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

Chiva-Blanch G *et al*. Cell activation and diet

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**Abstract**

Protein energy malnutrition is the main cause of immunodeficiency and, secondarily, of several infections. However, immune cell activation is involved in several pathophysiological processes that play a crucial role in the appearance of cardiovascular disease or cancer. The aim of this review is to update the knowledge of the modulation of immune cell activation by different dietary patterns and its components focusing on cardiovascular disease or cancer. While a westernized high-saturated fat high-carbohydrate diet is positively associated with low-grade inflammation, vegetable- and fruit-based diets rich in monounsaturated fatty acids, polyunsaturated fatty acids and polyphenols, key nutrients of Mediterranean diet, decrease the levels of cellular and circulating inflammatory biomarkers thereby reducing the risk of related chronic diseases.

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**Key words:** Mediterranean diet; Immune cell activation; Leukocyte adhesion; Inflammation; Fatty acids; Fruits; Vegetables; Polyphenols; Cardiovascular disease; Cancer

**Core tip:** Immune cell activation is involved in several pathophysiological processes that play a crucial role in the appearance of cardiovascular disease or cancer. The aim of this review is to update the knowledge of the modulation of immune cell activation by different dietary patterns. A westernized high-saturated fat high-carbohydrate diet is positively associated with low-grade inflammation, but a Mediterranean diet, rich in vegetables and fruits decrease the levels of cellular and circulating inflammatory biomarkers thereby reducing the risk of related chronic diseases.

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**INTRODUCTION**

Although some food compounds can originate several immune reactions such as allergies or celiac disease[[1](#_ENREF_1)], most of nutrients in the diet are essential for maintaining the function of immune cells. Thus, protein energy malnutrition is the main cause of immunodeficiency worldwide[[2](#_ENREF_2)] and deficits of nutrients commonly included in the diet such as vitamin E, vitamin C, β-carotene, selenium, copper, iron and zinc modify different immune functions related to infections caused by bacteria, viruses or parasites. A deficiency in vitamin E diminishes the ability of the immune system to respond to infectious microorganisms and under some conditions, a pharmacological level of vitamin E is needed to achieve an optimal immune response suggesting that the Recommended Dietary Allowances (RDA) for vitamin E might not be adequate for immunological vigor and health[[3](#_ENREF_3)]. Therefore, the knowledge of the effects of nutrition on immune function now extends beyond clinical nutrient deficiency. A growing body of literature demonstrates the immune benefits of increasing the intake of some specific nutrients. Compared with human infants fed formula without nucleotides, infants fed breast milk or formula supplemented with nucleotides had higher natural killer (NK) cell activity and interleukin (IL)-2 production[[4](#_ENREF_4)] and consequently, improved immune function. On the other hand, in an elderly population, zinc supplementation eliminated the effect of seasonal variations on the incidence of infections and also decreased their mean incidence compared to a placebo group (common cold, cold sores, and the flu)[[5](#_ENREF_5)].

In addition to protection against infections, immune cell activation is involved in several pathophysiological processes. Cell activation is a complex process, implying several plasma membrane-associated events in which chemokines and adhesion molecules play a pivotal role. These processes ultimately result in proliferation, target cell lysis, increased production of cytokines and the expression of immune cell activation markers.

Many chronic diseases, such as atherosclerosis, cancer, neurodegenerative disorders, rheumatoid arthritis, and even aging, are due to chronically increased pro-inflammatory cytokines and oxidative stress, and in consequence, due to immune cell activation. Therefore, dietetic strategies to decrease low-grade inflammation and immune cell activation may be useful tools for preventing or decreasing the progression of many chronic disorders.

Many studies have focused on the mechanisms by which one single nutrient or compound alters immune cell activation, but these studies have the limitation that the interactions between the different compounds of food are not considered. There is an increasing interest to consider a whole dietary pattern in addition to single compounds in order to have a holistic approach of the effects of diet on cell activation.

The aim of this review is to update the knowledge of the modulation of immune cell activation by diet and its components from a chronic disease point of view through human interventional studies, those which provide the greatest scientific evidence.

