Circulating immune cell activation and diet: A review on human trials

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Abstract

The World Health Organization (WHO) recognizes that diet plays an important role in the prevention of several low-grade inflammatory diseases such as diabetes, atherosclerosis, metabolic syndrome and obesity. All of these diseases are characterized by elevated concentrations of markers in the systemic circulation (e.g.: C-reactive protein (CRP), interleukins, fibrinogen and adhesion molecules including E-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular adhesion protein-1 (VCAM-1)).

This review focuses on the evidence obtained from epidemiological, dietary intervention and supplementation studies in humans supporting the role of monounsaturated and polyunsaturated fatty acids and other specific components of the diet in the prevention or delay of diabetes, cancer, cardiovascular disease and obesity. Thus, we provide an update of the knowledge of the relationship between diet and the modulation of immune cell activation by different dietary patterns and also highlight the importance of the overall quality and composition of the diet to protect against the previously mentioned disorders.

Introduction

Human health is influenced by numerous factors some of which are modifiable [1,2]. In this regard, diet is a key element because of its impact and affordability [3]. Nevertheless, although the prevalence of nutritional deficiencies has decreased, they continue to be responsible for thousands of deaths worldwide [4] as are many non-communicable diseases such as cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), and cancer [5], which have also been related to nutritional patterns and represent more than 50% of global deaths [4].

The functionality of the immune system is closely related to nutritional patterns throughout life. In healthy conditions, diet and nutrients can regulate immune activity by direct interaction with the immune cells, via receptor-mediated signalling, or indirectly, by modulation of microbiota metabolites [6]. For instance, there is growing evidence that nutritional status of the mother or food exposure during gestation may modify the probability of allergies in postnatal life [7]. In addition, breastfeeding has a key role in maturation of the immune system in newborns [8,9], ensuring the proliferation of a healthy and balanced microbiota which is necessary for correct immunological development [9]. These mechanisms are also present throughout the ageing process, albeit with adaptations, because of their association with immunosenescence [10,11].

Multiple single nutrients have shown beneficial effects on the immune system, such as vitamin A, required for maintenance of normal adaptive immunity [12] and ω-3 polyunsaturated fatty acids (PUFAs) which are related to immune response. In particular, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are involved in the regulation of the formation and action of pro-inflammatory eicosanoid, and are converted into anti-inflammatory molecules [13,14]. However, it is important consider limitations in the study of specific nutrients study since possible interactions with other diet components may be overlooked.

Overall, traditional dietary patterns have undergone changes in recent years [15]. Rapid urbanization has led to a rise in the availability of processed foods making the consumption of a Western diet increasingly more frequent. This diet is characterized by low vegetable and fruit consumption, a high presence of refined grains and high fat meat, enriched in salt, saturated fatty acids (SFA), ω-9 MUFA (monounsaturated acid or acid oleic), and is frequently associated with excess caloric intake [16]. Thus, the Western diet is low in dietary fibre [17] and high in compounds such as phosphatydicholine and L-carnitine, which together seem to alter the microbiota and promote a state of systemic low-grade inflammation even in healthy subjects [18,19]. Rocha et al. [20] have suggested that SFA may induce inflammatory response via toll-like receptor 4 (TLR4), promoting pro-inflammatory transcript factors and activate pro-inflammatory cytokines and chemokines, which are associated with multiple chronic diseases as discussed below.

By contrast, plant-based diets like the Mediterranean diet (MeDiet) and vegetarian diets have been recommended for the maintenance of health [21]. The MeDiet, is related to anti-inflammatory processes [22–24], being composed of fruits, vegetables and the use of olive oil,
and fish consumption [25]. It is rich in dietary fibre which is correlated with an abundance of faecal short chain fatty acids (SCFA), that are key to the development of healthy microbiota [11]. Other dietary patterns are also enriched in fibre including those of rural African or traditional Japanese diet as well as diets from other Asian countries. These diets frequently include large amounts of rice, beans, fermented or pickled fresh foods and fish, being rich in SCFA and ω-3 fatty acids and associated with low rates of chronic inflammatory diseases [26,27].

