

MEDITERRANEAN DIET - THE NEW RECIPE

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The new dietary guidelines have come up with new friends and newer foes of heart concerning diet. Cholesterol remains the biggest trumpeted enemy of heart but its relationship to intake of so far banned items like butter, cheese and meat has been deemphasized.¹ Newer enemies of heart are being discovered in the form of Trimethyl amine oxide (TMAO). Diet-gut interactions, their role as cardiovascular risk and effect of different dietary regimens are being studied more extensively.²

A metabolite trimethylamine N-oxide (TMAO) has recently been identified as the first potential link between the gut microbiota and coronary artery disease. Trimethylamine (TMA) is produced by gut microbiota from food items consisting of L-carnitine, choline, and phosphatidylcholine, and is subsequently oxidized by hepatic flavin-containing monooxygenases to TMAO.² In animal models TMAO has been shown to effect cholesterol transportation, and the precursors promote formation of foam cell and accelerate atherosclerosis, but not when adding antibiotics to the drinking water, suggesting a microbiota-dependent mechanism.² In many studies conducted on both sides of Atlantic increased plasma levels of TMAO have been shown to predict myocardial infarction, stroke, poor clinical outcome in heart failure patients and all-cause mortality.³⁻⁵

TMAO was studied as a potential risk stratification marker in the setting of acute coronary syndrome (ACS) in two independent populations from USA and Switzerland. Elevated levels of TMAO were found to predict incident coronary events (MACE) at 30 days and 6 months in addition to traditional risk factors and electrocardiographic data. The authors suggest that TMAO assessment may have a role to play in risk identification in patients presenting with ACS to emergency room.⁶

However, it must be realized that TMAO has not been predictive as a marker in other studies and it is still shrouded in mystery. Though Westernized diet containing items like eggs and red meat has been proposed to elevate TMAO, fish and seafood also increase it.⁴ TMAO increases after bariatric surgery, whereas it should have decreased as it reduces cardiovascular risk.⁷ The estimation of TMAO may be erroneous in deranged hepatic and renal dysfunction - earlier helping in oxidation and latter in elimination.⁸ Recently 'drug the bug' strategy has been studied to reduce TMAO in animal models employing TMA inhibitors.⁹ Besides drugs, nutritional interventions are being studied as diet shapes the gut microbiota and may affect cardiovascular risk profile. Mediterranean diet was

studied in this background and shown to reduce TMAO urinary outputs in individuals with strict adherence to Mediterranean diet, irrespective of background diet being vegan, vegetarian or omnivorous.¹⁰

Interesting questions are now being raised in this scenario, can gut microbiota variation be used to stratifying treatment? Is there a possible use of TMAO as a clinical biomarker? There is a need for adequately powered trials to establish causal and clinically relevant relationship between gut microbiota and coronary artery disease.¹¹

Mediterranean diet was studied in a randomized trial to test the efficacy of two Mediterranean diets (one supplemented with extra-virgin olive oil (EVOO) and another with nuts), was compared with a control diet (advice on a low-fat diet), for primary cardiovascular prevention. The PREDIMED trial (Prevención con Dieta Mediterránea) was a parallel-group, multicenter, randomized trial.¹² A total of 7447 persons were randomly assigned to one of the three study groups. Their baseline characteristics were comparable. Drug-treatment regimens were similar for participants in the three groups, and they continued to be balanced during the follow-up period.¹³