**EFFECTS OF DIET ON INFLAMMATORY CHRONIC DISEASES**

Chronic inflammatory diseases are defined by long-term inflammatory processes directed at a particular endogenous or exogenous antigen and considered as an underlying pathophysiological mechanism linking behavioral factors and obesity to risk of chronic disease. Inflammation is characterized by a complex biological cascade of molecular and cellular signals that alter physiological responses. At the site of the injury, cells release molecular signals such as cytokines that cause a number of changes in the affected area, such as dilation of blood vessels, increased blood flow, increased vascular permeability, exudation of fluids containing antibodies and invasion by monocytes and macrophages and, to a lesser extent, lymphocytes, through the expression of integrins and other adhesion molecules. In addition, lesion progression is associated with the predominance of the proinflammatory M1 over the antiinflammatory M2 macrophage phenotype, which can be switched to M1 by several transcription factors, chemokines and lipid accumulation in macrophages[[6](#_ENREF_6),[7](#_ENREF_7)].

Elevated levels of inflammatory biomarkers such as C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), IL- 6 and 18, fibrinogen and adhesion molecules [E-selectin, intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion protein 1 (VCAM-1)] have been shown to predict type 2 diabetes, cardiovascular disease (CVD) and cancer[[8-13](#_ENREF_8)]. In this setting, the activation of the inflammasome has been linked to the pathogenesis of obesity, type 2 diabetes and atherosclerosis[[14-19](#_ENREF_14)]. Several studies have suggested that the development of tolerance and control of inflammation are strongly correlated with specific immune mechanisms that may be altered by an inadequate supply of either macronutrients or micronutrients. Therefore, the intake of some nutrients or specific dietary patterns may influence the concentrations of inflammatory biomarkers and therefore, the risk and/or progression of inflammatory diseases.

A westernized high-fat high-carbohydrate diet is positively associated with low-grade inflammation, and therefore, contributes to disease development and progression. Likewise, these types of diets can have direct adverse effects on human physiology[[20](#_ENREF_20)] resulting in chronic immune and inflammatory imbalances. Overall, the intake of a high-fat, high-carbohydrate westernized diet has potent direct and indirect effects on local as well as systemic inflammation. This has led to a dramatic upswing in the incidence of inflammatory diseases such as rheumathoid arthritis, inflammatory bowel disease, diabetes, and non-alcoholic fatty liver disease, among others[[21](#_ENREF_21)]. On the other hand, vegetable- and fruit-based diet and a priori healthy dietary patterns appeared to be inversely related to inflammatory biomarkers; this fact is particularly well supported by intervention studies investigating the effects of Mediterranean diet on health.

**EFFECTS OF DIET ON CARDIOVASCULAR DISEASE AND METABOLIC SYNDROME**

CVD is the main cause of mortality worldwide and is principally caused by the appearance and progression of atherosclerotic lesions. Although atherosclerosis has been historically considered an oxidative disease, nowadays it is considered a systemic disease characterized by low-grade arterial inflammation, in which the cell and endothelial expression of adhesion molecules and chemokines participate in the recruitment of circulating leukocytes to the vascular endothelium and further migration into subendothelial spaces. In addition, the metabolic syndrome is a risk factor CVD, which also has an immunological and inflammatory component. Immune cell infiltration of adipose tissue giving rise to chronic low-grade inflammation is, in-part, responsible for the pathogenesis of insulin resistance in obesity[[22](#_ENREF_22)] and lastly, CVD.

As explained before, the western diet enriched in total fat (and an imbalanced ratio of n-6:n-3[[23](#_ENREF_23)]), animal protein, n-6 polyunsaturated fatty acids (PUFA) and refined sugars, leads to an increased proinflammatory status[[24](#_ENREF_24)] and is, therefore, considered as a risk factor for the development of CVD[[25](#_ENREF_25)]. On the other hand, several studies have highlighted that a Mediterranean-like diet decreases cardiovascular risk[[26-29](#_ENREF_26)], by up to 30% in a high cardiovascular risk population[[30](#_ENREF_30)]. Several mechanisms have been proposed for the effects observed, and some of them, which will be discussed below, are related to immune cell activation.

