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Dietary Patterns, Foods, Nutrients and Chronic Inflammatory Disorders

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Abstract

The World Health Organization (WHO) recognizes that diet plays an important role in the prevention of several non-infectious diseases. Unhealthy diets that include high intake of red and processed meat, sweets and desserts, potatoes, French fries, and refined grains) is associated with high plasma inflammatory biomarkers and a greater risk of cardiovascular disease (CVD), type 2 diabetes (T2D), cancer and other chronic diseases. On the other hand, prudent dietary patterns such as Mediterranean diet as well as intake of fruit, vegetables, extra virgin olive oil, walnuts, legumes, whole grains, fish, cocoa, coffee, tea and wine is associated with a reduced plasma inflammatory biomarkers and a lower risk of CVD, T2D and other chronic diseases. In respect to nutrients, excessive intake of carbohydrates, saturated fat, trans- fatty acids, and omega- 6 polyunsaturated fatty acids (PUFA) may activate the innate immune system, leading to an excessive production of pro inflammatory cytokines associated with a reduced synthesis of anti-inflammatory cytokines. On the other hand, omega-3 PUFA, vitamin E and polyphenols could counter the effects of several inflammatory markers, decreasing, for example, the secretion of circulating and cellular factors involved in the atherosclerotic process.

This review explains how healthy dietary patterns, foods and nutrients can reduce chronic inflammatory processes related to CVD, T2D, obesity or cancer and therefore be a good tool to prevent the development of these disorders.

Keywords: Dietary pattern; Nutrition; Food; Mediterranean diet; Inflammation; Adhesion molecules; Cytokines

Introduction

Increasing evidence suggests that diet plays a major role in the modulation of the inflammatory response [1], in addition to age [2], sex [3], obesity [4], smoking habits [5], alcohol consumption [6], and physical activity [7]. In fact, the World Health Organization (WHO) recognizes that diet plays an important role in the prevention of several non-communicable diseases. Unhealthy diets, as well as other adverse behaviors in lifestyle, seem to be the main factors responsible for cardiovascular disease (CVD), type 2 diabetes (T2D), cancer and other chronic diseases [8]. Dietary patterns rich in refined starches, sugars, saturated fats and Trans fatty acids, and poor in omega-3 fatty acids, natural antioxidants and fiber from fruit, vegetables and whole grains may activate the innate immune system, leading to an excessive synthesis of proinflammatory cytokines and a reduced production of anti-inflammatory cytokines [9].

The complexity and cumulative/synergistic effect of the foods that make up a dietary pattern help to determine how diet affects health and the inflammatory process [10,11]. Nowadays, it is difficult to determine the long-term role of individual foods or nutrients on specific health outcomes [12]. An extensive detailed review (1) has shown that among the components of a healthy diet, foods such as whole grains, vegetables, fruit, and fish, and nutrients such as fiber, monounsaturated fatty acids (MUFA), polyunsaturated fatty acids (PUFA), vitamin C, vitamin E, and carotenoids are all associated with lower inflammation, while saturated fatty acids (SFA), trans fatty acids (TFA), and high-glucose and high-fat meals may induce postprandial inflammation and, hence, are considered as pro-inflammatory factors.

This review analyzes the mechanisms by which diet can reduce chronic inflammatory processes related to CVD, T2D, obesity or cancer [13-16], as well as gout and celiac disease [17,18], among others, thereby making a healthy diet a good tool to prevent the development of these diseases.

Factors of Chronic Low-grade Inflammation

Inflammation involves interactions among many cell types and the production of a great number of chemical mediators as defence mechanisms that protect the host from infection and other insults [19,20]. Inflammatory response involves the synthesis and secretion of anti-inflammatory cytokines, inhibition of proinflammatory signalling cascades, shedding of receptors for inflammatory mediators and activation of regulatory cells which are directly linked to the presence of inflammatory diseases.

Nowadays, although there is not a uniform definition of low-grade inflammation [21], several biomarkers as C-reactive protein (CRP), interleukins, fibrinogen and adhesion molecules such as E-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular adhesion protein-1 (VCAM-1) have been reported to be associated with a systemic low-grade systemic inflammation. Therefore, low-grade inflammation is considered as a subclinical condition (systemic or local, and often chronic) characterized by increased concentration of plasma and/or cellular biomarkers of inflammation (e.g. CRP, platelet or leukocyte counts) without any apparent clinical sign. Recently,

chronic low-grade inflammation has also been associated with a pathophysiological mechanisms linking risk factors or metabolic disorders such as T2D [22-24], atherosclerosis [25], metabolic syndrome (MetS) [26,27] and CVD [28], which are characterized by raised concentrations of inflammatory markers in the systemic circulation.

