Anti-Inflammatory Effect of the Mediterranean Diet: An Overlooked Beneficial Association

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The Mediterranean diet and in particular the traditional Cretan diet has served, in the second half of the twentieth century, as a prototype for dietary recommendations worldwide. The traditional Cretan diet has been shown to be associated with the lowest coronary heart disease and cancer mortality rates, even compared to other Mediterranean diets, as it was evaluated in large epidemiological studies such as the Seven Countries Study (Christakis et al., 1965). The Cretan cohort of the Seven Countries Study had the lowest age-adjusted all cause mortality after 20 years of follow-up (Menotti et al., 1990). The beneficial effects of this diet, in terms of cardiovascular disease and cancer prevention, have subsequently been confirmed by other studies (Singh et al., 1992; Renaud et al., 1995; de Lorgeril et al., 1998; de Lorgeril et al., 1999; Trichopoulou et al., 2003).

The traditional Cretan diet is characterized by a high consumption of fruit, vegetables, legumes, and whole grains, frequent consumption of fish, moderate intake of alcohol, mainly wine, moderate consumption of milk and dairy products, and low consumption of meat and animal products. The traditional diet of Crete was high in total fat but this was mainly due to a high content in monounsaturated fatty acids (MUFA), whereas it was low in saturated fatty acids (SFA) (Kafatos and Mamalakis, 1993). Analyses of the dietary pattern of the diet of Crete revealed a number of protective substances, such as, selenium, glutathione, a balanced ratio of (ω-6):(ω-3) essential fatty acids (EFA), high amounts of fiber, antioxidants, vitamins E and C, some of which have been shown to be associated with the lower risk of cancer.

PARTICULAR NUTRIENTS AND FOODS OR WHOLE DIETARY PATTERNS?

The beneficial effects of Mediterranean diets in disease prevention have been mainly assessed in terms of single nutrients or isolated food items that are rich in certain nutrients.

Monounsaturated fatty acids are the main source of fat in the traditional Cretan diet and the main source of MUFA in this diet is olive oil, which is used mainly to dress salads and to cook (Kromhout et al., 1989). The lowest rates of cardiovascular disease and cancer in the Cretan cohort of the Seven Countries Study were attributed to the high olive oil intake and the low SFA intake of the Cretan diet.

High-MUFA diets, especially olive oil enriched diets, have been found to improve significantly cardiovascular disease risk factors, even compared to low-fat diets; high-MUFA diets reduce serum low density lipoprotein (LDL) levels without reducing high density lipoprotein (HDL) levels (Kris-Etherton et al., 1999; Pelkman et al., 2004). It has been shown that a diet rich in oleic acid (C18:1 ω9) compared to a diet rich in linoleic acid (LA, C18:2 ω6) results in the enrichment of LDL molecules in MUFAs and these molecules are less prone to the early events of atherosclerosis such as monocyte chemotaxis and adhesion when exposed to oxidative stress (Tsimikas et al., 1999). It also helps to improve endothelial function and affects favorably postprandial factor VII activity in hypercholesterolemic men (Perez-Jimenez et al., 2002). Olive oil has also been beneficial in blood pressure levels (Trevisan et al., 1990; Ferrara et al., 2000) and on glucose metabolism (Trevisan et al., 1990).

It has, thus, been suggested, despite several methodological issues in the evaluation of dietary habits in Greece, that olive oil can be an important component of diets while maintaining total fat intake less than 30% of energy intake (Ferro-Luzzi et al., 2002).

Other randomized trials, however, used experimental diets based on the Mediterranean diet but without special consideration on olive oil, as a means of secondary prevention in patients sustained a first myocardial infarction. The Lyon Heart Study found a 50-70% reduction of the relative risk of mortality and second infarction (de Lorgeril et al., 1994; de Lorgeril et al., 1999) and the Indo-Mediterranean Trial found a 52% reduction of ischemic heart disease end points (Singh et al., 2002). Olive oil was not considered in either of these trials; in both trials MUFA intake was 10-12% of total energy, whereas the characteristic MUFA intake in the traditional Cretan diet is 15-20%. They had, instead, aimed in a high amount of α-linolenic acid

(ALA, C18:3 ω3) in the experimental diets. It has also been argued, that the emphasis given mainly on olive oil, as the protective agent of the Cretan diet in the Seven Countries Study was misleading since it could not account for the low cardiovascular disease mortality observed in the Japanese cohort of the Study; the Japanese diet was low in fat, accounting for only 11% of the energy intake compared to the 37% of energy from fat in the Cretan cohort. Both cohorts, however, had a high intake of ALA; in the Japanese cohort it was mainly obtained from canola oil and soybean oil whereas in the Cretan cohort it was mainly obtained from purslane, other wild plants, walnuts and figs (Simopoulos, 2001). The Cretan population except for a higher proportion of ALA in serum cholesteryl esters, had also a lower proportion of LA (Sandker et al., 1993).