While n-6 PUFA have been shown to exert an inflammatory effect[[31](#_ENREF_31)], it has been demonstrated that n-3 PUFAs have beneficial effects on cardiovascular and inflammatory diseases[[32](#_ENREF_32),[33](#_ENREF_33)], probably linked to the NFκB pathway[[34](#_ENREF_34)] and the inhibition of the inflammasome activation[[35](#_ENREF_35)]. Meta-analyses of randomized controlled trials studying the n-6 PUFA-specific effect on cardiovascular diseases[[36](#_ENREF_36)] showed a direct effect of n-6 fatty acids on the risk of non fatal and fatal heart failure, although linoleic acid could not be linked to an increase in systemic inflammatory biomarkers[[37](#_ENREF_37)]. Hypercholesterolemic subjects receiveing 2 diets low in saturated fat and cholesterol, and high in PUFA varying in α-linolenic acid (10.5% linoleic acid; 6.5% α-linolenic acid) and linoleic acid (12.6% linoleic acid; 3.6% α-linolenic acid) were compared with other who followed an average American diet (7.7% linoleic acid; 0.8% α-linolenic acid). The α-linolenic acid diet decreased circulating CRP, VCAM-1 and E-selectin plasma concentrations, and the 2 high-PUFA diets similarly decreased ICAM-1[[38](#_ENREF_38)], although other studies in hypercholesterolemic subjects observed no such results[[39](#_ENREF_39)]. In healthy women, a 2-wk intervention of a n-3 PUFA-enriched juice or a plain tomato juice decreased VCAM-1 levels but only the n-3 PUFA-enriched juice decreased ICAM-1 plasma concentrations[[40](#_ENREF_40)]. In addition, a high monounsaturated fatty acid (MUFA) intake has also been shown to exert anti-inflammatory effects. A crossover feeding trial observed that a breakfast rich in butter (saturated fatty acids, SFA) increased leukocyte mRNA expression of TNF-α compared to an olive oil (rich in MUFA, and concretely oleic acid) or walnut breakfast (rich in PUFA n6)[[41](#_ENREF_41)]. On the other hand, in overweight men, a low-fat and a very-low-carbohydrate diet resulted in significant decreases of TNF-α, IL-6, CRP and sICAM-1 but not P-Selectin[[42](#_ENREF_42)], although in another study with overweight or obese women with metabolic syndrome, the substitution of carbohydrates by PUFA resulted in no changes in CRP, TNF-α, IL-6, sICAM-1 and sVCAM-1 serum concentrations [[43](#_ENREF_43)]. It can be summarized that the overall quantity of fat intake, the sources and type of dietary fat, with special emphasis on α-linolenic acid and oleic acid, and the ratio of n-6:n-3 fatty acids in the diet, collectively play a crucial role in modulating inflammation.

Other dietetic compounds influencing immune cell activation are polyphenols. These products are antioxidant phytochemicals that have been found in vegetables, fruits and derivatives such as cocoa, red wine or tea, shown to decrease TNF-α and CRP levels[[44](#_ENREF_44)]. In healthy volunteers cocoa consumption reduced nuclear factor (NF)-κB activation in peripheral blood mononuclear cells[[45](#_ENREF_45)], and in men at high CVD risk, cocoa consumption decreased monocyte expression of very late antigen (VLA)-4, CD40 and CD36 and serum concentrations of P-selectin and ICAM-1[[46](#_ENREF_46)]. Grape polyphenols and specially resveratrol are among the polyphenols most frequently studied. In hemodialysis patients, red grape juice supplementation for 3-wk significantly reduced plasma monocyte chemoattractant protein 1 (MCP-1)[[47](#_ENREF_47)], and in overweight or obese subjects with metabolic syndrome, grapefruit supplementation for 6-wk decreased F2-isoprostane concentrations in those subjects with high baseline F2-isoprostane concentrations, but no changes in CRP and VCAM-1 were observed[[48](#_ENREF_48)]. These results suggest different responses to polyphenol intake depending on the pathophysiological conditions of the study subjects and probably the type of polyphenols administered in the intervention group. These differential effects were also observed after moderate red wine consumption, where in healthy male volunteers red wine consumption significantly reduced plasma concentrations of VCAM-1, ICAM-1 and IL-1α and VLA-4 lymphocyte expression and lymphocyte function-associated antigen (LFA)-1, Mac-1, VLA-4 and MCP-1 monocyte expression[[49](#_ENREF_49)]. On the other hand, in high cardiovascular risk subjects, moderate red wine consumption and dealcoholized red wine consumption (therefore, the non alcoholic fraction of red wine, mainly polyphenols) decreased serum concentrations of CD40 antigen, CD40 Ligand, ICAM-1, E-Selectin, IL-16 and IL-6, MCP-1 and VCAM-1 and inhibited the expression of LFA-1 in T-lymphocytes and Mac-1, SLex and CCR2 expression in monocytes[[50](#_ENREF_50)].