One of the best studied markers of clinical and subclinical inflammation is CRP, although several other inflammatory factors have also been associated with low-grade inflammation. Elevated plasma concentrations of CRP and other proinflammatory cytokines such as TNF-α, IL-6, IL-18 or soluble adhesion molecules (E-selectin, ICAM-1 and VCAM-1) have been associated with an increased risk of CVD, T2D or cancer [9,21,29-31]. Conversely, the adiponectin hormone has anti-inflammatory and antiatherogenic properties and is inversely associated with these disorders (CVD, T2D, obesity or cancer) [32,33].

A recent systematic review [34] supports the evidence of an association between dietary patterns and factors of inflammation, with the diet as a whole being more beneficial to health than a single specific nutrient or food.

Inflammation and Dietary Patterns

The relationship between diet and inflammatory markers has also been investigated in several cohort and intervention studies [35-37]. Thus, a prudent dietary pattern characterized by higher intake of fruit, vegetables, legumes, whole grains, poultry, and fish, is associated with a reduced plasma inflammatory biomarkers and a lower risk of cardiovascular heart disease (CHD), while a Western dietary pattern (high intake of red and processed meat, sweets and desserts, potatoes, French fries, and refined grains) is associated with high plasma inflammatory biomarkers and a greater risk of CHD.

The MedDiet should be considered a good example of a prudent dietary pattern. In the last two decades, several experimental and epidemiological studies have pointed out the benefits of the MedDiet and some of its components on health. Thus, the MedDiet has shown favorable effects on the incidence of MetS, plasma lipoprotein concentrations, endothelium vasodilatation, insulin resistance, and antioxidant capacity, as well as cardiovascular and cancer morbidity and mortality [38,39]. On the other hand, the Western diet has been positively associated with low-grade inflammation and contributes to an increased incidence of inflammatory diseases such as T2D, rheumatoid arthritis, inflammatory bowel disease and obesity, among others [40].

The MedDiet pattern is characterized by a high consumption of plant foods, whole-grain cereals, legumes, fish, nuts, olive oil as the main fat source, as well as a moderate consumption of wine and low consumption of meat, processed meat, bakery and sweets. It is associated with a lower degree of inflammatory factors (CRP, IL6, ICAM-1 and VCAM-1), suggesting an anti-inflammatory effect of its main food components [41,42]. Conversely, a Western pattern is positively linked to higher levels of CRP, IL-6, E-selectin, and ICAM-1 and VCAM-1 concentrations [43]. Moreover, a Western-type dietary pattern that increases chronic inflammation also raises the risk of developing T2D [44].

The beneficial effects of the MedDiet on health have basically been attributed to its high content of antioxidants, dietary fiber [45], MUFA and PUFA [46] and low glycemic load and glycemic index [47]. In particular, antioxidants and polyphenols have been shown to exert a protective role against ischemic CVD mainly due to their anti-inflammatory properties [48].

Some prospective cohort studies such as the Moli-sani study included 24,325 men and women (participants aged 35 years or older), in the Southern Italian area, and investigated whether the MedDiet as a diet rich in healthy compounds was closely associated with relatively lower blood pressure and plasma glucose, lipids, and CRP concentrations, as well as 10-year cardiovascular risk, and observed that consumption of healthy foods with high rather than low content of antioxidant vitamins and phytochemicals was associated with lower blood pressure and CRP plasma levels, at least in men [34]. Other observational studies have also evaluated similar associations. The ATTICA study included 1,514 (men 18 to 87 years old) and 1,528 women (18 to 89 years old) without previous history of cardiovascular disease [49] and found significant lower concentrations of CRP, IL-6, TNF-α, homocysteine, and fibrinogen, as well as a lower white blood cell count in healthy adults with higher adherence to the MedDiet. Moreover, in the Nurses' Health Study (690 women, ages 43-69 y, without previous CVD or diabetes), a MedDiet index score was significantly associated with lower concentrations of some molecules related to inflammation (CRP and E-selectin) and endothelial dysfunction [50].

Other epidemiological studies have also shown the protective role of the MedDiet on blood pressure and the incidence of hypertension, effect that have been ascribed to the high antioxidant content of this dietary pattern as is shown in a study that included 415 Australians aged 60-64 years, half men [51]. In a randomised crossover trial 58 subjects aged 30-64 with mild untreated hypertension were allocated to vegetarian diet or a control group for one of two six week periods. Results showed that vegetarians, who consume particularly high amounts of antioxidant vitamins and phytochemicals, tended to have lower blood pressure than non-vegetarians [52]. Again, in a substudy of the Moli-sani cohort that included 6,879 women (55 ± 12 years) and 6,892 men (56 ± 12 years) showed that the consumption of healthy foods with high vitamin and phytochemical content was associated with lower blood pressure and plasma CRP concentrations [53].

