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The Mediterranean Diet: A Protective Effect on Coronary Heart Disease

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## **Introduction**

Coronary heart disease (CHD) is the leading cause of death in the United States as well as in many developing and developed countries. (1) However, several studies studying the epidemiology of CHD across the world have found that there is a significantly lower incidence in Japan and Mediterranean Southern Europe, a difference which was found to be independent of serum cholesterol levels. (2,3,4) In addition, studies that have shown increases in disease rates among immigrants to the Western world demonstrate that the changes in disease rates are dependent on differences in lifestyle, including diet and exercise, and not just genetics. (5)

What is it about the Mediterranean diet that yields such a low rate of CHD? There is no single definition of a Mediterranean diet, as the region includes at least 16 different countries. However, it can be said that high intake of olive oil as an important fat source is the cornerstone of the traditional Mediterranean diet, resulting in a high intake of monounsaturated fatty acids (MUFA) and a low intake of saturated fatty acids (SFA). The diet is characterized by a high intake of vegetables, legumes, fruits and nuts, unrefined cereals, a moderately high intake of fish, a low intake of red meat and poultry, a low to moderate intake of dairy products (usually in the form of cheese or yogurt), a 0-4 time/week consumption of eggs, and a moderate intake of alcohol, usually in the form of wine during meals. (6,7,8,9)

### **Protective Mechanisms of the Mediterranean Diet.**

The success of the Mediterranean diet has been attributed to its alterations in the lipid profile and oxidative injury. Briefly, dietary fats have an important influence on plasma cholesterol levels, including low density lipoprotein (LDL). Under oxidative stresses, LDL can become oxidized which is vital in generating a form taken up by macrophages from the bloodstream into the subendothelial space, eventually leading to the formation of fatty plaques. (10)

Studies have shown that SFAs have cholesterol raising properties while substitution by MUFA or PUFA decreases plasma total cholesterol levels as well as low density lipoprotein (LDL) cholesterol concentrations. It seems, however, that PUFAs lower high density lipoprotein (HDL) levels as well. In addition, because PUFAs have two or more double bonds, they are more susceptible to lipid peroxidation, thus making LDL more atherogenic. MUFAs, on the other hand, maintain HDL levels and are more resistant to oxidative modifications. These slight differences are important as MUFAs can, for example, substitute other fatty acids, especially PUFAs in biologic membranes, which take the brunt of the oxidative stresses our bodies face. MUFAs are found in high concentration in olive oil, mostly in the form of oleic acid. (10,11)

However, it must be mentioned that omega-3 fatty acids, mainly  $\alpha$ -linolenic acid, a PUFA found in fish, fish oils, and vegetable oils like flaxseed and canola, has been shown in animals and humans to have anti-inflammatory properties to prevent the development of atherosclerotic lesions. (6,15) Many recent studies support the cardio-protective effects of omega-3 PUFAs. The United States Physicians' Health Study showed that consumption of greater than one serving of fish per week is associated with a 52% decrease in sudden cardiac death. (13, 16) The Nurses Health Study show that fish consumption once per week decreases the risk of CHD in women

([RR], 0.71, [CI], 0.58-0.87). (13, 17) Omega-3 fatty acids have been shown to prevent arrhythmia as well (6).

Virgin olive oil also contains numerous antioxidants including carotenes, alpha-tocopherols (vitamin E), phenolic compounds and coenzyme Q, which further prevent oxidative injuries. (10)

There are additional roles in the high consumption of fruits, vegetables, legumes, and cereal which are rich in antioxidants and fiber. Cereal fibers are most strongly associated with decreased risk of a myocardial infarction (18). Nuts such as walnuts and flaxseed are rich in alpha-linolenic acid (6). Low intake of red meat diminishes SFA.