However, protein energy malnutrition is associated with oedema, skin rash and anorexia [28], resulting in secondary immunodeficiency and vitamin A and zinc deficiencies that lead to infectious complications [29]. By contrast, some studies evaluating the effect of intermittent caloric restriction in humans without malnutrition and have reported a reduction in pro-inflammatory biomarkers [30–32].

Therefore, although activation of the immune system and the inflammatory process by diet-associated events is a complex process, there seems to be clear connection between diet, the immune system and the development of chronic inflammatory diseases.

This review provides an update of the knowledge of the mechanisms by which diet can modulate immune cell activation in chronic inflammatory diseases through the analysis of human interventional trials.

Effects of diet on chronic inflammatory diseases

The inflammatory process alters physiological responses and involves complex cell interactions and cascades of chemical mediators. One of the most characteristic effects of inflammatory activity is tissue invasion by monocytes, macrophages and lymphocytes, particularly pro-inflammatory M1 macrophages [33,34], leading to increased synthesis and secretion of pro-inflammatory molecules as well as inhibition of anti-inflammatory compounds and immune cell activation. Indeed, many of these cells or compounds and cells can be used as biomarkers of inflammatory status, including interleukins (IL-6, TNF-α, IL-18), adhesion molecules (e.g. E-selectin, intracellular adhesion molecule-1 (ICAM-1) or vascular adhesion protein-1 (VCAM-1), and C - reactive protein (CRP).

Chronic low-grade inflammation is associated with T2DM [35], CVD [36], obesity [37], metabolic syndrome (MetS) [38,39], depression [40], depressive disorders [41], certain types of cancer [42] and a higher risk of all-cause mortality in old age [43]. The relationship between diet and inflammatory markers has been reported in several cohort and intervention studies [44].

Obesity

Obesity can be defined as a complex disease of multifactorial causes which is due to an excessive accumulation of body fat [45]. It is characterized by the presence of macrophages infiltrated into adipose tissue (AT). This infiltration may be due to the death of hypertrophied fat cells and/or a hypersecretion of proinflammatory cytokines by AT, including interleukin-1 (IL-1β), IL-6, IL-8, tumor necrosis factor (TNF-α), complement C3, chemotactant molecules such as monocyte chemotactant protein-1 (MCP-1) and macrophage migration inhibitory factor (MIF), and immune cells such as dendritic and T cells, in addition to macrophages [46]. These pro-inflammatory cytokines can also substantially affect insulin sensitivity and endothelial dysfunction, promoting an increased risk for T2DM, CVD and cancer [47–49]. Thus, the production of these molecules is directly proportional to the amount of AT, although some retrospective studies have found higher concentrations of these markers in Western diets and in those with a predominant consumption of red meat [50]. Endothelial dysfunction leads to an increase in the expression of cell adhesion molecules (CAMs) on the surface of the endothelium, increasing their interaction with circulating leukocytes [48,49]. Several studies have described a correlation between dietary patterns and inflammatory response (MCP-1 and expression of CAMs). As shown in Table 1, Ziccardi et al. [51] reported a decrease in circulating levels of proinflammatory cytokines and endothelial function in apparently health obese women with different degrees of central adiposity after one year of follow up on the MeDiet. Thompson et al. [52] allocated 90 healthy obese men and women to one of 3 energy-restricted diets for 48 weeks. Their findings showed that CRP, leptin, fasting glucose, and insulin levels significantly improved, but there were no significant differences between the experimental diets and the control diet. On the other hand, using a crossover design, Zemel et al. [53] compared the effect of 2 isoenergetic diets supplemented with soymothes made with nonfat dry milk or soy-based placebo. They found an improvement in biomarker concentrations (TNF-α, IL-6, MCP-1 and adiponectin) in subjects consuming the dairy-based smoothies.

