Review Article

The effect of nuts on inflammation

Jordi Salas-Salvadó MD PhD[1], Patricia Casas-Agustench BSc[1], Michelle M Murphy PhD[2], Patricia López-Uriarte BSc[1] and Monica Bulló PhD[1]

[1]*Human Nutrition Unit, Department of Biochemistry and Biotechnology, Sant Joan Hospital, Faculty of Medicine and Health Sciences, Universitat Rovira i Virgili, Reus, Spain*
[2]*Unit of Preventive Medicine and Public Health, Department of Basic Medical Sciences, Faculty of Medicine and Health Sciences, Universitat Rovira i Virgili, Reus, Spain*

Inflammation is one of the recognised mechanisms involved in the development of atherosclerotic plaque and insulin resistance. Inflammatory or endothelial markers such as C-Reactive Protein (CRP), Interleukin-6 (IL-6), fibrinogen, Vascular Cell Adhesion Molecule-1 (VCAM-1) and Intracellular Adhesion Molecule-1 (ICAM-1) have been identified as independent predictors of cardiovascular disease (CVD) or diabetes in human prospective studies. Epidemiological and clinical studies suggest that some dietary factors, such as n–3 polyunsaturated fatty acids, antioxidant vitamins, dietary fiber, L-arginine and magnesium may play an important role in modulating inflammation. The relationship observed between frequent nut consumption and the reduced risk of cardiovascular mortality and type 2 diabetes in some prospective studies could be explained by the fact that nuts are rich in all of these modulator nutrients. In fact, frequent nut consumption has been associated with lower concentrations of some peripheral inflammation markers in cross-sectional studies. Nut consumption has also been shown to decrease the plasma concentration of CRP, IL-6 and some endothelial markers in recent clinical trials.

Key Words: nuts, inflammation, endothelial function, insulin resistance

INTRODUCTION

Several large epidemiological studies have associated the frequency of nut consumption with reduced risk of coronary heart disease (CHD), CVD, myocardial infarction, sudden death, and all causes of mortality, Type 2 diabetes (T2D) and other chronic disease.[1]

In the last two decades, a considerable number of clinical trials have consistently demonstrated beneficial effects on blood lipids and lipoproteins, primarily a decrease in Low-density lipoprotein (LDL) cholesterol, a classical CHD risk factor. This effect has been demonstrated consistently in different population groups, using different types of nuts (walnuts, hazelnuts, almonds, pecan, pistachio and macadamia nuts) and study designs. The favourable effects of tree nuts or tree nut oils on plasma lipid and lipoprotein profiles is a mechanism that appears to account for some of the cardio protective effects observed in the epidemiological studies.[2]

However, after analysing the predicted effect of changes in plasma lipoprotein profile induced by tree nut consumption on CHD mortality, some authors concluded that nuts only contribute to part of the total reduction in CHD mortality observed in epidemiological studies by this mechanism.[3] Hence, nuts have favourable effects on cardiovascular diseases probably via several other mechanisms such as: a) decreasing susceptibility to LDL oxidation, b) decreasing inflammation processes, c) improving endothelial function, and d) improving insulin sensitivity. The last three mechanisms are analysed in the present review.

Chronic inflammation has been shown to be involved in the aetiology and development of atherosclerosis plaque. In fact inflammation has been involved in each of the different stages of atherosclerosis. The earliest atherosclerotic lesion is almost purely an inflammatory lesion consisting of monocyte-derived, lipid-laden macrophages and T-lymphocytes. During the atheroma progression and growth, activated macrophages secrete a multitude of mediators that amplify inflammation and contribute to the damage of the tissues associated with the atheroma plaque. For example, increased expression of the proinflammatory citokines IL-6, IL-1 or Tumour Necrosis Factor (TNF) was demonstrated in atherosclerotic lesions, and both monocyte-derived macrophages and activated endothelium produce proinflammatory cytokines. So, the activation of the vascular endothelium is an early inflammatory event in the development of atherosclerosis leading to endothelial dysfunction and its consequences.[4]

Not only arteries are involved in the complex scenario of chronic inflammation that occurs in high cardiovascular risk patients with atheroma plaques. Cytokines and other proinflammatory mediators are also produced in various tissues in response to infection and in the adipose tissue of patients with metabolic syndrome. IL-6 produced by these cells, in

Corresponding Author: Dr J Salas-Salvadó, Human Nutrition Unit, Department of Biochemistry and Biotechnology, Faculty of Medicine and Health Sciences, Universitat Rovira i Virgili, C/Sant Llorenç, 21, 43201 Reus, Spain
Tel: + 34 977 759 312; Fax: + 34 977 759 322
Email: jordi.salas@urv.cat
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turn, stimulates the production of large amounts of acute-phase reactants, including CRP, serum amyloid A, and fibrinogen, especially in the liver.[5]

ANTI-INFLAMMATORY NUT COMPOUNDS

Nuts are complex food matrices containing diverse macro and micronutrients and other chemical constituents that may favourably influence inflammation and endothelial function. Examples of these are, omega-3 (ω-3) polyunsaturated fatty acids, dietary fibre, magnesium, L-arginine and some antioxidants.