In the recent years, the effects of a Mediterranean diet (MedDiet) as a dietary pattern and not a sum of nutrients have been considered from a multidisciplinary point of view. The MedDiet is characterized by a high intake of cereals, fruit and vegetable products (and therefore, polyphenols), a moderate consumption of fish, olive oil, nuts and wine, and a low intake of meat and dairy and industrial bakery products[[51](#_ENREF_51)]. According to scientific evidence, the MedDiet is currently considered the more anti-inflammatory dietary pattern, and this is translated to a decreased risk in cardiovascular mortality[[30](#_ENREF_30)]. In patients with metabolic syndrome, a 2-yr follow-up MedDiet reduced serum concentrations of CRP, IL-6, IL-7 and IL-18, accompanied with decreased insulin resistance and an improved endothelial function score[[52](#_ENREF_52)]. In older subjects with diabetes or ≥ 3 CVD risk factors randomly allocated to a 3-mo Med-Diet with supplemented with extra-virgin olive oil, a MedDiet supplemented with nuts and low-fat diet, after both MedDiets CRP, IL-6, ICAM-1 and VCAM-1 plasma concentrations decreased as did CD40 and CD49d monocyte expression, whereas IL-6, ICAM-1 and VCAM-1 increased after the low-fat diet[[26](#_ENREF_26)]. In addition, after 1 year both MedDiet groups showed lower plasma concentrations of IL-6, TNFR60, and TNFR80, whereas ICAM-1, TNFR60, and TNFR80 concentrations increased in the low-fat diet group[[27](#_ENREF_27)]. The MedDiet has also shown anti-inflammatory effects in healthy subjects. Four weeks of a MedDiet compared to an ordinary Swedish diet decreased the number of platelets and leukocytes and serum concentrations VEGF, although it did not change the CRP and IL-6 concentrations[[28](#_ENREF_28)], perhaps because of their low baseline concentration. Interestingly, in a middle-aged twin population, adherence to a MedDiet was highly associated with lower levels of IL-6 but not CRP[[29](#_ENREF_29)]. Overall, the MedDiet has an antiinflammatory and an inhibitory immune cell activation effect decreasing the onset and progression of CVD, while a low-fat diet or a westernized diet has the opposite effect.

**EFFECTS OF DIET ON CANCER**

Cancer is the second cause of mortality worldwide and is mediated by both the innate (nonspecific) and acquired (specific) immune systems[[53](#_ENREF_53),[54](#_ENREF_54)]. The molecular mechanisms by which chronic inflammation drives cancer initiation and promotion include increased production of pro-inflammatory mediators, such as cytokines, chemokines, reactive oxygen intermediates, increased expression of oncogenes, cyclooxygenases, lipoxygenases and MMPs (matrix metalloproteinases), and pro-inflammatory transcription factors such as NF-κB, that mediate tumor cell proliferation, transformation, metastasis, survival, invasion, angiogenesis, chemoresistance and radioresistance[[55](#_ENREF_55)]. Taking into account that adherence to ideal cardiovascular health, as proposed by the American Heart Association, is associated with a lower incidence of cancer[[56](#_ENREF_56)], one may suspect that dietary benefits on CVD may reduce the risk of cancer.

Although epidemiological studies have pinpointed that diet may influence more than one-third of human malignancies, probably through the high consumption of pesticides[[57](#_ENREF_57)], heavy metals[[58](#_ENREF_58)], heterocyclic amines from over-cooked meats and sex steroid hormones[[59](#_ENREF_59)], few interventional trials have focused on the modulation of angiogenesis and carcinogenesis through dietary patterns. A recent review[[60](#_ENREF_60)] of epidemiological studies concluded that there is no significant effect of n:3 PUFA on cancer risk. However these studies only accounted for absolute as opposed to relative levels of n:3 and n:6 PUFA. In fact, n:6 PUFA metabolites promote tumor angiogenesis through a variety of signaling pathways, encouraging epithelial cell proliferation and migration, and decreasing tumor apoptosis, while n:3 PUFA and their metabolites can reverse the pro-angiogenic consequences of high n:6 fatty acids. On the other hand, a MedDiet supplemented with nuts and walnuts (rich in n:6 and polyphenols) also associated with a high intake of vegetables, fruit and fish, decreased the risk of cancer mortality[[61](#_ENREF_61)].