In another study with a 3-month follow-up in healthy obese women, it was reported that weight reduction led to a decrease in soluble adhesion molecules, suggesting a downregulation of endothelial activation [54]. On the other hand, in a study carried out in overweight subjects after weight loss, Bladbjerg and et al. [55] also reported that monounsaturated fatty acids (MUFA) and low fat diets (LFD) had similar long-term effects on inflammation and endothelial cell function. A cross-sectional study of 730 overweight women aged 43–69 years from the Nurses’ Health Study [56] evaluated whether trans fatty acid intake could also affect biomarkers of inflammation and endothelial dysfunction including CRP, IL-6, soluble tumor necrosis factor receptor 2 (sTNFR-2), E-selectin, and sICAM-1 and sVCAM-1. It was found that trans fatty acid intake was positively related to plasma concentration of CRP (P<0.009), sTNFR-2 (P<0.002), E-selectin (P<0.003), sICAM-1 (P<0.007), and sVCAM-1 (P<0.001). Another study in the same cohort [57] evaluated the effect of a prudent diet and a Western diet on CRP, IL-6, E-selectin, and sICAM-1 and sVCAM-1. The results showed a negative correlation between a healthy dietary pattern and CRP, E-selectin, VCAM-1 and ICAM-1 and a positive correlation between a Western dietary pattern and the same biomarkers of inflammation similar to the results described in another study by Esmailizadeh et al. [58]. Diets rich in α-Linolenic acid (ALA) have also shown a greater decrease in E-selectin, VCAM-1, and ICAM-1 levels than other diets [59]. A randomised, crossover study in 11 healthy obese and overweight volunteers who consumed three high fat milkshakes rich in MUFA, SFA, or ω-3 PUFA showed a higher postprandial effect on NF-κB than SFA while CRP was increased in the three diets, TNF-α and VCAM tended to decrease following the meals in the three diets, and ω3-PUFA enhanced NF-κB activation compared to SFA after 6 hours of intervention [60]. It has been reported that plasma IL-6, TNF-α and VCAM-1 concentrations decreased in overweight men after a ω-6 PUFA-rich meal, while these markers increased after a SFA-rich meal [61]. In contrast, Manning et al. [62] showed that high-fat meals increased IL-6, independently of the type of fatty acid and had no impact on IL-8 and TNF-α concentrations.

Metabolic syndrome

Table 1 shows that in a 12-week parallel-group study [63] in 40 obese or overweight subjects with MetS receiving an adequate-dairy diet, TNF-α, IL-6 MCP-1 and CRP concentrations significantly reduced -35%, -21%, -24% and -47%, respectively, whereas adiponectin

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Table 1. Possibl...dishes through the analysis of human interventional trials.