The traditional Cretan diet was rich in vegetables including wild plants, which are rich sources of ω3 fatty acids and antioxidants, whereas the main source of fat, as mentioned earlier, was olive oil. People in Crete compared to the US population, have traditionally also consumed 30 times more fish, that is, a source rich in eicosapentaenoic acid (EPA, C20:5 ω3) and docosahexaenoic acid (DHA, C22:6 ω3). The classical analytical approach in epidemiological studies relied on the assessment of the effect of single nutrients on disease risk. There is now, a growing interest in the overall dietary patterns because it is now clear that specific food items and nutrients may have synergistic or antagonistic effects when consumed in combination, and therefore the emphasis on single nutrients may ignore potential interactions between dietary patterns and disease risk (Jacques and Tucker, 2001; Martinez-Gonzalez and Sanchez-Villegas, 2004). Olive oil, for example, is rich in oleic acid and is low in SFA and ω6 fatty acids. Oleic acid does not compete with the desaturation and elongation of ALA or the incorporation of ω3 fatty acids in the red cell membrane phospholipids, providing thus an additional benefit to the functions of ω3 fatty acids (Simopoulos, 1991).

CHRONIC DISEASES, INFLAMMATION, AND MEDITERRANEAN DIET

Atherosclerosis, the hallmark of ischemic heart disease (Ross, 1999), insulin resistance, and type 2 diabetes (Sjoholm and Nystrom, 2005), and obesity (Dandona et al., 2004) have been recognized as inflammatory processes. Epidemiological studies have shown a strong relationship between C-reactive protein (CRP) levels, and other markers of inflammation and the morbidity and mortality associated with coronary heart disease (Ridker et al., 2000). The lesions of atherosclerosis represent a series of highly specific cellular and molecular responses that can best be described as an inflammatory disease (Ross, 1986). C-reactive protein has been shown to be associated with the progression of the early atherosclerotic lesions both in adults (Hashimoto et al., 2001; Hashimoto et al., 2004), and healthy young children (Jarvisalo et al., 2002). Markers of low-grade inflammation, such as high-sensitivity CRP, have been suggested that can predict cardiovascular risk not reflected by traditional risk factors, and that inflammatory processes may be potential targets of therapy in preventing or treating atherosclerosis and its complications (Paoletti et al., 2004). Intensive statin treatment has recently been shown to reduce the rate of progression of atherosclerotic lesions; the reduced rate of progression was associated with greater reductions in the levels of atherogenic lipoproteins and of CRP as well (Nissen et al., 2005). Reduced progression of atherosclerosis with this treatment may be observed independent of the serum LDL cholesterol reduction (Ridker et al., 2005).

The traditional Cretan diet has been valued because of the abundance of antioxidants but also because of the more balanced intake of ω3 and ω6 PUFA from vegetable, animal, and marine sources, compared to westernized diets. Eicosanoids are a group of inflammatory mediators including prostaglandins, leukotrienes, and thromboxanes. These inflammatory mediators are derived from arachidonic acid (AA, C20:4 ω6), EPA, and dihomo-γ–linolenic acid (DGLA, C20:3 ω6) when these fatty acids are released from tissue phospholipids in response to a variety of stimuli. Arachidonic acid is the precursor of the 2-series of prostaglandins, whereas DGLA and EPA are precursors of prostaglandins of the 1- and 3-series, respectively, which have lower biological activity compared to the 2-series (Zhou and Nilsson, 2001). The composition of biological membranes in ω3 and ω6 PUFA depends on the dietary intake in these FA. It has been found that production of eicosanoids was substantially higher in animal models fed diets rich in AA compared to diets rich in EPA or oleic acid. The production of eicosanoids in these animal models is correlated with AA content in hepatic cell membranes (Li et al., 1994). The replacement of cell membranes AA with EPA in subjects fed fish oil results in decreased production of AA derived eicosanoids. Diet supplementation with fish oil-derived ω3 PUFA in humans, results also in

decreased monocyte and neutrophil chemotaxis and decreased production of proinflammatory cytokines (Calder, 2001). It has also been shown that dietary intake of ω3 PUFA was inversely associated with inflammation and endothelial activation markers such as CRP, interleukin 6 (IL 6), E-selectin, soluble intracellular adhesion molecule (sICAM), and soluble vascular adhesion molecule (sVCAM) (Lopez-Garcia et al., 2004). Similar effects, and in particular on CRP levels were not achieved with capsules supplementation of ω3 PUFA (Geelen et al., 2004); this finding clearly support the notion that it's not certain nutrients, but rather the whole dietary patterns and interactions between nutrients that account for the benefits of the Mediterranean diet.

Of particular interest are the effects of a Mediterranean-style diet, rich in MUFA, PUFA, and fiber with a low ratio in ω6/ω3 FA, in patients with the metabolic syndrome. In these patients, high sensitivity CRP, IL 6, IL 7, and IL 18 were reduced compared to subjects consuming a control diet after 2 years of intervention. The endothelial function score improved significantly in these subjects. There were also significantly less subjects in the intervention group who had still features of the metabolic syndrome after the 2 year period (Esposito et al., 2004). These findings are interesting in light of findings that the composition of adipose tissue in AA is higher in obese subjects compared to lean ones (Savva et al., 2004), which can to some extent account for the observed association between obesity status and inflammatory markers (Straczkowski et al., 2002; Weyer et al., 2002). In fact, low grade inflammation in obese subjects has been implicated in the pathogenesis of insulin resistance. Elevated serum tumor necrosis α and IL 6 could cause insulin resistance by interfering with insulin signaling and down-regulating peroxisome proliferator-activated receptor γ (Fernandez-Real et al., 2001).

