Mediterranean Diet Lowers Cardiovascular Risk Even Without Weight Loss

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Study Overview

Objective. To examine the effect of a Mediterranean diet on cardiovascular disease.

Design. Randomized controlled trial (the PREDIMED trial), conducted in 11 centers in Spain, with enrollment from October 2003 to June 2009. Study participants received either (1) a Mediterranean diet with recommendations to consume 50 g/day extra-virgin olive oil (1 L per week was provided at no cost to participants to account for needs of the participant's entire family), (2) a similar diet but with recommendations to consume 30 g/day mixed nuts instead of olive oil (15 g walnuts, 7.5 g hazelnuts, and 7.5 g almonds per day were provided at no cost), and (3) a control low-fat diet. Control participants received small nonfood gifts. Mediterranean diet participants attended educational group sessions every 3 months. In the control group, participants enrolled in the last 3 years of the study attended group sessions every 3 months, but participants enrolled in the first 3 years received only yearly reminders.

Setting and participants. 7447 patients age 55 to 80 years old recruited from a community-dwelling primary care population. Subjects were required to have high cardiovascular risk but no diagnosed cardiovascular disease at baseline. Subjects were either type 2 diabetics or had 3 or more cardiac risk factors (smoker, hypertension, elevated LDL cholesterol, low HDL cholesterol, BMI $\geq$ 25 kg/m^2, or family history of early coronary heart disease). Exclusions included prior documented cardiovascular disease, stroke, or peripheral artery disease; a "severe medical condition" that might limit ability to participate in the study; predicted survival of < 1 year; immunodeficiency or HIV-positive; substance abuse; and BMI > 40 kg/m^2. The study also excluded subjects who were predicted to be unlikely to change their dietary habits or those who may have difficulty complying with a Mediterranean diet for other reasons, such as religious reasons [1].

Main outcome measures. Major cardiovascular events (myocardial infarction, stroke, or death from cardiovascular causes).

Main results. In each of the groups, the mean age was 67 years, 97% were white, 14% smoked, over 90% were obese or overweight, over 80% had hypertension, over 70% had hyperlipidemia, and nearly 50% had type 2 diabetes. 59%, 54%, and 60% were female in the Mediterranean diet olive oil group, the Mediterranean diet nuts group, and the control group, respectively. After a median of 4.8 years

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of follow-up (interquartile range, 2.8–5.8), the dropout rate was 11.3% in the control diet group but 4.9% in the Mediterranean diet groups. Adherence with the assigned diets as measured by dietary recalls and biomarker measurements was good in all groups. Specifically, those assigned to the Mediterranean diets increased their olive oil, nut, fish/seafood, and legume consumption more than the control diet group (with appropriate higher increases in olive oil and nut consumption in those assigned to consume these specifically). By the end of follow-up, 288 total subjects experienced a primary endpoint with 96 events among those assigned to the Mediterranean diet with olive oil, 83 among those consuming the similar diet with nuts, and 109 on the control diet. These events translated to an incidence rate of 8.1, 8.0, and 11.2 per 1000 person-years. The adjusted hazard ratios for the primary endpoint were 0.70 (95% confidence interval [CI], 0.54–92) and 0.72 (95% CI, 0.54–0.96) for those assigned to the Mediterranean diet with olive oil and those assigned to the similar diet with nuts, respectively. Among secondary endpoints, which included the individual components of the primary endpoint and all-cause mortality, no difference was noted between groups except for a lower stroke rate among those on the Mediterranean diets. The study reported no notable adverse effects.

Conclusion. A Mediterranean diet, with a high dose of either olive oil or nuts, was associated with a lower cardiovascular event rate than a low-fat diet.

Commentary

Dietary change has long been a mainstay of clinical recommendations to reduce cardiovascular risk. Recommendations for specific diets have been less clear. Previously, observational data has shown impressive benefits of a Mediterranean-type diet. This diet consists of high intake of vegetables, fruits, whole grains, legumes, nuts, and olive oil; moderate fish and poultry; limited dairy; wine in moderation; and restrictions in sweets, red meat, and processed meats. A recent meta-analysis of 18 cohort studies with over 2 million people reported that higher adherence to a Mediterranean diet was associated with a significant reductions in overall mortality (8% reduction), cardiovascular incidence or mortality (10% reduction), and cancer incidence (6% reduction) [2]. Consistent with this, a systematic review of dietary factors causally linked to reductions in cardiovascular risk found the strongest case for subjects consuming a Mediterranean diet, a "high-quality diet," nuts, or vegetables [3]. In contrast, a high glycemic index diet and consumption of trans fatty acids had the strongest case for leading to higher cardiovascular risk. Because of randomized controlled trial evidence, this study reported that the strongest causal link was for the Mediterranean diet. A prior clinical trial of over 400 subjects after a first myocardial infarction (MI) found that those randomized to a Mediterranean diet had lower cardiovascular events after a follow-up period of 4 years compared with those randomized to a "prudent diet" [4]. The primary endpoint of cardiac death and nonfatal MI occurred in 14 participants on the Mediterranean diet and 44 on the control diet ($P < 0.001$), with any cardiovascular event occurring in 27 and 90 subjects respectively ($P < 0.001$).