| SUBJECTS | TYPE OF DIET | TIME OF INTERVENTION | EFFECT | REFERENCE |
|----------|-------------|----------------------|--------|-----------|
| Obesity  | Mediterranean-style diet. Caloric intake: 1300 kcal/day, [1250 to 1350 kcal/day] + Physical Activity. | 1-year | Weight loss: ↓ TNF-α, IL-6, P-selectin, VCAM-1, ICAM-1 | [51] |
| Healthy men and women aged 25 to 70 years. N=90 | 3 energy-restricted diets. The study compared a moderate (not low)-calorie diet with a high-calorie diet. | 48 weeks | ↓ CRP in all 3 diets | [52] |
| Overweight or mildly obese healthy men and women. Mean age: 31.0 ± 10.3 years. N=20 | 2 isoenergetic diets plus: - dairy-based smoothies (3 servings/d, made with nonfat dry milk). - soy-based placebo smoothies (3 servings/d) | 28 d, with a 4-wk washout between phase (crossover design) | ↓ TNF-α, IL-6, MCP-1, CRP and ↑ Adiponectin for dairy-supplemented diet whereas the soy exerted no significant effect. No changes for IL-15 with either of two diets. | [53] |
| Overweight individuals (men and women). Age 18–35 years. N=131 | Three diets: High-MUFA diet (20 % of energy), LFD (20–30 % of energy) and control diet or Danish diet moderated in fat (20–30 % of energy). | 6 months | MUF A and LFD: ↓ IL-6 ↓ CRP for all the diets | [55] |
| Healthy obese women, aged 19 to 68 years. N=18 | Lectures BW (4 times a day), exercise and behavioural modification (caloric restriction, especially by reducing fat intake, increasing the consumption of vegetables, legumes and grains, such as rice, and substitution of saturated with unsaturated fats). | 3 months | ↓ E-selectin and sCAM-1 and s-selectin | [54] |
| Healthy overweight women, aged 43 to 69 years. N=730 | Healthy dietary pattern: higher intake of fruit, vegetables, legumes, fish, poultry, and whole grains. Western dietary pattern: higher intake of red and processed meats, sweets, desserts, French fries, and refined grains. | Cross-sectional study | ↑ E-selectin, sCAM-1 and sICAM-1 and sVCAM-1, CRP | [56] |
| Healthy overweight women, aged 43 to 69 years. N=730 | Healthy dietary pattern: high in fruits, vegetables, tomato, poultry, legumes, tea, fruit juices, and whole grains. Western dietary pattern: rich in refined grains, red meat, butter, processed meats, high fat dairy products, sweets and desserts, pizza, potatoes, eggs, hydrogenated fats and sodas. | Cross-sectional study | Healthy dietary pattern: ↓ E-selectin, sCAM-1 and sVCAM-1, CRP | [57] |
| Healthy overweight or obese women, aged 40 to 60 years. N=486 | Healthy dietary pattern: high in fruit, vegetables, potato, poultry, legumes, tea, fruit juices, and whole grains. Western dietary pattern: rich in refined grains, red meat, butter, processed meats, high fat dairy products, sweets and desserts, pizza, potatoes, eggs, hydrogenated fats and sodas. | Cross-sectional study | Healthy dietary pattern: ↓ E-selectin, sCAM-1 and sVCAM-1, CRP | [58] |
| Men (n=20; 36 – 60 y) and women (n=3; 55 – 65 y) with moderate hypercholesterolemia (5.17 and 6.21 mmol/L) and overweight/obesity. | Three diets: a standard diet (13% saturated, 13% MUFA and 9% PUFA), a diet rich in PUFA and ALA (8% saturated, 12% MUFA and 17% PUFA) and a diet rich in PUFA and LA (8 % saturated, 12% MUFA and 16% PUFA). | 6 weeks | Diet Rich in ALA: ↑ E-selectin, VCAM-1, ICAM-1 more pronounced than the other diets | [59] |
| Healthy obese and non-obese men and women. N=11 | Three high fat milkshakes rich in MUFA, SFA, or ω3-PUFA | 6-hours | MUF A and PUFA: ↓ ICAM-1, ↓VCAM-1 SFA: ↓ VCAM-1, ↓ICAM-1 | [60] |
| Healthy obese and non-obese women. Age: 18-70 years. N=131 | Healthy dietary pattern: high in fruit, vegetables, tomato, poultry, legumes, tea, fruit juices, and whole grains. Western dietary pattern: rich in refined grains, red meat, butter, processed meats, high fat dairy products, sweets and desserts, pizza, potatoes, eggs, hydrogenated fats and sodas. | Cross-sectional study | Healthy dietary pattern: ↓ E-selectin, sCAM-1 and sVCAM-1, CRP | [57] |
| Healthy obese and non-obese women. Age: 18-70 years. N=29 | Five test meals with at least a week between each meal potato starch with or without added canola oil, olive oil, and cream and a high fibre cereal (All-bran) | 6-hours | ↑ IL-6, CRP and TNF-α for obese IL-6 levels in high fibre cereal < IL-6 levels in high-fat meals (potato, cream, olive oil and canola oil) | [62] |
| Overweight or obese men and women with MetS. Mean age: 37. N=40 | 2 weight-maintenance diets: adequate-dairy (>3.5 servings of dairy products/day) and a low-dairy (<0.5 servings of dairy products/day) diet | 12-weeks | Adequate-dairy diet: ↓ TNF-α, IL-6, MCP-1 and CRP ↓Adiponectin | [63] |
| Overweight and obese men and women with one or more risk factors for the metabolic syndrome, aged 24 to 64 years. N=99 | Energy restricted very-LC or an isocaloric conventional HC. Caloric intake for both diets: ~1433 kcal/day for women and ~1672 kcal/day for men. | 8 weeks | ↑ E- and P-selectin, ICAM-1 and VCAM-1 for both diets. ↓CRP for both diets, although decrease more for HC than LC | [64] |
| Overweight and obese men and women with one or more risk factors for the metabolic syndrome, aged 24 to 64 years. N=49 | Two diets: a LFD and a restricted-calorie LC. Caloric intake for both diets: ~1433 kcal/day for women and ~1672 kcal/day for men. | 52 weeks | ↓ E- and P-selectin, ICAM-1 and CRP improved similarly in both groups. = VCAM-1 for both diets | [65] |
| Overweight or obese men with MetS, aged 46 to 76 years. N=31 | Diet: 12–15% fat, 15–20% protein, and 65–70% complex carbohydrate, and fibre ≥ 40 g per/day + Physical Activity | 21 days | ↓ P-selectin, ICAM-1, MMP-9, MIP-1α and CRP independently of weight loss | [66] |
| Overweight subjects, men and women, with MetS, aged 30 to 65 years. N=121 | Two diets: Milk group: consume 3-5 portions of dairy products daily (milk, yogurt, cream, cheese, etc.). The control group: usual diet. | 6 months | No significant changes in IL-6, CRP, TNF-α, E-selectin for any type of diet | [67] |
Men and women with 3 or more criteria MetS. Mean age: 44. N=180

