Journal of Allergy and Immunology

Review Article ISSN: 2514-4812

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 phosphatidylcholine 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 troll-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,

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Key words: *adhesion molecules, cytokines, dietary pattern, nutrition, inflammation metabolic syndrome*

Received: March 15, 2017; **Accepted:** April 25, 2017; **Published:** April 27, 2017

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 picked 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], dementia [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, chemoattractant molecules such as monocyte chemoattractant 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 smoothies 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 Esmaillzadeh *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 ω3-PUFA showed a higher postpandrial effect on NF-κβ 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-κβ 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 ncreased 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

Table 1. Possibles mechanisms by which diet can modulate immune cell activation in chronic inflammatory diseases through the analysis of human interventional trials.

SUBJECTS	TYPE OF DIET	TIME OF INTERVENTION	EFFECT	REFERENCE
	Obesity			
Healthy obese and non-obese premenopausal women aged 25 to 44 years. N=96	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 obese. Aged 25 to 70years. N=90	3 energy-restricted diets. The study compared a moderate (not low)-calcium diet with a high-calcium 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	MUFA 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 (calorie 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	↓ sICAM-1 and sE-selectin	[54]
Healthy overweight women, aged 43 to 69 years. N=730	Effect trans fatty acid intake.	Cross-sectional study	↑ E-selectin, and sICAM-1 and sVCAM-1, CRP and sTNFR-2	[56]
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	*Healthy diet:* ↓ E-selectin, sICAM-1 and sVCAM-1, CRP *Western diet:* ↑ E-selectin, and sICAM-1 and sVCAM-1, CRP	[57]
Healthy overweight or obese women, aged 40 to 60 years. N=486	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, CRP, and sVCAM-1, CRP *Western diet:* ↑ CRP, sVCAM-1, sICAM-1, IL-6	[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	*MUFA and PUFA:* = ICAM-1, =VCAM-1 *SFA:* ↑ VCAM-1, =ICAM-1	[60]
Healthy obese and overweight men. Age: 18-70 years. N=15	Two diets: SFA: a butter meal (2 muffins providing 50 g butterfat) ω6-PUFA*:* a margarine meal (40 g margarine plus 10 g safflower oil). A crossover intervention.	8-hours	*ω6-PUFA:* ↓ IL-6, TNF-α, soluble TNF receptors I and II (sTNFr) and sVCAM-1	[61]
Healthy obese and non obese women. Age: 30–70 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 obeses IL-6 levels in high fibre cereal < IL-6 levels in high-fat meals (potato, cream, olive oil and canola oil)	[62]
	METABOLIC SYNDROME			
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: A MeDiet (high consumption of whole grains, fruits, vegetables, nuts, and olive oil) A control diet or prudent diet (carbohydrates, 50%-60%; proteins, 15%-20%; total fat, 30%).	2-years	*MeDiet:* ↓CRP, IL-6, IL-7, and IL-18	[68]
Postpubescent girls with MetS. Mean age: 14.2 years. N=60	Two diets: DASH diet menu cycles or usual dietary advice (UDA)	6-weeks (4-weeks washout) (crossover clinical trial)	*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 bolus of intravenous glucose (0.33 g/kg). 3. Three consecutive bolus of intravenous glucose (0.33 g/kg)+ glutathione infusion.	Baseline, 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 MeDiet; or a non calorie-restricted LC diet. Calorie- restricted : 1500 (women) and 1800 (men) Kcal/day	2-years	↓ CRP and ↑ Adiponectin for MeDiet 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, sE-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-1ra	[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 *Win and Gin*: IL-1α No changes in E-Selectin, TNF-α and MCP-1 concentrations with either beverage.	[78]
T2DM patients (men and women). N=24	Two diets: 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 3 or more major cardiovascular risk factors). Aged between 55 and 80 years. N= 112-772 (PREDIMED Study)	Three diets: MeDiet + EVOO (50 mL daily) MeDiet + nuts (30 g daily) 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 CD40 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: 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 CD36 expression of monocytes ↓P-Selectin and ICAM	[91]

67 high-risk, male volunteers. Aged between 55 and 75 years	30 g alcohol/d, the equivalent amount of DRW, RW or G	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]
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.	6h Crossover trial with three-day washout period	*RT:* ↑ IL-10 TSOO: ↓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]

BW : Body Weight, C: Cocoa Powder, DRW: Dealcoholized Red Wine, EVOO: Extra Virgin Olive Oil, FFQ: Food Frequency Questionnaire, G: Gin, HC: High-Carbohydrate Diet, LA: Linolenic Acid, LC: Low-Carbohydrate Diet, LFD: Low Fat Diet, M: Skim Milk, Mets: Metabolic Syndrome, Mediet: Mediterranean Diet, MUFA: Monounsaturated Fatty Acids, PUFA: P, RT: Raw Tomatoes, RW: Red Wine, SAA: Serum amyloid A; SFA: Saturated Fatty Acid, TS: Tomato Sauce, TSOO: Tomato Sauce With Refined Olive Oil, T2DM: Type 2 Diabetes Mellitus

