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Does diet alter cardiovascular risk?

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Abstract

Cardiovascular disease continues to be the main cause of morbidity and mortality in the 21st century. The first steps in the prevention and treatment of this disease are to follow a healthy diet and to exercise regularly. The Mediterranean diet has been considered as a model of healthy eating. Several cohort studies and two randomized intervention-feeding trials have concluded that an increase in the adherence to a traditional Mediterranean diet significantly reduces the incidence of cardiovascular events and mortality. An analysis of intermediate markers of vascular risk have shown that the Mediterranean diet improves classical and novel risk factors including blood pressure, lipid profile, lipoprotein particles, insulin sensitivity, and carotid atherosclerosis. Interestingly, the effects of diet on the lowering of blood pressure are independent of salt intake and persist for a long time. These effects have been attributed to the antioxidant, anti-inflammatory, and vasodilatory properties of this diet. However, these protective effects of a traditional Mediterranean diet could potentially be even further enhanced by changing common olive oil to extra-virgin olive oil, increasing the intake of whole grain cereals, nuts, oily fish, and legumes; and, above all, reducing sodium intake. ■ Heart Metab. 2014;63:8–12

Keywords: Atherosclerosis; cardiovascular disease; cardiovascular risk; diet; inflammation; Mediterranean diet; olive oil; polyphenols; salt, vegetables; wine.

Cardiovascular disease (CVD) is the main cause of mortality worldwide and is principally caused by the appearance and progression of atherosclerotic lesions. Atherosclerosis has long been considered as an oxidative disease, which accumulates lipids in the artery wall. However, today it is considered a systemic disease involving low-grade arterial inflammation in which the cell and endothelial expression of adhesion molecules and chemokines participate in the recruitment of circulating leukocytes to the vascular endothelium and migration into subendothelial spaces causing atherosclerotic lesions. Inflammation is characterized by a complex biological cascade of molecular and cellular signals that alter physiological responses. At the site of the injury, cells release molecular signals such as cytokines that cause a number of changes in the affected area, such as dilation of blood vessels, increased blood flow, increased vascular permeability, or exudation of fluids.

Behavioral risk factors are responsible for about 80% of CVD,[1] the most important ones being unhealthy diet, physical inactivity, tobacco use, and excessive use of alcohol. The effects of unhealthy diet and physical inactivity manifest within individuals as increased blood pressure (BP), raised plasma glucose and lipid concentrations, and overweight or obesity. Treatment of these cardiovascular risk factors may delay the progression of atherosclerosis and the appearance of its main clinical manifestations, cardiovascular events, and mortality.

Abbreviations

BP: blood pressure; **CVD:** cardiovascular disease

The consumption of some key foods (eg, whole grain cereals, fruits, vegetables, nuts, fish, and a moderate alcohol intake) reduces the risk of cardiovascular disease. However, the Mediterranean diet, as a whole dietary pattern, was ranked as the dietary factor with the highest level of scientific evidence in terms of protection against coronary heart disease.[2] Thus, a meta-analysis of cohort studies showed a 10% reduction in fatal and nonfatal cardiovascular events associated with a 2-point increase in a 9-point score of adherence to the traditional Mediterranean diet.[3] Nevertheless, the highest level of scientific evidence is only achieved with the performance of randomized clinical trials with "hard" end points as their main outcome. Until now, only two field trials fulfill these criteria, the Lyon Diet Heart Study[4] and the PREDIMED trial (PREvención con DIeta MEDiterránea).[5] The first study showed an almost 70% reduction in cardiovascular mortality in subjects with a previous infarction after following a Mediterranean diet, and the PREDIMED trial observed a 30% decrease in cardiovascular events in an asymptomatic high-risk population *(Figure 1)*.