Two diets:
1. A Med Diet (high consumption of whole grains, fruits, vegetables, nuts, and olive oil)
2. A control diet or prudent diet (carbohydrates, 50%-60%; proteins, 15%-20%; total fat, 30%).

2-years
Med Diet: ↓CRP, IL-6, IL-7, and IL-18. [68]

Postpubescent girls with MetS. Mean age: 14.2 years. N=60

Two diets:
1. DASH diet menu cycles or usual dietary advice (UDA)
2. DASH diet: ↓CRP
No changes for TNF-α, IL-2, IL-6 or adiponectin concentrations for either diet. [69]

TYPE 2 DIABETES

12 subjects (men and women) diagnosed with T2DM and 20 healthy subjects (men and women).

Three diets:
1. One bolus injection of 0.33 g/kg glucose followed by a varying 30% glucose infusion.
2. Three consecutive boluses of intravenous glucose (0.33 g/kg).
3. Three consecutive boluses of intravenous glucose (0.33 g/kg)+ glutathione infusion.

Baseline, and 2 and 4 hours. Random order and separated by at least a 3-day interval (crossover design)
Control group: IL-6, TNF-α and IL-18. [72]

Diabetic obese men or women, aged 40 to 65 years. N=322

Three diets: calorie-restricted LFD; a calorie-restricted Med Diet; or a non-calorie-restricted LC diet.
Calorie-restricted: 1500 (women) and 1800 (men) Kcal/day
2-years
↓ IL-6; ↑ CRP and ↑ Adiponectin for Med Diet and LC. [73]

Obese and non-obese men and women with co-morbidities (T2DM or arterial hypertension). Age: 18 to 65 years. N=126

1000/1200 Kcal/day for women and men, respectively + physical aerobic activity.
1-year
Weight loss: ↓ sICAM-1, s-selectin and endothelin [74]

902 diabetic women in the Nurses’ Health Study.