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) in men and women with overweight or obesity on markers of endothelial function and CVD risk in the short-term. The results showed a decrease in endothelial markers, E- and P- selectin and ICAM-1 (P< 0.001), independently of the diet and observed a small, albeit significant, increase in VCAM-1. However, a similar study with a LFD and a LC diet showed an improvement in adiponectin and E-Selectin levels in both groups (P < 0.01 for time) in the long-term [65], although ICAM-1 only decreased with the LC diet and no changes were observed in VCAM-1. In addition, in overweight or obese men with MetS, Roberts and *et al.* [66] showed a reduction in oxidative stress and inflammatory parameters or markers related to vulnerability plaque such as MMP-9, after one month of intervention with diet and physical exercise, independently of weight loss since the magnitude of weight loss was minimal. A parallel-group intervention study [67] reported no changes in CRP, IL-6 and TNF-α concentrations with either of two diets (a diet based on the consumption of 3–5 portions of dairy products daily and control group) after 6 months of intervention in 121 overweight subjects with MetS. On the other hand, a randomised, single-blind trial assessed the effect of a MeDiet on endothelial function and vascular inflammatory markers in 180 patients with the MetS after two years of follow-up [68]. The findings showed that serum concentrations of CRP, IL-6, IL-7, and IL-18 had significantly reduced in patients consuming the MeDiet and the endothelial function score improved in the intervention group but remained stable in the control group. Finally, the CRP levels of teenagers with MetS reduced after six weeks of a Dietary Approaches to Stop Hypertension (DASH) diet, independently of weight loss or the lipid profile. Nonetheless, there was no significant modification in TNF-α, IL-2, IL-6 or adiponectin levels in this population [69].

Type 2 diabetes

As shown in **table 1**, several observational [70] and interventional [71] studies have reported that high intake of refined grains causes rapid swings in blood glucose and insulin concentrations, may increase hunger, and elevate free fatty acid levels thereby promoting hyperglycaemia and increasing circulating levels of free radicals and proinflammatory cytokines such as IL-6, IL-18, and TNF-α [72]. On the other hand, Shai and *et al.* [73] compared the effectiveness and safety of three weight-loss diets on healthy obese individuals over 2 years of intervention. The diets were: a calorie- restricted LFD, a calorie- restricted MeDiet or a non– calorie- restricted LC diet,. After a weight loss of 4.7 kg in the LC diet, 4.4 kg for the MeDiet and 2.9 kg in the LFD, CRP levels decreased in both the LC diet and the MeDiet. Moreover, the results of weight loss due to laparoscopic gastric banding indicate that weight loss is more important than glycaemic control in regulating circulating levels of ICAM-1, endothelin-1, E-selectin in morbidly obese subjects [74]. In the Nurses' Health Study [75] including 902 diabetic women 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) were observed after whole grain and bran intake. While a significant decrease in IL-18 and a significant increase in adiponectin concentrations were observed in an interventional study with coffee carried out in 47 subjects under the age of 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%) levels, as well as monocyte and endothelial adhesion molecules. Finally, Ceriello *et al.* [79] suggested that the MeDiet 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. Salas-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 MeDiet 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 MeDiet may also exert a modulatory effect on the expression of genes related to plaque stability, such as MMP-9, even after a short-term in an elderly high-risk population [83]. After a 3- and 12-month and 3- and 5-year intervention, the MeDiet also demonstrated anti-inflammatory effects on the expression of adhesion molecules in 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), all of which are related to the atherosclerotic process [84-88]. In particular, antioxidants and polyphenols have been shown to exert a protective role against ischaemic CVD mainly due to their anti-inflammatory properties [89,90]. Monagas *et al.* [91] studied the effect of a 4-week randomised crossover trial with 40 g cocoa powder in skimmed milk daily vs. skimmed milk alone in 42 older subjects with high cardiovascular 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. Also a recent critical review [92] including 33 randomised clinical trials 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. Furthermore, Chiva-Blanch *et al.* [93] also reported that red wine and gin interventions increased anti-inflammatory IL-10 and decreased IL-16, while red wine but not gin decreased IL-6 plasma concentrations in high cardiovascular risk patients. Valderas-Martinez *et al.* [94] carried out a randomised, controlled feeding intervention trial to evaluate the postprandial effects of a single dose of raw tomato (RT), tomato sauce cooked without oil (TS) and tomato sauce cooked with refined olive oil (TSOO) on markers of inflammation and CVD. They found that tomato intake decreased some inflammatory biomarker concentrations such as LFA-1, IL-6, IL-18, MCP-1 and VCAM-1, and increased plasma IL-10 concentrations. Moreover, their findings demonstrated that tomato, especially that cooked and enriched with oil, enhanced the effects of tomato intake on the cardiovascular system, since the effects of TSOO on plasma inflammatory biomarker concentrations were greater than those of RT and TS.

Cancer, dementia and other pathologies

In a tranversal 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-α), 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-α, 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% and10%, respectively. Contrarily to ω-3, ω-6 PUFA (linoleic acid) has shown to exert an inflammatory effect [100].

Brymora *et al.* [101] reported that a low-fructose diet in subjects (n=28, age 59 ± 15 years, 17 males/11 females) with chronic kidney disease can reduce inflammation (CRP and ICAM-1), and may also have potential benefits on blood pressure after 6 weeks of follow-up. In a recent comparative study, Gasbarrini *et al.* [102] evaluated innate and adaptive immunity expression in celiac disease and non-celiac gluten sensitivity. Their results demonstrated that subjects with celiac disease had a higher presence of IL-6 and IL-21 and adaptive immunity markers, while subjects with non-celiac gluten sensitivity showed an increase in the expression of TLR-2, an innate immunity marker, compared to patients with celiac disease.

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.

Acknowledgements

This work has been partially supported by PIE14/00045 from the Instituto de Salud Carlos III, Spain.

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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