The relationship between diet and inflammatory markers has also been investigated in intervention studies. In this respect, a 4-week Swedish study [36] in 22 healthy subjects, 10 women and 12 men, aged between 36 and 51 year, and with normal blood lipid and glucose values and BMIs just at the cutoff for overweight evaluated whether a Mediterranean-style diet would change inflammatory factors, vascular endothelial growth factor (VEGF) and serum phospholipid fatty acid composition. The results showed a reduction in leukocyte and platelet counts, and VEGF concentration by 10%, 15%, and 15%, respectively. Neither CRP nor IL-6 changed significantly. Likewise, in a similar intervention study in patients with MetS and high plasma CRP concentrations, 99 men and 81 women with mean age of 44 year, a MedDiet intervention improved endothelial dysfunction and reduced markers of vascular inflammation (hs-CRP (P=0.1), IL-6 (P=0.4), IL-7 (P=0.4), and IL-18 (P=0.3), as well as decreased insulin resistance (P<. 001) [37].

In the large intervention PREDIMED (Prevención con Dieta Mediterránea) trial, that included 7,447 subjects (50% men 55-80 year, and 50% women, 60-80 year), who have diabetes or who meet at least three or more other CVD risk factor), showed that a MedDiet rich in extra virgin olive oil (EVOO) or nuts reduces the risk of CVD by 30% after a mean follow-up of near 5 years, when compared to a low-fat diet [54]. This study also demonstrated that a higher adherence to the

MedDiet is associated with a reduced incidence of diabetes, MetS, hypertension and other cardiovascular risk factors, oxidative stress, vascular inflammation, and endothelial dysfunction [55]. In addition, a group of patients with MetS following a MedDiet pattern showed reduced serum concentrations of CRP, IL-6, IL-7 and IL-18, decreased insulin resistance and improved endothelial function [37]. Furthermore, the MedDiet may also exert a modulation effect on the expression of genes related to plaque stability, such as MMP-9, even in an elderly high-risk population after a short-term [56]. Interestingly, a recent study reported the long-term anti-inflammatory effect (5 years) of the Mediterranean diet enriched with extra-virgin olive oil and nuts, that may explain, at least in part, the effects of healthy dietary patterns in the prevention of CVD at long-term (CITA teva del J Nutr.).

Finally, a Spanish study on obese children from 12 to 17 years of age showed that adiposity measures such as the body mass index (BMI) and waist-to-hip ratio were significant predictors of serum levels of hs-CRP or leptin, and concentrations of adiponectin were positively linked to a Mediterranean dietary pattern [57].

Inflammation and Single Foods Related to the MedDiet

Few studies have related fruit and vegetable consumption to inflammatory status. Thus, observational studies such as the Massachusetts Hispanic Elders Study [58] (445 Hispanic and 154 non-Hispanic white older subjects, ≥ 60 y) showed that high consumption of fruit and vegetables was inversely associated with plasma CRP (-27%) and homocysteine (-17%) concentrations. Regarding diabetes risk, a meta-analysis of the effects of fruit and vegetable consumption did not show any significant benefit, except for green leafy vegetables [59]. However, findings from large prospective studies in which 66,105 women (Nurses' Health Study), 85,104 women (Nurses' Health Study II), and 36,173 men (Health Professionals Follow-up Study) were available for analysis, suggest that consumption of some fruits, such as apples, blueberries, and grapes, was associated with a lower risk of developing diabetes [60]. On the other hand, interventional studies have also shown similar results. Twelve healthy volunteers (6 men and 6 women between 20 and 32 year old and normal BMI), were enrolled in a 14-day intervention study. . Plasma CRP concentrations (≥ 40%) fell in both men and women after drinking 500 ml/day of orange juice for 14 days [61]. However, other randomized intervention trials failed to demonstrate such associations. Thus, controlled parallel 6-week dietary intervention trial in healthy volunteers (n=77, 19-52 y) did not show any association between the consumption of vegetables, berries, and apples and CRP levels [62], and another randomized study showed a negative correlation between vegetable intake in the diet [63] and circulating adhesion molecules (sICAM-1 and sVCAM-1), and proinflammatory cytokines (IL-6 and TNF-α).