Dietary habits (including consumption of dairy products) were evaluated using a validated FFQ
Cross-sectional study
Whole grains and bran: ↓ CRP and TNF-R2. [75]

Healthy men and women with a high risk of T2DM. Age > 65 years. N=47

During the first month, participants refrained from drinking coffee.
In the second month they consumed 4 cups coffee/d.
In the third month 8 cups/d coffee/d.
(1 cup = 150 mL)
3-months
(3-stage clinical trial)
8 cups/d coffee/d: ↓ IL-18 and ↑ adiponectin
No changes for CRP, leptin, SAA, IL-6, MIF and IL-1α. [76]

Healthy adult men between 30 and 50 years of age. N=40

Consumed 30 g ethanol per day as wine or gin
2-months with 15 days of washout each intervention
Win: ↓ leukocyte adhesion molecules expression
↓ VCAM-1 and ICAM-1
↓ CRP, IL-6, IL-1α, MIF and IL-1ra
Win and Gin: IL-1α
↓ TNF-α and IL-18
No changes for CRP, leptin, SAA, IL-6, MIF and IL-1ra. [78]

T2DM patients (men and women). N=24

Two diets:
1. MeDiet enriched in MUFAs (50 mL, 4 tablespoons EVOO/day; approximately 1L/week), or a control LFD.
12-weeks
MeDiet: ↓ICAM-1 and IL-6. [79]

CARDIOVASCULAR DISEASE

1514 men (18–87 years old) and 1528 women (18–89 years old) free of CVD.

Dietary habits (including consumption of dairy products) were evaluated using a validated FFQ
Cross-sectional study
↓14 servings of dairy products per week: ↓ CRP, IL-6, and TNF-α. [80]

339 men and 433 women, aged between 55 and 80 years at high cardiovascular risk. PREDIMED Study

Dietary habits were evaluated using a validated semi-quantitative 137-item FFQ and the administration of a 14-item questionnaire indicating the degree of adherence to the traditional MeDiet.
Cross-sectional study
Higher consumption of fruits and cereals: ↓ IL-6 EVOO; ↓ VCAM-1 Nuts: ↓ICAM-1. [24]

Men and women, between 45–84 years who were free of clinical CVD at baseline. N=6,080 participants.

Dietary habits (consumption nuts and seeds, mainly) were evaluated using a self-administered FFQ and dietary supplement form to assess the participants’ diet and supplement used.
Cross-sectional study
↓CRP, IL-6. [81]

Men and women with high risk for CVD (T2DM or 1 or 3 or more major cardiovascular risk factors). Aged between 55 and 80 years. N= 112-772 (PREDIMED Study)

Three diets:
1. MeDiet + EVOO (50 mL daily)
2. MeDiet + nuts (30 g daily)
3. LFD (reducing all types of fat and increasing consumption of lean meats, low-fat dairy products, cereals, potatoes, pasta, rice, fruits and vegetables)

3-months
1,3 and 5 years
MeDiet+EVOO or nuts: ↓ IL-6, CRP, ICAM-1, VCAM-1 at 3 and 12 months.
↓P-Selectin, IL-18, TNFR60 and TNFR80 at 1-year.
E- and P- Selectin showed trend to diminish at 3 months.
↓ IL-6, MCP-1, CRP and TNF-α also were reduced after 3 and 5 years intervention.
Leukocyte adhesion molecules: ↓CD11a, CD11b, CD49d and CD49 at 3, 12, 36 and 60 months.
Control group: ↑ MMP-9, TGF-β1, ICAM-1 at year. [84-88]

40 men volunteers with high risk for CVD. Aged> 55 y

Two diets:
1. C+M intervention: Two 20-g sachets of soluble C per day (one for breakfast and another for the afternoon snack or after dinner) (total: 40 g/d) with 250 mL M each (total: 500 mL/d)
M intervention: 500 mL M/d

4-week randomised crossover trial
↓M+ C; ↓ VLA-4, CD40, CD49d and CD16 expression of monocytes ↓P-Selectin and ICAM [91]
67 high-risk, male volunteers. Aged between 55 and 75 years  
30 g alcohol/day, the equivalent amount of DRW, RW or G  

40 healthy subjects  
4 diets:  
a single dose of RT (7.0 g of RT/kg of body weight (BW))  
TS (3.5 g of TS/kg BW)  
TSOO (3.5 g of TSOO/Kg BW and 0.25 g of sugar dissolved in water/kg BW)  
Water  
Volunteers were asked to follow a polyphenol-free diet.  