This PREDIMED study was a large randomized trial comparing 2 different variants of a Mediterranean diet with a traditional low-fat diet. Subjects enrolled in the Mediterranean diet groups received group sessions every 3 months, and they were provided with free supplements of either extra virgin olive oil or mixed nuts, with instructions to consume these supplements. The control participants enrolled in the first 3 years of the study received only yearly instruction to follow a low-fat diet, with a subsequent protocol change for the last 3 years of enrollment, during which control participants also received group counseling sessions every 3 months. Adherence to the Mediterranean diets was good, with appropriate increases in olive oil and nut consumption as the primary drivers of dietary change associated with the intervention. After nearly 5 years of follow-up, subjects on the Mediterranean diet had lower cardiovascular event rates than subjects on the control diet, with 13 and 26 fewer events in the olive oil and nut diets compared with the control diet.

This study is important because it demonstrates the possibility of changing cardiovascular risk with diet even in the setting of greater calorie consumption. The Mediterranean diet groups consumed more total calories than the control diet group. They also consumed more fat; the diet group with supplemental olive oil even consumed more saturated fat than the control diet group. No data on body weight change is provided for the study; however, with calorie intake higher with the Mediterranean diet groups, the only expected weight difference would be higher weight in these groups.

Several limitations were evident with this study. The most important limitation was the lack of equitable treatment between intervention and control groups during the

early phase of the trial. For the first 3 years of the trial, control subjects received only annual information about a low-fat diet while the Mediterranean diet groups received quarterly group sessions. The investigators recognized this discrepancy halfway through the study and remedied it, but there remained a discrepancy for likely one-half of the subjects (no specification of the rate of enrollment provided). They compared hazard ratios before and after the protocol change and found a lower hazard ratio for cardiovascular events after (*P* for interaction with time of enrollment was 0.21), suggesting that this limitation did not affect the results. Another limitation was the lack of strong objective evidence regarding adherence to the control low-fat diet compared with the Mediterranean diets. Urine levels of hydroxtyrosol, a component of olive oil, were higher in a subsample (750 participants) of the group taking supplemental olive oil, as were plasma alpha-linolenic acid, a component of walnuts, in the group taking supplemental nuts. Overall fat intake, measured by dietary self-report, in the control diet group was lower at the end of the intervention compared with baseline, but no similar stringent objective measures were available to confirm adherence. Also, dropout was higher in the control group than in the other groups. Such differential adherence could explain differences in outcomes, especially with the small absolute differences found in this study. Similarities between results among complete cases (dropouts excluded) and all subjects with imputation used to estimated outcomes in dropouts were reassuring. While not a limitation of the study, the small outcome differences are notable as well. With enough analyses, the significance of these results disappears. For example, excluding events during the first year of follow-up, hazard ratios comparing event rate differences between groups were no longer statistically significant (though the hazard ratios were similar to the overall hazard ratios).

Regardless, with a dietary study, to find differences at all is notable. A diet trial is fundamentally less precise than a pharmaceutical or medical device trial. Controlling a patient's entire dietary intake is impossible, and overlap between arms of a diet study is substantial. The authors addressed this concern, in part, by providing olive oil and nut supplements free to participants in the Mediterranean groups, thereby giving them easy access to a recommended component of the diet. Ultimately, these study findings, coupled with the prior observational studies and clinical trials, provide a firm evidence base to recommend a Mediterranean diet for adults with high cardiovascular risk. While patients should receive counseling that weight loss may be unlikely, with the higher calorie content of this diet compared to other diets, additional downsides appear minimal.

The PREDIMED results most clearly support the use of mixed nuts and olive oil, the 2 dietary changes most encouraged during this trial. Self-reported dietary recalls and objective serum and urine measures confirmed that participants in the Mediterranean diet group increased olive oil and nut consumption more than other diet components. Legumes and fish/seafood consumption also increased to a lesser degree in subjects on the Mediterranean diet. An interesting area for future research would be a study that examined cardiovascular events in groups solely provided olive oil and/or mixed nuts versus a control group. Ultimately, a study like this would lead to more practical and simple applications than PREDIMED, which supports a complete dietary shift.

Applications for Clinical Practice

Physicians should feel confident recommending a Mediterranean diet to patients at high cardiovascular risk. Evidence from PREDIMED suggests that increasing olive oil and nut consumption may underlie this lower cardiovascular risk.

—Jason P. Block, MD, MPH

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