

# **Mediterranean Diet and Risk of Cardiovascular Disease**

**Lubna Qureshi**

**Nutritional Pathophysiology**

**NTDT 5320**

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The agrarian lifestyle has been an inevitable part of human civilization. Early days of human civilization inculcated the use of farmland which enhanced the consumption of fresh produce. Agrarian societies not only focused on fresh produce but on strenuous labor as well that was deemed necessary to produce fresh fruits and vegetables. With evolving times modern machinery took place of arduous physical labor and fresh produce was replaced by convenient processed foods. During the past century, developed countries experienced an influx of mechanically processed foods that came with its own consequences of food and lifestyle related diseases. As new eating practices advanced, death rate due to debilitating disease increased alarmingly. Despite of global changes in dietary habits and lifestyles, people living along the Mediterranean Sea, specifically Greek Isles and southern parts of Italy, exhibited healthier outcomes. The lifestyle differentiation of a subgroup gave birth to several research studies. Numerous studies concluded that Greek population had higher life expectancy at the age of 45 years than any other national group.<sup>1</sup>

The studies opened doors to delve deep into the factors that involved better health outcomes. Further research pointed out the Mediterranean diet, based on grains, legumes, and rich in fresh fruits and vegetables and shy on meat and dairy and animal fat, with olive oil as the principal fat, as a crucial component of a healthful lifestyle.<sup>2,3</sup> In mid 20<sup>th</sup> century, Ancel Keys, initiated a series of research based on the low rates of heart disease among the population of Greek Isles. The research, initially performed in seven countries, identified the effects of fat and fatty acids on risk of coronary heart disease.<sup>1</sup> The studies also recognized the protective effects of diets based on plant sources. Keys' research found the region's diet low in fat as compared to

American diet which was rich in meat and dairy fat thus posing a risk for increased cholesterol, leading to coronary heart disease.<sup>1</sup>

Since the first data from the seven countries study by Ancel Keys, several studies in different populations have recognized a beneficial role of the Mediterranean diet on the occurrence of cardiovascular diseases and chronic degenerative diseases. The causal relationship of Mediterranean diet with lower incidence of cardiovascular is specifically congruent with other studies that support similar findings.

The involvement of several pathophysiologic mechanisms is anticipated to reveal the beneficial effects of the Mediterranean diet on the cardiovascular system. Some mechanisms such as the diet's antithrombotic, anti-inflammatory, and antioxidant effects as well as its inverse relation with blood pressure and endothelial dysfunction markers exhibit strength of association.<sup>7,8,9</sup>

Numerous nutritional components of Mediterranean diet, that is rich in oleic acid, omega-3 fatty acids, fiber, B-group vitamins, and antioxidants, but low in saturated and polyunsaturated fats, exhibit consistent association with decreased cardiovascular disease risk and markers.

Western contemporary lifestyle, often sedentary in nature, and consisting of diets high in saturated fat and sugars and low in omega-3 fatty acids, fruits, vegetables, and fiber primarily contributes to the high prevalence of cardiovascular disease. Atherosclerosis, known as the disease of old age, is a systemic coronary heart disease initiated at the cellular level. Dysfunctions of epithelial cells, in response to metabolic derangements or physical force (such as hypertension), instigate a cascade of events resulting in atherosclerosis.<sup>4</sup> Endothelial microparticles (EMPs) are considered a surrogate marker of vascular dysfunction as elevated EMP concentrations are observed in patients suffering from cardiovascular diseases.<sup>5</sup> The replacement of injured mature endothelial cells is performed by endothelial progenitor cells

(EPCs). The patients with cardiovascular disease, and multiple coronary risk factors exhibit a reduced number of EPC that leads to the speculation that atherosclerosis is caused by dietary factors affecting the consumptive loss of endothelial repairing capacity.<sup>5</sup> However, it is imperative to recognize the involvement of multiple factors, in biological mechanisms, contributing to a certain outcome. Thus, there are other studies suggesting that aging could be another factor effecting the number and properties of EPCs.<sup>6</sup>

Marin et al, hypothesizes that circulating EMPs, a risk factor for several pathologic processes, are influenced by diet.<sup>5</sup> To investigate the influence of dietary fat on the release of EMPs, a randomized cross over trial was performed. Twenty healthy elderly subjects followed 3 diets which consisted of, a saturated fat diet, a low-fat, high-carbohydrate diet and a Mediterranean diet, for four weeks. The study results indicated that consumption of the Mediterranean diet was associated with a lower concentration of total microparticles and a higher number of EPCs than the consumption of saturated fat diet, and low-fat, high-carbohydrate diet. The findings suggested, “a decrease in endothelial damage and endothelial dysfunction associated with improved regenerative capacity of the endothelium after the intake of the Mediterranean diet, which is rich in virgin olive oil, as compared with the other 2 diets.”<sup>5</sup> The analysis of plasma EMPs suggested that consumption of the Mediterranean diet led to lower plasma concentrations of these microparticles than did consumption of the other 2 diets. In addition, Marin et al speculated that elevated EMPs could also result from oxidative stress.<sup>5</sup>