4-week randomised crossover trial (there were no washout periods between interventions).  
RW and G: ↑ IL-10  
RW, RDW and G: ↑ CD40L and CD40a. [IL-16, MCP-1, VCAM-1  
RW and RDW: ↓ ICAM-1 and ↓ IL-6. [93]  

30 g alcohol/day, the equivalent amount of DRW, RW or G  

40 healthy subjects  
4 diets:  
a single dose of RT (7.0 g of RT/kg of body weight (BW))  
TS (3.5 g of TS/kg BW)  
TSOO (3.5 g of TSOO/Kg BW and 0.25 g of sugar dissolved in water/kg BW)  
Water  
Volunteers were asked to follow a polyphenol-free diet.  

4-week randomised crossover trial (there were no washout periods between interventions).  
RW and G: ↑ IL-10  
RW, RDW and G: ↑ CD40L and CD40a. [IL-16, MCP-1, VCAM-1  
RW and RDW: ↓ ICAM-1 and ↓ IL-6. [93]  

4h Crossover trial with three-  
day washout period  
RT: ↑ IL-10  
TSO: ↓ IL-6, VCAM-1 and ↓ CD36 (monocytes) and CD11b (T-lymphocytes) expression  
RT, TS and TSOO: ↓ MCP-1, ↓ IL-10  
TS and TSOO: ↓ IL-18. [94]  

Concentrations increased by 53%. No changes were observed in subjects on a low-dairy diet. Another study [64] compared the effect of a very-low-carbohydrate diet (LC) and an isocaloric high-carbohydrate (HC) diet on inflammatory markers such as CRP and IL-6 [81]. In the large intervention PREDIMED study [74], in 7,447 healthy men (median age, 65 years) who did not have T2DM but had an elevated risk for the development of T2DM, [76], CRP, leptin, Serum amyloid A (SAA), IL-6, MIF and IL-1ra concentrations did not change. A meta-analysis of 20 cohort studies found that moderate alcohol consumption also protects against diabetes [77]. Estruch et al. [78] described the different effects of red wine and polyphenol-free gin consumption in a prospective randomised 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 showed an additional effect of decreasing CRP (-21%), VCAM-1 (-17%) and ICAM-1 (-9%) concentrations, as well as monocyte and endothelial adhesion molecules. Finally, Ceriello et al. [79] suggested that the MeDi diet supplemented with olive oil, prevents acute hyperglycaemia effects on endothelial function, inflammation and oxidative stress, and improves the action of GLP-1 in the management of T2DM.  

Cardiovascular disease  
According to several cross-sectional studies, the consumption of dairy products is inversely associated with low-grade systemic inflammation [24, 80]. As shown in Table 1, the ATTICA study [80] including 3,042 subjects without CVD, found that TNF-α (-20%), IL-6 (-9%) and CRP (-29%) concentrations were lower in subjects consuming ≥2 servings of dairy products per day than in individuals consuming ≤1 serving per day. Sala-Salvadó et al. [24] found that lower IL-6 concentrations were associated with a higher consumption of fruits and cereals. In addition, a higher consumption of nuts and extra virgin olive oil (EVOO) were correlated with lower ICAM-1 and VCAM-1 concentrations, respectively. The Multi-Ethnic Study of Atherosclerosis (MESA) reported that frequent nut and seed consumption was associated with lower levels of inflammatory markers such as CRP and IL-6 [81]. In the large intervention PREDIMED (Prevención con Dieta Mediterránea) trial including 7,447 subjects (50% men 55–80 years and 50% women, 60–80 years) with diabetes or who met at least three or more other CVD risk factors it was found that a MeDi diet rich in EVOO or nuts reduced the risk of CVD by 30% after a mean follow-up of nearly 5 years compared to a LFD [82]. This study also demonstrated that higher adherence to the MeDi diet may also exert a modulatory effect on the expression of genes related to inflammation [24, 80].
Cancer, dementia and other pathologies