Several studies have shown the effect of EVOO against the oxidation of LDL particles [64]. EVOO also seems to have an effect on inflammation processes. Thus, a double-blind study in healthy middle-aged males, in which they consumed either a MUFA diet or a control diet for 2 months, showed that consumption of EVOO led to a decrease of ICAM-1 [65]. *In vitro* studies have also shown a decrease in the expression of VCAM-1 and NF-κβ [66] and reduced monocyte adhesion to endothelial cells [67]. The consumption of vegetable oils such as EVOO in healthy women from Teheran, 40-60 y without CVD, diabetes, cancer, or stroke, was associated with lower plasma concentrations of TNF-α, ICAM-1 and CRP [68].

Nuts, another staple of the MedDiet, are rich in PUFA (α-linolenic acid in the case of walnuts), fiber, phytosterols, folic acid and vitamin E and polyphenols [69]. Several large prospective studies such as the Iowa Women's Health Study (34,111 postmenopausal women, aged 55 to 69 years, without known CVD), Adventist Health Study (31,208 California Seventh day Adventists where two-thirds of the cohort were female), the Nurses' Health Study (86,016 middle-aged women, 30-55 years) and the Physician's Health Study (22,071 US male physicians, 40 to 84 years, free of CVD) have confirmed that frequent consumption of nuts is associated with a lower risk of CVD [70]. Additionally, the consumption of nuts has also been associated with decreased IL-6, CRP and fibrinogen levels in a cross-sectional sub-study of the PREDIMED trial (339 men and 433 women) [71] and decreased plasma concentrations of VCAM-1, ICAM-1 and sE-selectin in intervention studies with 12 hypercholesterolemic patients [72]. Moreover, the relatively high arginine content of nuts may explain their potential cardioprotective effect, since consumption of arginine-rich foods is associated with lower CRP levels [73].

The PREDIMED study analyzed the effects of a MedDiet rich in EVOO or nuts and a low fat diet (LFD) on four soluble adhesion molecules (ICAM-1, VCAM-1, IL-6 and CRP) in the first 772 participants recruited after a 3-month follow up [54]. The results of this study showed decreased concentrations of these four adhesion molecules in the MedDiet groups supplemented with EVOO and nuts compared to the controls, while plasma concentrations of CRP only decreased in the MedDiet supplemented with EVOO group ($P<0.05$; all). The PREDIMED study has also demonstrated a significant reduction in the expression of adhesion molecules on leukocyte cell membranes (T-Lymphocytes and monocytes), and circulating endothelial adhesion molecules (VCAM-1, ICAM-1, E- and P-Selectin), cytokines (IL-1, TNF-α, IL-6, CRP, TNFR-60 and TNFR-80 etc.) and molecules related to atherosclerotic plaque instability (IL-18, MMP-9) after 3 and 12 months of an intervention with a MedDiet plus EVOO or nuts [55].

Whole grains are good sources of fiber, vitamins E and B, and some trace minerals such as iron, magnesium, and zinc [74]. Several observational [75] and interventional [76] studies have shown that high intake of refined grains causes rapid swings in blood glucose and insulin concentrations, may increase hunger, and elevate free fatty acid levels and therefore promote hyperglycemia and increased circulating levels of free radicals and proinflammatory cytokines, such as IL-6, IL-18, and TNF-α [77]. A recent meta-analysis of 45 prospective studies that included 7,068 cases of CHD, 2,337 cases of stroke, 26,243 cases of CVD, 34,346 deaths from cancer, and 100,726 all cause deaths [78] concluded that whole grain intake is associated with a reduced risk of CHD, CVD, and total cancer, as well as a low mortality by all causes, respiratory and infectious diseases, diabetes, and all non-cardiovascular, non-cancer causes. Inflammatory markers (CRP and tumor necrosis factor- receptor 2, (TNF-R2)) were analyzed in 902 diabetic women in the Nurses' Health Study [79]. The results showed significant decreases in CRP (P for trend=0.03 and 0.007, respectively) and TNF-R2 (P for trend=0.017 and 0.06, respectively) after whole grain and bran intake.

Furthermore, an increased frequency of fish consumption was associated with lower CRP and IL-6 concentrations in a cohort of 727 women from the Nurses' Health Study I cohort, aged 43-69 years, free of CVD, cancer, or diabetes mellitus [80]. Data from a Danish study [81] of 269 subjects referred for coronary angiography and the NANHES study [82] of 4,900 adults, ≥ 18 years, did not find any

association between fish consumption and CRP concentration. In contrast to these findings, a study in 3,102 with 1,514 men and 1,528 women Greek adults, ≥ 18 years, free of CVD or atherosclerotic disease reported that fish consumption was dose-dependently associated with lower CRP (-33%), IL-6 (-33%), TNF-α (-21%) and serum amyloid A (SAA) (-28%) concentrations and white blood cell counts [83].