Oxidative stress is a pathophysiological pathway considered to influence atherosclerosis development and cardiovascular disease risk. Studies have shown consistent association between the Mediterranean diet and reduced cardiovascular disease risk due to decreased oxidative stress. The Twin Heart Study analyzed the association between Mediterranean diet and plasma markers

of oxidative stress.<sup>7</sup> Fasting plasma Glutathione (GSH, reduced form) and glutathione disulfide (GSSG, oxidized form) concentrations specify the GSH/GSSG ratio. The higher GSH/GSSG ratio is indicative of lower oxidative stress. A diet rich in antioxidants such as vitamin C, vitamin E, carotenoids, polyphenols, zinc, and selenium, and efficient anti-oxidative enzymatic activity may decrease the utilization of the GSH/GSSG antioxidant pathway. Decreased utilization may hinder recycling of GSH/GSSG indirectly contributing to higher levels of GSH/GSSG.<sup>7</sup>

Another plausible mechanism suggests the decrease in lipid hydroperoxides, by reducing them into alcohols and inhibiting their production, through GSH/GSSG redox. Decreased lipid hydroperoxides are known to lower oxidized low-density lipoproteins thus indirectly inhibiting atherosclerosis.<sup>7,10</sup> The decrease in oxidative damage is attributed to the protective effect of Mediterranean diet rich with antioxidant components.<sup>5,8</sup>

Although, Dai et al suggests strong association between the Mediterranean diet and oxidative stress but biological plausibility cannot be neglected. Dai-et-al proposed association with GSH/GSSG but the Mediterranean diet was weakly associated with the glutathione redox potential. The analysis discovered that glutathione redox potential was more sensitive to a change in concentration of GSH than of GSSG. In addition, adherence to the Mediterranean diet was not significantly associated with GSH concentrations.<sup>7</sup>

Studies suggest that Mediterranean diets, rich in virgin olive oil or nuts, reduce systolic blood pressure in high-risk cardiovascular patients.<sup>8,10</sup> An ongoing randomized trial, PREDIMED study, suggests that the Mediterranean diet effects the altered lipid metabolism in hypertensive patients, influencing the structural membrane properties.<sup>8</sup> The yearlong interventional experiment assessed the effect of a Mediterranean-style diet on erythrocyte membrane properties in hypertensive participants. The study explored molecular and structural bases, essential for the

effect of a Mediterranean diet supplemented with nuts or virgin olive oil, as natural sources of linolenic or oleic acid, respectively and compared it with a low-fat diet. The analysis suggested that dietary lipid management can alter the structural properties of erythrocyte membranes in addition to a decrease in blood pressure. The cholesterol and phospholipids concentrations in lipid composition were significantly altered as decreased cholesterol and increased phospholipids were evident. The study also hypothesized that increase in the membrane fluidity could be associated to the decreased cholesterol: phospholipids ratio. The results showed that, compared with a low-fat diet, the Mediterranean diets, rich in virgin olive oil or nuts reduced systolic blood pressure and serum total cholesterol and triglyceride concentrations and increased serum high-density lipoprotein cholesterol concentration.<sup>8,10</sup> However, the histological functional implications cannot be neglected where membrane phospholipids are involved. The study also points out towards a possible link between erythrocyte membrane properties and serum inflammatory markers attesting the involvement of cellular mechanisms indirectly affecting the outcome.<sup>8</sup>

Several studies have expressed consistent association between adherence to the Mediterranean diet and enhanced preservation of left ventricular systolic function. The presentation of left ventricular systolic dysfunction (LVSD) has a significant effect on the prognosis of patients hospitalized with an Acute Coronary Syndrome (ACS).<sup>9</sup> Anti-inflammatory properties of the Mediterranean diet are considered major contributors to the enhanced function. Inflammation and oxidative stress associated with ACS, effect infarct size that mainly determines the post-infarction survival and prognosis. In addition, infarct size is the most important factor that affects the ventricular remodeling process. Oleuropein, which is found in olive oil, primary source of monounsaturated fat intake, exhibited promise in reducing infarct size and protecting a

reperfused myocardium from oxidative damage.<sup>9,10</sup> To evaluate the relation between the Mediterranean diet and the development of (LVSD) at hospitalization, and the 2-year prognosis of patients after (ACS) Chrysohoou et al, initiated a study. The research specified the importance of dietary pattern modification in primary and secondary prevention of ACS. Chrysohoou et al, concluded that long term adherence to the Mediterranean diet is associated with a better prognosis of patients with ACS.<sup>9</sup> However, it is important to understand that it is overall dietary habits that contribute to overall and cardiovascular mortality and morbidity. There might be many limiting factors that may weaken the association. For example, the results, based on specific study subjects cannot be generalized. In addition, the duration of dietary approach is significant in associating strength with ultimate result.