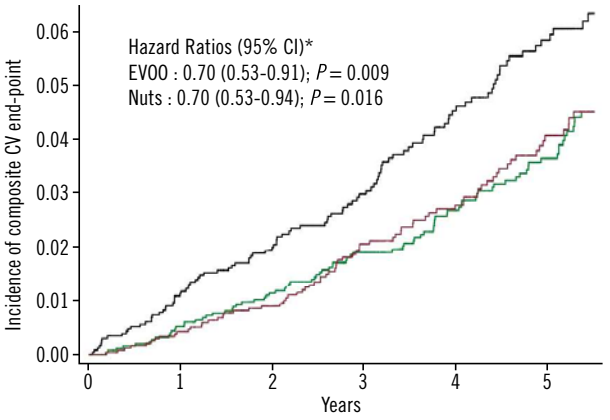

Fig. 1 *Kaplan-Meier estimates of incidence of all major cardiovascular events. All major cardiovascular events: (i) acute myocardial infarction; (ii) stroke; or (iii) cardiovascular death are estimated in the three intervention groups: (i) Mediterranean diet + extra-virgin olive oil (green line); (ii) Mediterranean diet + nuts (red line); and control group (black line).* * Hazard ratios *stratified by center (Cox model with robust variance estimators). Modified from reference 5. Copyright © 2013 Massachusetts Medical Society. All rights reserved.*
Abbreviations: *CV, cardiovascular; EVOO, extra-virgin olive oil.*

Diet, oxidative stress, inflammation, and atherosclerosis

A Western high-fat high-carbohydrate diet is positively associated with low-grade inflammation, and therefore, contributes to the development and progression of atherosclerosis. The classical Western diet is rich in total fat (and an unbalanced ratio of n-6 to n-3 fatty acids), animal protein, n-6 polyunsaturated fatty acids, and refined sugars, which altogether lead to an increased pro-oxidant and proinflammatory state,[6] and may, therefore, be considered as another risk factor for the development of CVD.[7] On the other hand, several studies have highlighted that a Mediterranean diet decreases cardiovascular risk in healthy and high-risk populations.[8] The Mediterranean diet should be considered as an integrated dietary pattern, not a sum of nutrients. In fact, overall dietary patterns may improve health to a greater extent than isolated foods or nutrients.[7] The Mediterranean dietary pattern is characterized by a high content of cereals, fruits, and vegetables (and, therefore, polyphenols), a moderate consumption of olive oil, fish, seafood, nuts, fermented dairy products (yogurt and cheese), poultry, and wine (especially red wine), and a low intake of meat, processed meat, sweets, and industrial bakery products.[9] The table enclosed summarizes the main dietary recommendations given to the participants included in the PREDIMED trial *(Table I)*. The overall quantity of fat intake, and the sources and type of dietary fat, with a special emphasis on α-linolenic acid and oleic acid, and the ratio of n-6 to n-3 fatty acids in this diet, collectively play a crucial role in modulating inflammation, oxidation, and CVD.

The description of the biological mechanisms by which the Mediterranean diet exerts its protective effects adds plausibility to the results obtained in the cohort and clinical trials performed. Several studies have analyzed the effects of the Mediterranean diet on both classical and novel vascular risk factors. In these studies, the Mediterranean diet improved BP, insulin sensitivity, lipid profile, and lipoprotein particle characteristics, without significant changes in body weight or abdominal adiposity. A nonenergy-restricted Mediterranean diet was also very useful in preventing new cases of diabetes and managing metabolic syndromes in high-risk subjects. Scientific evidence has also shown that the Mediterranean diet has a powerful antioxidant and anti-inflammatory effect, both being relevant mechanisms by which this diet decreases the incidence of myocardial infarction, stroke, and cardiovascular mortality.[5] The Mediterranean diet also reduces carotid intima-media thickness and may even induce plaque regression as measured by ultrasonography.