Dairy products add important nutrients to the diet such as carbohydrates, protein, calcium, potassium, and micronutrients such as vitamin D. Recent cross-sectional studies suggest that the consumption of dairy products is inversely associated with low-grade systemic inflammation [84,85]. Indeed, the ATTICA study [85] has shown a lower reduction of CRP (-29%), IL-6 (-9%) and TNF-α (-20%) in individuals consuming >14 servings of dairy products/week than those with an individual consumption of <8 servings/wk. A recent review of 8 randomized controlled trials (RCTs) [86] in overweight and obese adults suggested that dairy product consumption has no adverse effect on low-grade systemic inflammation among overweight and obese adults, ≥ 18 years.

Foods such as cocoa, coffee and tea have also been investigated in apparently healthy individuals or in subjects at different cardiovascular risk to determine possible associations with low-grade inflammation. Thus, the Moli-sani cohort study of men and women aged ≥ 35 year [87] found that 312 of 824 subjects who regularly ate up to 1 serving (20 g) of dark chocolate every 3 days had significantly lower serum CRP concentrations than either non-consumers or higher consumers. However, meta-analyses of RCTs including data from 5 [88] and 10 [36] individual trials, respectively, did not find any changes in CRP values with cocoa consumption. Monagas et al. [89] studied the effect of a 4-week randomized cross-over trial of 40 g cocoa powder in skimmed milk daily vs. only skimmed milk in 42 older subjects (69.7 year), 19 men and 23 women with diabetes or high CV risk, on plasma concentrations of sICAM-1 and sP-selectin and on monocyte expression of VLA-4; CD49d, CD36 and CD40 and found a significant reduction of all these inflammatory factors after the cocoa powder intervention. A recent critical review [90] that included 33 randomized clinical trials (RCTs) concluded that acute cocoa consumption may reduce inflammation by a reduced activation of monocytes and neutrophils, a decrease in the expression of adhesion molecules (VCAM-1, ICAM-1, E- and P-selectin) and 4-series leukotrienes in serum as well as a decrease in the activation of NF-κβ in peripheral leukocytes. On the other hand, cross-sectional studies [91] as the larger cross-sectional BELSTRESS study have also reported a relationship between green tea consumption and low concentrations of several inflammatory factors (CRP and SAA) in regular tea drinkers on 1031 healthy men. While an interventional study (47 subjects younger than 65 y, free of T2D but with an elevated risk of T2D) with coffee has reported a significant decrease of IL-18 and a significant increase of adiponectin concentrations [92], whereas CRP, leptin, SAA, IL-6, MIF and IL-1ra concentrations did not change.

Nowadays, there is enough evidence scientific from both epidemiologic studies and RCTs to conclude that moderate alcohol intake, mainly in the form of wine or beer, is cardioprotective [93]. A meta-analysis of 20 cohort studies showed that moderate alcohol consumption also protects against diabetes [94]. Estruch et al. [95] described the different effects of red wine and polyphenol-free gin consumption in a prospective randomized crossover study on 40 healthy men (mean age, 37.6 years) who consumed 30 g ethanol per day as either wine or gin for 28 days. Both wine and gin showed anti-inflammatory effects by reducing plasma fibrinogen and IL-1α levels. However, wine had the additional effect of decreasing hs-CRP (-21%), VCAM-1 (-17%) and ICAM-1 (-9%), as well as monocyte and endothelial adhesion molecules.

Inflammation and Nutrients of the MedDiet

With respect to chronic activation of inflammatory response, diet and lifestyle play an important role in the development of several chronic diseases. As shown in the literature, nutrients can theoretically modulate this phenomenon (Table 1).