Participants were followed for a median of 4.8 years (interquartile range, 2.8 to 5.8). The primary end point was a composite of major cardiovascular events (myocardial infarction, stroke, or death from cardiovascular causes). Interim analyses prompted early termination of the trial. A total of 288 primary-outcome events occurred: 96 in the group assigned to Mediterranean diet with extra-virgin olive oil (3.8%), 83 in the group assigned to a Mediterranean diet with nuts (3.4%), and 109 in the control group (4.4%). Taking into account the small differences in the accrual of person-years among the three groups, the respective rates of the primary end point were 8.1, 8.0, and 11.2 per 1000 person-years. The unadjusted hazard ratios were 0.70 (95% confidence interval [CI], 0.53 to 0.91) for a Mediterranean diet with EVOO and 0.70 (95% CI, 0.53 to 0.94) for a Mediterranean diet with nuts as compared with the control diet ($p = 0.015$, by the likelihood ratio test, for the overall effect of the intervention). Regarding components of the primary end point, the comparisons of stroke risk and total cardiovascular risk reached statistical significance but not myocardial infarction. The Kaplan-Meier curves for the primary end point diverged soon after the trial started, but no effect on all-cause mortality was apparent. In this trial, an energy-unrestricted Mediterranean diet supplemented with either EVOO or nuts resulted in an absolute risk reduction of approximately 3 major cardiovascular events per 1000 person-years, for a relative risk reduction of approximately 30%, among high-risk persons who were initially free of cardiovascular disease. These results support the benefits of the Mediterranean diet for cardiovascular risk reduction. For any therapy, including drug therapy, this magnitude of benefit is impressive; for a dietary intervention, such results are truly remarkable.¹³

However the trial has been criticized that firstly, the control group did not achieve a low fat intake as total fat was 37% of energy intake in the control group and 41% of energy intake in the other two groups; saturated-fat intake was low and similar in the three groups, approximately 9% of energy intake. Secondly, it was observed that the differences between the randomized groups may have resulted from the supplemental foods and not the dietary advice. The amount of EVOO and nuts provided to participants was substantial (1 liter of EVOO per week and 30 g of mixed nuts per day). Thirdly, the reduction in cardiovascular disease was most impressive for stroke that is highly dependent on blood pressure.¹⁴ Fourthly, this study endorses previous observational studies showing that Mediterranean diets and olive oil are associated with reduced risk of stroke.¹⁵⁻¹⁶ Fifthly, PREDIMED investigators had earlier reported that at 3 months after randomization, the group receiving EVOO and mixed nuts had substantially lowered blood pressure.¹⁷ Sixthly, beneficial effects of EVOO and nuts have been documented in many studies. EVOO even in much smaller amounts, than that used in the study, delays gastric emptying and decreases postprandial hyperglycemia.¹⁸ Being high in monounsaturated fatty acids this reduces blood pressure and glycated hemoglobin levels in diabetics.¹⁹ Additionally, nuts like almonds reduce LDL cholesterol levels by 3 to 19%.²⁰

The traditional Mediterranean diet is characterized by high intake of plant foods like fruit, vegetables, whole grain breads, cereals, potatoes, beans, legumes, nuts, and seeds. Fresh fruit as typical daily dessert and olive oil as the principal source of fat. It is rich in dairy products mainly low fat cheese and yogurt. Fish and poultry are consumed in low to moderate amounts with zero to four eggs consumed weekly and red meat used in low amounts. Wine is utilized in low to moderate amounts, normally with meals. The diet is low in saturated fat, with total fat ranging from 25% to 35% of energy throughout the region. The Mediterranean diet is attractive for its palatability and health benefits.¹⁴ Some earlier observational cohort studies and a secondary prevention trial - the Lyon Diet Heart Study showed consistent benefit in reduction of cardiovascular risk with increasing adherence to Mediterranean diet.¹⁵⁻¹⁷

This is the first of its kind study to document the effects of Mediterranean diet in primary prevention trial, supplemented with EVOO or nuts, resulted in a substantial reduction in the risk of major cardiovascular events among high-risk persons. The results support the benefits of the Mediterranean diet for the primary prevention of cardiovascular disease. Newer research has identified new foes and friends in terms of diet to prevent cardiovascular disease. TMAO has been targeted as the new enemy and Mediterranean diet has been extensively studied to reduce it. This study, with all the criticism, opens a new window of hope in the realm of primary prevention of cardiovascular disease.

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