### **Evidence that the Mediterranean Diet Lowers the Risk of CHD.**

#### *HALE Project*

Most recently, the HALE Project (Healthy Ageing: a Longitudinal Study in Europe population) studied the single and combined effect of adherence to a Mediterranean diet, moderate alcohol consumption, physical activity, and nonsmoking status on all-cause and cause-specific mortality in elderly European men and women aged 70-90 yearsold from 11 European countries. The study, conducted between 1988 and 2000, followed 1507 healthy men and 832 women and determined the 10 year mortality from all causes, CHD, CVD, and cancer. Individuals with CHD, CVD, cancer, and diabetes were excluded from the study at the start since these conditions not only increase the risk of mortality, but they were potential causes of changes in diets and lifestyle. (12)

Participants were categorized into a low risk group based on their adherence to the Mediterranean diet as set by the authors. The low risk group included those with a score of at least 4. The diet score consisted of 8 components: 1) ratio of monounsaturated:saturated fat, 2) legumes, nuts, and seeds, 3) grains, 4) fruit, 5) vegetables and potatoes, 6) meat and meat products, 7) dairy products, and 8) fish. The sex-specific median intake values were used as the cut-off points to determine the risk category. Participants were given a 1 for each category if their consumption was greater than the sex-specific median and 0 if it was less. However, for the dairy and meat categories, a 0 was given if their consumption was greater than the median and a 1 if it was less. Note in this study alcohol intake was not considered as part of the Mediterranean diet but was instead a separate protective factor. (12)

The results show that adherence to a Mediterranean diet is associated with a lower mortality rate from all causes, but most significantly CHD (hazard ratio [HR], 0.61; 95% confidence interval [CI], 0.43-0.88). HRs were controlled for age, sex, years of education, BMI, and other confounders. In addition, adherence to all four protective lifestyle factors was associated with a mortality rate due to CHD of less than one third of those with only one protective lifestyle factor, stressing the importance of exercise and nonsmoking. The population attributable risk (an estimate of the percentage of CHD mortality in the population that could have been prevented had all participants adhered to all protective lifestyle factors) was 64%. (12)

Important limitations of this study include the relative absence of individuals not adhering to any protective lifestyle factors as well as selective participation in different cohorts of the study. In addition, only an elderly population was followed, limiting the applicability of this data to patient populations interested in managing CHD. (12)

#### *Further Studies on the Benefits of the Mediterranean Diet*

A previous study comes to a similar conclusion. In a population-based, prospective investigation involving 22,043 adults in Greece, followed for a median duration of 44 months, Trichopoulos et al showed that adherence to a Mediterranean diet was related to a lower total mortality rate as well as mortality rate due to CHD. Again, individuals with CHD, diabetes, or cancer at enrollment were excluded. Adjustments were made for age, sex, BMI, physical activity level, and other confounders. (9)

Adherence to the diet was assessed by a 10-point Mediterranean diet scale. The sex-specific median was used as the cut-off for point assignment. One point each was assigned for eating more vegetables, legumes, fruits and nuts, cereal, fish, more monounsaturated: saturated fats, and moderate alcohol consumption (men: 10-50 g/day and women 5-25 g/day). One point each was assigned for eating less meat/poultry and dairy products. (9)

The study found that a two point increment increase in the Mediterranean diet score was associated with a 25% reduction in death from any cause ([HR], 0.75, [CI], 0.64-0.87), a 24% reduction in death from cancer ([HR], 0.76, [CI], 0.59-0.98), but most significantly, a 33% reduction in death from CHD ([HR], 0.67, [CI], 0.47-0.94). Interestingly, however, associations between individual components of the Mediterranean diet did not significantly affect mortality, except for intake of fruits and nuts and the ratio of monounsaturated: saturated fatty acids. It is possible that the foods have small contributions that are only seen as significant when they are combined. (9)

Another interesting point is that the benefits found were significant only in individuals over 55 years of age. This may be a reflection of the small sample size of participant deaths of those under 55 years of age. (9,13) This study, like the Knoop study, had a large size, but a longer follow up time may have yielded even stronger results. (1,9,13)

#### *The Mediterranean Diet as Secondary Prevention of CHD*

Effects of a Mediterranean-style diet have also been studied as a means of secondary prevention of CHD. The Lyon Heart Study, a randomized controlled trial with a follow up of 27 and 46 months, found that adherence to a Mediterranean diet compared to a prudent Western diet, a diet similar to the National Cholesterol Education Program (NCEP) Step I diet, resulted in a 70% reduction in coronary events and cardiac deaths, despite similar plasma cholesterol levels. (6,8,13)