More light has recently been shed on the potential gene and diet interaction regarding inflammatory processes. A variant 5-lipoxygenase genotype, the enzyme involved in the production of Leucotrienes from AA, has been identified in a subpopulation with atherosclerosis. Increased AA intake significantly enhanced the atherogenicity of the genotype, whereas increased ω3 PUFA intake inhibited the leucotriene-mediated inflammation which is implicated in the procedure of atherosclerosis in this subpopulation (Dwyer et al., 2004). Leucotrienes have also been identified as mediators in other inflammatory and allergic conditions such as asthma, and leucotriene receptor antagonists are now used in the treatment of these conditions (Bisgaard, 2001). Dietary interventions including oil administration rich in γ-linolenic acid and EPA have been shown to reduce the levels of inflammatory mediators in patients with asthma (Spector and Surette, 2003).

The severity and exacerbations of Rheumatoid arthritis (RA) have also been shown to be influenced by diet. A number of epidemiological studies identified a protective role in Mediterranean type dietary patterns rich in fish, olive oil and vegetables (Recht et al., 1990; Linos et al., 1991; Shapiro et al., 1996; Linos et al., 1999). Few randomized controlled trials have evaluated dietary interventions in the treatment of patients with RA with different results (Darlington et al., 1986; Kjeldsen-Kragh et al., 1991; Sarzi-Puttini et al., 2000). More recently, a randomized controlled study evaluated the short term efficacy of a Mediterranean dietary pattern based on traditional Cretan diet in patients with active RA, compared to a control diet (omnivorous). The group feeding the Mediterranean diet experienced a significant improvement in a composite disease activity index, physical function and this was interpreted as a suppressed disease activity (Skoldstam et al., 2003). It has been argued that the dietary induced reduction in disease activity in RA patients is due to altered eicosanoids precursors profile. In particular, the concentration of AA and DGLA in plasma phospholipids was reduced after a vegan diet (Haugen et al., 1994). Interestingly, diets low in AA have been shown to reduce the symptoms associated with disease activity. Compared to patients fed a western diet, these patients had a higher enrichment of erythrocyte lipids with EPA, and they had a lower production of eicosanoids especially with fish oil supplementation (Adam et al., 2003). A diet low in ω6 FA supplemented with fish oil has also led in significant reduction in inflammatory markers such as CRP or soluble tumor necrosis factor receptor p55 (sTNFα p55) in patients with active RA (Sundrarjun et al., 2004).

CONCLUSIVE COMMENTS

The Mediterranean diet and especially the Cretan subtype, has been valued for the prevention of certain chronic diseases and is associated with longevity. Olive oil which is rich in MUFA has been mainly thought of as the main health promoting constituent. Accumulated evidence, however, suggests that the Mediterranean diet offers substantial anti-

inflammatory effects that can account for the beneficial effects of this diet in certain inflammatory diseases. It seems that these effects are achieved, at least in part, by a balanced ratio in ω3/ω6 fatty acid intake. Numerous methodological issues have hampered the extensive evaluation of the anti-inflammatory effects of this dietary pattern in certain inflammatory diseases in large randomized controlled trials. These include sampling procedures, survey methods regarding dietary recalls and history methods used in the dietary evaluation of humans and their validation, and the accuracy of the existing food composition tables used for the conversion of food intakes to nutrient intakes. Additional methodological issues include the difficulty in monitoring patient compliance, the high number of subjects that withdraw the studies prematurely, and also the difficulty in funding dietary trials because of the lack of commercial interests (Ferro-Luzzi et al., 2002; Kjeldsen-Kragh, 2003). Despite the lack of large randomized controlled trials on the efficacy of Mediterranean diet in several inflammatory diseases, existing data suggest that this diet is associated with an attenuated inflammatory profile. Existing data support also the recent attempt to produce coherent population nutritional goals based on the Mediterranean dietary pattern, which has proved safe with no adverse effects.

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ABSTRACTThe traditional Cretan diet of the 1960s has served as a prototype for dietary recommendations worldwide. This diet has been associated with the lowest coronary heart disease and cancer mortality rates compared with other Mediterranean diets. Subsequent studies have confirmed the beneficial effect of this diet both in primary and secondary prevention of cardiovascular disease, diabetes and cancer. All these diseases are now recognized as inflammatory processes. Similarly, Mediterranean diet has been proven beneficial in prevention and disease severity in other inflammatory diseases. Evidence suggests that the balanced dietary intake of ω3/ω6 fatty acids as part of the whole Mediterranean dietary pattern account for this beneficial effect.

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