order to eliminate selection bias we tried to set objective criteria, both for patients and controls. However, insignificant misclassification may exist, since a small percentage of asymptomatic coronary patients may be wrongly assigned to controls, even if they were evaluated by a cardiologist. Also, in case-control studies, it is usually observed that patients who had a recent adverse event are more likely to place greater emphasis (overestimate) on several factors related to the disease than the control group (recall bias). In order to reduce this type of bias and analyze accurate information we made an effort to obtain accurate information from the patients as well as from their relatives or their accompanying persons. However, overestimation of the effect of the investigated combination may still exist. Concerning the medical information, we tried to avoid recall bias by obtaining accurate and detailed data from subjects medical records. However, over/under estimation may still exist, especially in the measurement of nutritional and smoking habits, and the onset of the investigated cardiovascular risk factors. Moreover, the coronary patients who died at entry or the day after were not included in the study. This bias could influence our results, but, since the proportion of deaths during the first two days was estimated between 2–4%, we believe that the inability to include the fatal events did not alter significantly our findings. Furthermore, regarding the potential effect of uncontrolled – unknown confounders, we tried to reduce it using the same study base, both for patients and controls.

Competing interests

None declared.

Contribution of authors

CP: design of the study and drafted the manuscript, DP: design of the study, data analysis and drafted the manuscript, CC: design of the study, IP: drafted the manuscript, LP: drafted the manuscript, DT: drafted the manuscript, PT: design of the study and CS: design of the study.

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