These findings that the Mediterranean diet delayed intima-media thickness and, more importantly, delayed plaque progression may explain, at least in part, the reduction in cardiovascular events observed in the Mediterranean diet arms of the PREDIMED trial. Nutrigenomic studies have observed that the Mediterranean diet has a protective effect on the expression of several proatherogenic genes involved in vascular inflammation, foam cell formation, and thrombosis. However, an even healthier Mediterranean dietary pattern may be obtained by changing common olive oil to extra-virgin olive oil, increasing the intake of whole grain cereals, fatty fish, nuts, and legumes, maintaining a moderate consumption of wine, preferably with meals, and, above all, decreasing salt intake.

Mediterranean diet

Recommended	**Goal**
1. Olive oil*	≥4 tbsp/day
2. Tree nuts and peanuts†	≥3 servings/week
3. Fresh fruits	≥3 servings/day
4. Vegetables	≥2 servings/day
5. Fish (especially fatty fish), seafood	≥3 servings/week
6. Legumes	≥3 servings/week
7. "Sofrito"‡	≥2 servings/week
8. White meat instead of red meat	preferable
9. Wine with meals (optionally, only for habitual drinkers)	≥7 glasses/week

Discouraged	**Goal**
1. Soda drinks	<1 drink/day
2. Commercial bakery, sweets, pastries§	<3 servings/week
3. Spread fats	<1 serving/day
4. Red and processed meats	<1 serving/day

Table I *Summary of dietary recommendations to participants in the Mediterranean groups included in the PREDIMED trial. After reference 5: Estruch et al. N Engl J Med. 2013;368:1279-1290. Copyright © 2013 Massachusetts Medical Society. All rights reserved.*

**Including oil used for frying or salads, or consumed from meals eaten out of home. In the group allocated to the Mediterranean diet with extra-virgin olive oil, the goal was to consume ≥50 g/day (4 tbsp ≈40 g/day) of the polyphenol-rich olive oil supplied, instead of the ordinary refined variety, which is poor in polyphenols.*

†In participants allocated to the Mediterranean diet with nuts the recommended consumption was one daily serving (30 g, distributed as 15 g walnuts, 7.5 g almonds, and 7.5 g hazelnuts).

‡"Sofrito" is a sauce made with tomato, onion, and/or garlic, which is slowly simmered with olive oil.

§Commercial bakery, sweets, or pastries (not homemade), including cakes, cookies, biscuits, or custard.

Diet and hypertension

Hypertension is certainly a major risk factor for cardiovascular morbidity and mortality. Indeed, 9.4 million deaths each year (16.5% of all deaths) are attributed to hypertension,[10] accounting for 54% of stroke and 47% of coronary heart disease events.[11]

Excess salt (sodium chloride) intake plays a major role in the pathogenesis of elevated BP and endothelial dysfunction.[12] High dietary salt intake represents a risk factor for the development of CVD by increasing BP and reducing vascular nitric oxide bioavailability, thereby limiting endothelium-dependent dilation. In a recent review, a moderate reduction in salt intake (mean reduction -4.4 g/day) resulted in clinically significant decreases in systolic and diastolic BP, both in normotensive and hypertensive subjects.[13] In addition, in a recent 6-week crossover trial in normotensive overweight and obese subjects, the 3 g/day reduction in salt intake (from 9 g/day to 6 g/day) improved flow-mediated dilation and decreased plasma endothelin-1.[14]

Current diets are estimated to contain 6 g/person/day of salt (≈2400 mg/day of sodium). The American Heart Association recommends a sodium intake of ≈1500 mg/day (≈4 g/day of salt). The World Hypertension League estimated that nearly 30% of hypertension cases might be attributed to a high dietary salt intake[15]; therefore, reduction in the dietary salt consumption should be the first step in the treatment of hypertension. Another wise strategy to decrease BP is to increase the intake of foods rich in BP-lowering compounds. Again, the Mediterranean diet is rich in foods containing BP-lowering agents such as potassium and polyphenols. Potassium is present in fresh fruits, vegetables, and whole grain cereals—all key foods of the Mediterranean diet. A recent population-based study in 1285 subjects has observed an inverse association of urinary potassium excretion, a surrogate marker of potassium intake, with systolic and diastolic BP only in subjects consuming more than 6g of salt daily, partially counteracting the effects of a high salt diet.[16] Polyphenols are also abundant in fresh fruits, vegetables, whole grains, extra-virgin olive oil, and wine. In a study performed in nonhypertensive high-cardiovascular risk males, red wine polyphenols decreased both systolic and diastolic BP about 6