Mediterranean-style dietary pattern is directly associated with not only decreased CVD risk but also correlates with avoiding metabolic syndrome traits. Metabolic syndrome is a group of risk factors that substantially increase the risk for heart disease and other health conditions such as Diabetes and stroke. With the rise in prevalence of metabolic syndrome in the United States it became imperative to explore the possibilities of a practical diet that may generate protective effects against metabolic syndrome. The Framingham Heart Study Offspring Cohort investigated the inverse relationship between a Mediterranean-style dietary pattern and metabolic syndrome incidence.<sup>11</sup>

The research suggested that long-term consumption of Mediterranean-style diet may be an effective dietary strategy for protection against metabolic syndrome. The study concluded that, “if a Mediterranean-style diet delays or prevents metabolic syndrome, then individuals following this diet will be less likely to develop T2DM and CVD.” The findings supported the dose

relationship with long term intake of the Mediterranean-style diet and reduced progression of atherogenic dyslipidemia.<sup>11</sup>

Temporal relationship in the study was apparent; as dietary information was measured before the outcome occurred strengthening the causal implication between the Mediterranean-style dietary pattern and the study's outcomes. However some limitations questioned the reliability of the outcome. For example, the observation showed that of the 5 components that compose the metabolic syndrome incidence, only 4 components (waist circumference, fasting plasma glucose, triglyceride, and HDL cholesterol) were individually associated with the Mediterranean-style dietary pattern. In addition, the study adjusted for confounders but the possibility of residual confounders cannot be rule out. For example, BMI is not considered an accurate measure of adiposity and its adjustment posed as a residual confounder.<sup>11</sup>

A meta-analysis focusing on the prospective studies, comprising more than 1.5 million healthy subjects suggested that greater adherence to a Mediterranean diet is significantly associated with a reduced risk of overall mortality and cardiovascular mortality.<sup>12</sup> The analysis also investigated the Mediterranean dietary pattern and cancer incidence and mortality, and incidence of Parkinson's disease and Alzheimer's disease.

The cumulative analysis of 12 cohort studies showed consistent association among the results. The analyses exhibited a beneficial role for greater adherence to a Mediterranean diet on cardiovascular mortality. The results supported a two point increase in the score for adherence to a Mediterranean diet suggesting a 9% reduction in overall mortality and a 9% reduction in mortality from cardiovascular diseases. The analyses concluded that, "greater adherence to a Mediterranean diet is associated with a significant improvement in health status, as seen by a significant reduction in overall mortality."<sup>12</sup>

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Although the Mediterranean dietary pattern shows promise in regards to CVD, we cannot neglect the experimental evidence involved. For example, the heterogeneity of the diet, which is based on multiple components of the foods, cannot allow to be grouped uniformly. In addition, as mentioned earlier, the adjustment for potential confounders always poses a risk for residual confounding within the studies. Additionally, several studies address the dietary pattern of the Mediterranean diet which may not be significantly identical to the originally defined Mediterranean diet. Biases can also hamper the strength of association. Significantly crucial is the fact that multiple modifiable and non-modifiable factors affect physiologic conditions. Generality of the hypothesis can be challenged with specific subjects. Contrary to all the promising effects of Mediterranean diets, depicted by the studies presented, one has to distinguish the overall effect on the risk of CVD rather than focusing on individual components. However, the results depicted by meta- analyses exhibit clinical relevance in terms of public health for reducing the risk of premature death in the general population. The findings are congruent with guidelines and recommendations from major scientific associations that support Mediterranean-dietary pattern as primary and secondary prevention of major chronic diseases. Mediterranean-dietary pattern is not only supported and recommended due to its nutritional adequacy but it is also appreciated for its gastronomic qualities, by health organizations. Dietary Guidelines for Americans, enumerates the Mediterranean dietary pattern as an essential instrument for the prevention of cardiovascular disease. Its implication as a tool for health promotion and disease prevention not only opens new doors for research but also portrays a lifestyle that is as healthful as Agrarian dietary traditions.

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