Omega-3 fatty acids are inflammatory antagonists, while omega-6 fatty acids are precursors of inflammation. Omega-3 fatty acids are dietary PUFAs. The plant form of omega-3 PUFA is a short-chain fatty α-linolenic acid obtained from plant oil (leafy vegetables, walnuts, soy bean oil, canola oil and flaxseed oil) [96]. The marine forms of omega-3 PUFA are the long-chain fatty acids: docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) and may be obtained from seafood, fish and algae (96). The first evidence of the important role of dietary intake of omega-3 (PUFAs) in inflammation was provided by epidemiological observations of the low incidence of autoimmune and inflammatory disorders, such as psoriasis, asthma and type-1 diabetes in a population of Greenland Eskimos who consumed PUFA-rich foods compared with gender- and age-matched groups living in Denmark [97]. Nowadays, we know that the benefits of omega-3 fatty acids play an important role in the prevention and treatment of CVD, hypertension, arthritis, other inflammatory and autoimmune disorders and cancer [97]. Thus, omega-3 fatty acids may inhibit the synthesis of proinflammatory cytokines, such as TNF-α, IL-1, and IL-2 and decrease expression of adhesion molecules on the endothelium, although results from *ex vivo* human studies are not conclusive [9]. Observational studies [98], the Health Professionals Follow-up Study (40 to 75 years at baseline) and the Nurses' Health Study (25 to 42 years at baseline), have shown an inverse association between plasma concentration of receptors 1 and 2 of TNF-α and the intake of omega-3 fatty acids EPA and DHA on 405 healthy men and 454 healthy women. In addition, 727 women included in the cross-sectional Nurses' Health Study [80], showed low concentrations of many factors of inflammation (CRP, IL-6) and endothelial activation (E-selectin) in the highest quintile of omega-3 fatty acid intake. In the ATTICA study, subjects who consumed at least 300 g of fish per week had 33% lower CRP values compared with non-fish consumers [83]. On the other hand, an interventional study has also shown significant reductions of CRP, VCAM-1 and E-selectin after dietary supplementation with α-linolenic acid (ALA) (6.5% from total energy) on 23 patients (20 men, 26-60 year, and 3 women, 55-65 year) [99]. In another study, dietary supplementation with ALA (15 ml of linseed oil/day) for 3 months in 50 dyslipidemic patients, mean age 41, significantly decreased CRP, SAA and IL-6 concentrations by 38%, 23%, and 10%, respectively. Contrarily to omega-3, omega-6 PUFA (linoleic acid) have been shown to exert an inflammatory effect [100]. A meta-analysis of RCTs (15 studies, 8 parallel and 7 crossover) on the effect of omega-6 PUFA on CVD showed a direct effect of omega-6 on the risk of non-fatal and fatal heart failure, although linoleic acid could not be linked to an increase in systemic inflammatory factors [101].

In addition, high MUFA intake has also been shown to exert anti-inflammatory effects. The Nurses' Health Study (80,082 women who were between 34 to 59 years of age and had no known CHD, stroke, cancer, hypercholesterolemia, or diabetes) showed a significant association between high intake of trans or saturated fats and an increased incidence of CHD, whereas high PUFA and MUFA intakes

were associated with a decreased risk [102]. In addition, a 5-week intervention study in men aged 25-60 years who received a saturated fatty acid diet including stearic, lauric, myristic and palmitic acids showed higher concentrations of CRP, fibrinogen, IL-6 and sE-selectin compared to those who followed-up a diet rich in oleic acid [103].

Experimental *in vitro* and *in vivo* evidence also supports the potential beneficial effects of flavonols to reduce the transcription and secretion of adhesion molecules and proinflammatory cytokines (IL-1β, TNF-α) [90]. The beneficial effects of cocoa polyphenols depend on the amount consumed, their bioavailability, and the biological activity of the metabolites [104]. *In vitro* studies have shown that flavanols may increase the synthesis of anti-inflammatory cytokines such as IL-4 or IL-5, while epicatechin, catechin, and dimeric procyanidins inhibit the activation of NF-κβ such as matrix metalloproteinases at multiple stages *in vitro* [104].

The antioxidant components of fruit and vegetables (vitamins and flavonoids) reportedly contribute to their anti-inflammatory effects [105]. An inverse association has been shown between dietary total antioxidant capacity, serum carotenoids and vitamins, and markers of inflammation in several observational studies [106]. A 4-weeks randomized controlled trial in 64 healthy and non-smoking men showed that subjects assigned to high consumption (8 servings/day) of carotenoid-rich vegetables and fruit had significantly reduced CRP concentrations compared to those who consumed 2 servings/day [107]. On the other hand, supplementation with antioxidants [63] to the diet has been demonstrated to reverse the endothelial dysfunction induced by a high saturated fat meal consumption, increasing circulating adhesion molecules (sICAM-1 and sVCAM-1) and proinflammatory cytokines (IL-6 and TNF-α) on twenty-five (13 men and 12 women) healthy subjects aged 23-40 year.

King et al. [82] and Ajani et al. [108] found dietary fiber intake to be associated with lower CRP serum concentrations in 3,920 participants. CRP and TNF-R2 were measured in the Nurses' Health Study in 902 diabetic women [79] and it was found that high intake of cereal fiber was also inversely associated with lower concentrations of CRP (P for trend=0.03) and TNF-R2 (P for trend=0.01). Moreover, the concentrations of CRP and TNF-R2 were 18 and 8%, respectively, lower in the highest quintile of cereal fiber compared with the lowest quintile. Interventional studies have shown that high fiber intake triggers a greater inhibition of plasma IL-18 concentrations and greater stimulation of adiponectin plasmatic levels [76].