and 2 mm Hg respectively, possibly through a nitric oxide-mediated mechanism.[17] In the PREDIMED trial, polyphenol intake was also negatively associated with BP and prevalence of hypertension.[18] Additionally, subjects allocated to the Mediterranean diet groups of the PREDIMED trial had lower systolic and diastolic BP compared with those allocated to the low-fat diet group at 3 months of intervention,[19] and these effects were maintained for 4 years of follow-up.[20] Since these effects of the Mediterranean diet on BP and other risk factors were observed very early in the trial, it seems that it is never too late to change our dietary habits with an ensuing measurable benefit on the surrogate markers of cardiovascular risk.

Diet, diabetes, and other cardiovascular risk factors

Several epidemiological studies observed an association between higher adherence to the traditional Mediterranean diet and a decreased risk of diabetes. These results have been confirmed in randomized clinical trials that found that intensive lifestyle modifications, which promote weight loss through energy-restricted diets and increased exercise, reduce the incidence of diabetes. In the pilot study of the PREDIMED trial, we already observed that a Mediterranean diet supplemented with extra-virgin olive oil or nuts increases insulin sensitivity at 3 months of the intervention.[19] The final analysis of the effects of the Mediterranean diet on incident diabetes in the PREDIMED cohort demonstrated that a Mediterranean diet supplemented with extra-virgin olive oil decreased new cases of diabetes by 40% compared with a low-fat diet, after a follow-up of nearly 4 years. These results are an extension of prior studies showing that long-term lifestyle intervention reduces the incidence of diabetes in high-risk subjects, but added that the diet may exert this beneficial effect by itself, without other lifestyle changes.

Replacing carbohydrates with dietary fat lowers the plasma triglyceride concentration and increases the high-density lipoprotein cholesterol (HDL-C) concentration, while substituting monounsaturated fatty acids for saturated fatty acids lowers low-density lipoprotein cholesterol (LDL-C) concentration. In the PREDIMED trial, the lipid profile did not change in the low-fat diet group (control group), while HDL-C increased in both the Mediterranean diet groups, especially when supplemented with extra-virgin olive oil. This effect has been attributed to the minor components of extra-virgin olive oil; mainly polyphenols.[19] Since low-fat diets usually lower both plasma HDL-C and LDL-C concentrations, a fat-rich Mediterranean diet may be a better nutritional option for high-risk subjects. In addition, the Mediterranean diet shifts lipoprotein subfractions to a less atherogenic pattern. Thus, the Mediterranean diet, especially when it is supplemented with nuts, reduces plasma concentrations of medium-small and very small LDL-C particles, decreases LDL-C particle number, and increases large LDL-C particle concentration, whereas both the Mediterranean diets used in the PREDIMED trial, increased large HDL-C concentration. These changes, which were evident within 1-year of intervention with the Mediterranean diet, may contribute to the reduction in cardiovascular events observed in the PREDIMED trial.

Conclusions

There is ample evidence supporting the notion that diet has a direct effect on several cardiovascular outcomes. A Western diet rich in saturated fats, sugar, and salt, and poor in fiber, minerals, vitamins, and antioxidants increases cardiovascular risk perhaps by promoting inflammation and, subsequently, the appearance and progression of atherosclerosis and hypertension. In contrast, the traditional Mediterranean diet decreases the incidence of cardiovascular events and mortality by reducing classical and novel vascular risk factors. These protective effects may be even greater if we upgrade the health effects of this dietary pattern by reducing dietary salt intake. Thus, we encourage clinicians to promote the Mediterranean diet and reduction in salt intake to reduce the cardiovascular risk for their patients. ■

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