In this study, the Mediterranean diet followed usual guidelines except margarine was supplied by the study to replace butter and cream. This margarine SFA and MUFA contents were similar to those in olive oil, except the margarine was higher in linoleic and  $\alpha$ -linolenic acid. Overall, the

experimental group averaged 30% of calories from fat, 8% from saturated fat, 13% from monounsaturated fat, 5% from polyunsaturated fat, and 203 mg/d of cholesterol while as a group they had a lower intake of linoleic acid, but a higher intake of oleic acid,  $\alpha$ -linolenic acid, and dietary fiber. Participants in the control group averaged 34% of calories from fat, 12% from saturated fat, 11% from monounsaturated fat, 6% from polyunsaturated fat, and 312 mg/d of cholesterol. (6,8) These facts demonstrate that they type of fat and not the amount of fat consumed is important for decreasing the risk of CHD. (13)

Similar results were found in another secondary prevention trial of 1000 patients with CHD or risk factors, who were randomized to an Indo-Mediterranean style diet or a control group following a diet similar to the NCEP Step 1 diet. (14) The experimental group consumed more fruits, vegetables, walnuts, almonds, whole grains, and mustard or soy bean oil, as rich sources of  $\alpha$ -linolenic acid instead of fish or fish oil supplements. The study found a reduced number of total cardiac end points in the intervention group (39 vs. 76 events,  $p < 0.001$ ), sudden cardiac deaths (6 vs. 16 events,  $p = 0.015$ ) and nonfatal myocardial infarctions (21 vs. 43 events,  $p < 0.001$ ). Similar to other trials mentioned, this study found a reduction in serum cholesterol levels in both groups, although a greater reduction was found in the experimental group. (13,14)

An important methodological issue in this study was participant adherence to the diet and lifestyle advice. However, considering the strong results, such an issue may have been minimal.

A recent study has assessed the effect of a Mediterranean style diet on endothelial function and vascular inflammatory markers in patients with metabolic syndrome, thus supporting the mechanism for cardio-protective effects of MUFAs and PUFAs as mentioned above. 180 patients were randomized to a Mediterranean-style diet vs. a cardiac prudent diet (with total fat less than 30% of calories). After two years, mean body weight, serum concentrations of C-reactive protein, IL-6, IL-7, IL-18, and insulin resistance decreased more in patients in the experimental group while endothelial function improved. (19)

## **Conclusion**

The studies mentioned are just a handful of those supporting the Mediterranean diet as a mean of reducing the primary and secondary risks of CHD. Many current diet strategies for patients are aimed at lowering blood cholesterol via a low-cholesterol diet may be less effective than consuming a Mediterranean-style diet that is high in omega-3 fatty acids as well as antioxidants. We have shown that cardiac end points are reduced in patients often independently of serum cholesterol levels.

Additional studies assessing intermediate end points and inflammatory, cytokine, or cholesterol markers would be useful. Such studies would prove useful in further understanding the mechanisms of diet success. Furthermore, more long term studies following younger individuals would be useful as many of the current studies have not noted any significant effects in such a population. (1) In addition, it is important to mention that we were unable to find studies that did not support the use of the Mediterranean diet in individuals with CHD. While several versions of the Mediterranean diet were used, all showed at least minor benefits in CHD

mortality or risk of CHD. The scarcity of negative studies seems to indicate the effectiveness of the diet.

Until further studies are done, doctors must continue to be advocates of a healthy lifestyle beyond the daily prescription of medication. It is important to emphasize the value of modifying those lifestyle factors that are in our control. Patients with CHD would benefit from decreased consumption of red meats and dairy products, with a subsequent increase in fish, nuts, fruits, vegetables, legumes, and whole grains. And finally, it cannot be forgotten that diet in addition to moderate physical activity, lowers mortality due to all causes and is the most effective strategy towards health.

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