Cereals are considered a basic food. In fact, wheat is one of the key elements of the MedDiet and contributes to 50% of calories in industrialized and developing countries. Currently there is no doubt that gluten, the main protein complex in wheat, barley, and rye, is a mixture of alcohol-insoluble ("glutenins") and alcohol-soluble ("gliadins") proteins. Gluten consumption has been linked to a wide range of disorders, including celiac disease, wheat allergy, or non-celiac gluten sensitivity. Celiac disease has been regarded as a malabsorption of nutrients with attendant diarrhoea and weight loss which affects genetically predisposed individuals due to permanent intolerance gluten content in the diet [17,109,110]. This disease, with a prevalence of approximately 1% in Western countries, is characterized by a chronic inflammatory condition mediated by CD4 + T lymphocytes that trigger to an increase of proinflammatory cytokines such as IFN-γ, TNF-α or IL-18 and a decrease of regulatory cytokines or anti-inflammatory as IL-10 and TGF-β1 [109]. A recent comparative study has evaluated the innate and adaptive immunity expression in celiac disease and non-celiac gluten sensitivity, demonstrating a higher presence of IL-6 and IL-21, adaptive immunity markers, only in celiac disease, while the expression of TLR-2, innate immunity marker, was increased in non-celiac gluten sensitivity but not in celiac disease [17]. A recent study on 74 children (mean age of 7.6 years and 24 men) with this disease has demonstrated an inflammatory response represented by the appearance of joint effusion may be induced by exposure to gluten [111].

On the other hand, high phytate and antioxidant content of MedDiet have however demonstrated to be beneficial in preventing the formation of new or recurrent calculi. For many aspects, MedDiet has proven to be effective in the prevention of kidney stone onset and relapse because of its mainly composition: low intake of animal proteins and the high intake of fruits and vegetables [18]. Besides, MedDiet that is characterized by a high content of antioxidant substances, such as beta-carotene and vitamin E [112]. Some evidences in the nephrolithiasis field have shown that low levels of antioxidants such as alpha-carotene, beta-carotene and beta-cryptoxanthin are associated to kidney stones [113]. Also, a high dietary intake of vitamin E may be protective against calcium oxalate crystal deposition in the kidneys [114]. There are some reports in the literature that have shown that high consumption of cereals, nuts and legumes are associated to a high urinary excretion of phytate, exerting a protective role against the formation of renal calculi.

Sugar consumption has increased in the Western world during the last decades. The excessive consumption of high-sugar soft drinks has been associated with the occurrence of hypertension and hyperuricemia in adolescents [115,116]. The acute ingestion of fructose was accompanied by increased intracellular, kidney stones [117] and gout [118] and circulating uric acid [119]. The Atherosclerosis Risk in Communities Study revealed an association of high consumption of sugar-sweetened soda with prevalent hyperuricemia and chronic kidney disease (CKD) [120]. A recent study in patients with CKD stage 2 and 3 found a decrease of CRP and ICAM, fasting serum insulin levels, and blood pressure after reduce the intake of fructose contained in the diet for 6 weeks [121].

Nutrition and Inflammation

Table 1 shows a summary of the key role of nutrients in both promoting and combating inflammatory processes. Evidence linking nutrients with inflammatory processes comes from clinical and epidemiologic studies.

Proinflammatory Nutrients	Effect	Studies
Excess calorie intake	Stimulation of adipose cell growth and proliferation, and promotion of abdominal obesity, thereby increasing	Consumption of 1,800 kcal/day (30% reduction from baseline) over several years decreased serum concentrations of CRP, TNF-α, and proinflammatory growth factors, and reduced body fat and BMI, and improved glucose tolerance, insulin sensitivity, and lipoprotein profiles [122].