Intake of total catechin, epicatechin, kaempferol, and myricetin and consumption of black tea were associated with a decreased risk of stage III/IV or stage IV prostate cancer in the Netherlands Cohort study[[62](#_ENREF_62)], probably because of the anti-inflammatory and antiproliferative effects of flavonoids observed *in vitro*[[63](#_ENREF_63)]. In prostate cancer men, 30 d of low-fat diet decreased 19 cytokines and angiogenic factors including proangiogenic factors (stromal-cell derived-1α) and myeloid factors (granulocyte-colony-stimulating factor -GC-SF-, macrophage colony-stimulating factor -M-CSF-) and vascular endothelial growth factor (VEGF), probably through the NF-κB pathway[[64](#_ENREF_64)]. Regarding breast cancer, diets high in n-6 PUFA have a clear stimulating influence on breast cancer development, whereas diets rich in extra virgin olive oil mainly have a negative modulatory effect[[65](#_ENREF_65)]. A recent meta-analysis[[66](#_ENREF_66)], showed a significant inverse association with the highest fiber intakes and the risk of esophageal cancer, probably through weight control and therefore, inflammation status control. The isothiocyanate sulforaphane [SF; 1-isothiocyanato-4(R)-methylsulfinylbutane] is abundant in broccoli sprouts in the form of its glucosinolate precursor (glucoraphanin). SF is powerful bactericidal against *Helicobacter pylori* (*H. pylori*) infections, which are strongly associated with the worldwide pandemic of gastric cancer. *H. pylori*-infected patients were randomly assigned to feeding of broccoli sprouts (70 g/d; containing 420 micromol of SF precursor) for 8 weeks or to consumption of an equal weight of alfalfa sprouts (not containing SF) as placebo. Intervention with broccoli sprouts, but not with alfalfa, decreased the levels of urease measured by the urea breath test and *H. pylori* stool antigen (both biomarkers of *H. pylori* colonization) and serum pepsinogens I and II (biomarkers of gastric inflammation). Therefore, daily intake of sulforaphane-rich broccoli sprouts for 2 mo enhanced the chemoprotection of the gastric mucosa against *H. pylori*[[67](#_ENREF_67)]. In colorectal cancer (CRC) patients, drinking a slurry of black raspberry powder 3 times-a-day for 9 wk increased granulocyte macrophage colony-stimulating factor (GM-CSF) and decreased IL-8 plasma concentrations and CD105 colorectal tissue expression[[68](#_ENREF_68)], while in another large CRC cohort, red and processed meat intake before CRC diagnosis was associated with higher risks of death due to all causes and from CVD but not CRC. Although red and processed meat consumption after CRC diagnosis was not associated with mortality, survivors with consistently high (median or higher) intakes before and after diagnosis had a higher risk of CRC-specific mortality compared with those with consistently low intakes[[69](#_ENREF_69)]. Nonetheless, it should be taken into account that, in addition to the diet, colon cancer risk is influenced by the balance between microbial production of health-promoting metabolites and potentially carcinogenic metabolites[[70](#_ENREF_70)]. In summary, few interventional studies have been performed investigating the link between diet, immune cell activation and cancer, but it can be postulated that a MedDiet brings together all the dietary protective nutrients related to cancer and specially cancers of the digestive system decreasing its risk of appearance[[71](#_ENREF_71)], although there are still not enough data to develop guidelines regarding specific foods and cancer risk.

**FUTURE PERSPECTIVES**

Dietary intake in relation to low-grade inflammation has been investigated in a number of studies exploring nutrients, foods or dietary patterns. Although there is increasing evidence that dietary patterns modulate immune cell activation and low-grade systemic inflammation, there is still a long way to understand the interactions between dietary compounds, dietary patterns, microbiota metabolites and individual polymorphisms and how these affect the body response to the intake of a determined food compound. The integration of dietary behaviors is warranted, given the fact that nutrients or foods are rarely eaten alone, and dietary patterns consider synergistic or antagonistic biochemical interactions among nutrients as well as different food sources of the same nutrient.

**CONCLUSION**

As summarized in Figure 1, there is compelling scientific evidence that a Mediterranean Diet rich in MUFA, PUFA (with an adequate ratio of n3:n6), polyphenols and with mild-to-low carbohydrate, animal protein and SFA content is the most effective pattern to prevent immune cell activation and inflammation related to chronic diseases by decreasing the expression of leukocyte adhesion molecules and circulating inflammatory biomarkers.

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**Figure 1** **Summary of the anti-inflammatory effects of the Mediterranean Diet.**

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