In a transversal study, Souza et al. [95] investigated the relationship between the anthropometric profile (body mass index (BMI) and waist-to-hip ratio), food intake frequency, the lipid profile and fasting glycaemia and serum adipokine (adiponectin and PAI-1) and adhesion molecules levels (ICAM-1 and VCAM-1) in a subgroup of women derived from a cohort of 10,000 women. A total of 145 women over 40 years of age participated in this study. No association was found between dietary intake and the amount of calories/day ingested and serum adipokine and adhesion molecule levels. A linear correlation was found between serum VCAM-1 levels and the BMI. A cross-sectional study examined fibre intake and 17 cytokines and chemokines in 88 healthy participants in the EPIC-Italy study and observed an association between cereal fibre and decreased levels of predominantly pro-inflammatory cytokines (IL-1β, IL-4, IL-5, IL-6, IL-13, and TNF-a), although there were no associations with fruit and vegetable fibre [96]. Recently, Schmandt et al. [97] reported that weight loss (a 10%) reduces colorectal inflammation and the risk of colorectal cancer. Weight loss was associated with a significant decrease in a variety of inflammatory cytokines including TNF-a, IL-6, IL-8, and MCP-1, as well as downregulation of markers of proinflammatory pathways, prostaglandin metabolism and transcription factors.

On the other hand, the consumption of nuts has also been associated with decreased plasma concentrations of VCAM-1, ICAM-1 and sE-selectin in a crossover study in 12 healthy subjects and 12 patients with hypercholesterolemia after intaking 2 high-fat meals including 25 g of olive oil or 40 g of walnuts [98]. In addition, an interventional study has also shown significant reductions in CRP, VCAM-1 and E-selectin after dietary supplementation with α-linolenic acid (ALA) (6.5% from total energy) in 23 hypercholesterolemic patients (20 men, 26-60 years, and 3 women, 55-65 years) [99]. Finally, dietary supplementation with ALA (15 ml of linseed oil/day) for 3 months in 50 dyslipidemic patients with a mean age of 41 years, significantly decreased CRP, SAA and IL-6 concentrations by 38%, 23% and 10%, respectively. Contrarily to ω-3, ω-6 PUFA (linoleic acid) has shown to exert an inflammatory effect [100].

Conclusion

This review demonstrates that a Mediterranean-style diet rich in whole grains, fruits, vegetables, legumes, walnuts, and olive oil might be effective in reducing both the prevalence of the most frequent chronic diseases such as T2DM, CVD, obesity or MetS compared to Western dietary patterns mainly characterized by a high intake of SFA. Diet, weight loss by hypocaloric diets with different macronutrient distribution or by surgical intervention, regular practice of physical activity and healthy lifestyle seem to be associated with a reduction of the low-grade inflammatory state linked to all these diseases. Benefits in antiinflammatory status are associated with a higher consumption of dietary fibre, whole grain, ω-3 fatty acids and dairy products, among others. One of the mechanisms responsible for these protective effects is the reduction of cell adhesion molecules (VCAM-1, ICAM-1, E-and P-Selectin), chemokines, interleukins and other inflammatory biomarkers after the adoption of a healthy dietary pattern.

Thus, polices or nutritional recommendations focused on these healthy dietary patterns and healthy foods should be promoted by governments and scientific societies as tools for the prevention of CVD, diabetes, obesity, cancer or MetS, among other diseases.

Conflict of interest

The authors have no conflict of interest.

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Author contributions

Casas R and Ruiz-León AM substantially contributed to the conception and design and the drafting of the article; Estruch R critically revised the article for important intellectual content; and Casas R, Ruiz-León AM and Estruch R approved the final version of the manuscript for publication.
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