	the risk of diabetes, metabolic syndrome, and other chronic diseases.	
Excess in carbohydrate consumption	Association with chronic diseases such as obesity, metabolic syndrome, and T2D.	Association between consumption of a high glycemic index (GI) diet with risk of death from inflammatory disease (digestive, respiratory, nervous system, and endocrine disorders) three times greater than women eating a low-GI diet. In addition, levels of NF-kβ were three times higher among lean subjects consuming high-GI meals [123]. High-GI diets rich in refined carbohydrate may stimulate proinflammatory IL-6 production and push the liver to generate CRP [124].
Trans fatty acids	Association with high risk for sudden cardiac death.	Patients with chronic heart failure showed significant associations between trans fatty acid level of red blood cell membranes and plasma biomarkers of inflammation, including IL-1, IL-6, and TNF-alpha [125]
Saturated fatty acids	Association with inflammatory processes by stimulating macrophage production and secretion of the proinflammatory cytokines TNF-α, IL-6, and IL-8.	In mice, a diet containing 12% saturated fat resulted in increased body fat and elevated levels of proinflammatory cytokines [126].
Omega-6 polyunsaturated fatty acids	Ratios from 10:1 to 20:1 (omega-6: omega-3 fatty acids) have been associated with an increased risk of chronic inflammatory diseases, including atherosclerosis, cardiovascular disease and rheumatoid arthritis.	Linoleic acid and arachadonic acid (proinflammatory eicosanoids) have potent negative effects on platelet aggregation, blood pressure, and immune system function since trigger proinflammatory cytokine production [127]
Anti-Inflammatory Nutrients		
Omega-3 polyunsaturated fatty acids (EPA and DHA)	Suppression of production of proinflammatory eicosanoids and stimulation of the synthesis of anti-inflammatory eicosanoids from arachadonic acid. In addition, reduction of generation of proinflammatory cytokines.	Fish oil supplementation (4 g/day) for a minimum of six weeks showed a significantly decreased plasma levels of TNF-αamong individuals with type 2 diabetes and reduced cellular content of proinflammatory cytokines IL-1β, IL-6, and IL-8 in healthy subjects [128]. Besides, consuming approximately 85 g of fatty fish (eg, salmon, herring) five times per week for eight weeks resulted in significant lowering of plasma levels of proinflammatory cytokines TNF-α and IL-6 among elderly Chines women with dyslipidemia [129] Also, omega-3 fatty acid alpha-linolenic acids (ALA) from walnuts, canola oil or flaxseed oil appear to be substantially less effective in their anti-inflammatory effects than EPA and DHA [128].
Vitamin E (alpha-tocopherol)	High capacity to scavenge free radicals and prevent lipid oxidation. Inhibition of the release of proinflammatory cytokines and reduction of CRP levels. Gamma-tocopherol decreases proinflammatory NF-kβ and TNF-αactivity, and inhibits prostaglandin synthesis (131)	Dietary intakes of alpha-tocopherol were inversely related to plasma levels of proinflammatory CRP and IL-6 [130]. Besides, alpha- and gamma-tocopherol may have a synergistic effect on inflammation [131]. This finding was observed in a randomized double-blind trial involving subjects with MetS, in which supplementation with 800 mg/day of a combination of alpha- and gamma-tocopherol was more effective in reducing plasma CRP and TNF-α levels than were either supplement alone [132]. A clinical study demonstrated a significant reduction in joint stiffness and pain following twice-daily supplementation with 600 mg of alpha-tocopherol, although plasma inflammatory biomarkers weren't changed [131].
Polyphenols	These aromatic compounds are found in fruits, vegetables, grains, cocoa, coffee, extra virgin olive oil, and tea.	Many polyphenols show powerful anti-inflammatory effects. Polyphenols inhibit enzymes involved in prostaglandin and leukotriene synthesis, prevent free radical formation, decrease proinflammatory cytokine production, and block the activity of proinflammatory signaling systems [133,134]. Increases in polyphenol intake are associated with decreased inflammatory biomarkers, suggesting a dose-dependent anti-inflammatory effect of these compounds. In addition, high polyphenol intake improves cardiovascular risk factors– mainly blood pressure and the lipid profile. However, the effect of dietary polyphenols on human inflammatory biomarkers requires further study because of wide variation in the polyphenol content of foods, differences in postprandial plasma concentrations, and inadequate knowledge of tissue stores [133].

Table 1: Summary of the key role of nutrients that promote or combat inflammatory processes.

Conclusion

The present review provides evidence that a prudent dietary pattern (e.g. Mediterranean diet) characterized by high intake of olive oil, fruits, vegetables, legumes, whole grains, poultry, and fish may play an important role in the risk of CHD, cancer, and all-cause mortality, as well as mortality by respiratory disease, infections or diabetes compared with a Western dietary pattern, that is associated with a greater risk. To date, dietary components (flavonoids, MUFA, PUFAs, antioxidants, vitamins, etc.) that promote or prevent chronic low-grade inflammation have been little studied, making intervention studies

including different time points necessary to identify and describe these components.

Since low consumption of fruit and vegetables, together with physical inactivity, are now among in the main causes of mortality in developed countries, people should be encourage to adopt a healthy lifestyle that include to choice of healthy sources of carbohydrates, fat, and proteins, to increase consumption of fruits and vegetables, to practice regular physical activity and to avoid smoking in order to reduce incidence of the most prevalent chronic diseases (T2D, CVD, obesity, and metabolic syndrome). Thus, polices or nutritional recommendations focused on these healthy dietary patterns and healthy foods should be promoted by governments and scientific societies.

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