MAGNESIUM

Whole grains, green leafy vegetables, legumes and nuts are the principal sources of magnesium in the diet. Magnesium intake is critical in maintaining intracellular homeostasis, which has been hypothesised to be one of the common antecedents for the pathogenesis of insulin resistance and CVD. In prospective studies, dietary magnesium intake was inversely associated with the incidence of metabolic syndrome,[7] T2D,[8] hypertension[9] and CVD.[10] However, the pathophysiological mechanisms underlying these beneficial effects are not fully understood.

Cross-sectional studies have suggested an inverse association between magnesium intake and CRP peripheral concentrations.[11] In the Nurses' Health Study, magnesium intake was inversely associated with some markers of inflammation such as CRP, E-Selectin or VCAM-1.[12] Also, in this study, a negative relationship was observed between the intake of nuts and green vegetables and some inflammatory markers. Some lines of experimental evidence have also suggested that magnesium intake may have beneficial effects on endothelial function.[13] These findings have led to the suggestion that the metabolic effects of magnesium intake may be due, at least in part, to magnesium's effects on systemic inflammation.

DIETARY FIBER AND GLYCAEMIC RESPONSE

Fasting and postprandial hyperglycaemia can reduce the availability of nitric oxide[14] and increase free radical production, which also activates inflammation by modulating Protein Kinase C (PKC) and nuclear Factor-kappa B (NF-kB) function.[15] Refined starches and sugars cause a rapid increase in blood glucose and insulin levels, and a subsequent decrease in glycaemia, which leads to hunger and a decrease in fat oxidation. The intake of high glycaemic index foods is an important stimulus for inflammation via this mechanism. For the same reason, foods that contribute to a decrease in the glycaemic response to the diet can be useful in alleviating inflammation. In fact, recently nuts were shown to reduce the glycaemic impact of ingested carbohydrate-rich foods,[16] due to their high fibre and unsaturated fat content.[17]

A cross-sectional study performed in diabetic patients from the Health Professionals' Follow-Up Study supports this hypothesis. In this study, subjects whose diets had a low glycaemic load and were high in dietary fibre, had higher plasma levels of adiponectin, a molecule with anti-inflammatory properties that protects against diabetes and atherosclerosis.[18] Also recently, in two more cross-sectional studies, plasma levels of CRP have been observed to be negatively related to total fibre intake in 524 healthy adult subjects[19] and in patients with diabetes, hypertension or obesity from the NHANES study.[20] These associations were maintained when variables were adjusted for other confounding dietary and non dietary factors. Some intervention studies support the hypothesis that fibre can improve inflammation.[21] In fact, recent epidemiological studies suggest that a high consumption of dietary fiber or cereals decreases the risk of diabetes or atherosclerosis and is associated with a decrease in weight gain.[22,23]

ω-3 FATTY ACIDS (ALFA-LINOLENIC FATTY ACID)

It has been suggested that omega-6 (ω-6) substitution by ω-3 fatty acids can improve the synthesis of eicosanoids that have fewer inflammatory properties. Several anti-inflammatory effects have been proved with omega-3 fatty acids, especially those derived from marine sources (eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)). However, there is also substantial evidence that ω-3 of plant origin such as from walnuts, flaxseed or canola oil leads to similar anti-inflammatory effects compared to marine ω-3 fatty acids.

In an experimental study on human monocytic THP-1 cells,[24] it was observed that polyunsaturated fatty acids have an inhibitory effect on LPS-stimulated inflammatory response, with alpha-linolenic acid (ALA) and DHA being more beneficial than linoleic acid (LA). Several cross-sectional studies support the hypothesis that ω-3 fatty acid intake, especially in the form of EPA and DHA, have anti-inflammatory properties.[25-27] Furthermore, total ω-3 and ALA intake was inversely associated with plasma concentrations of some inflammatory and endothelial parameters in a sample of individuals from the Nurses' Health Study.[28]

Several intervention studies also support the anti-inflammatory effect of ALA in humans. In dyslipidaemic patients, a decrease in serum concentrations of peripheral inflammatory proteins has been observed after dietary supplementation with plant ALA.[29] This anti-inflammatory effect seems to be higher when the background diet was rich in saturated fatty acid and poor in monounsaturated fatty acids (MUFA).[30] Also, after comparing three diets (average American, diet rich in LA and diet rich in ALA), and using a cross-over design, Zhao et al. observed that ALA appears to reduce CVD risk by increasing high-density lipoprotein (HDL) concentrations and inhibiting vascular inflammation and endothelial activation beyond its lipid-lowering effects.[29] The same authors show that the increase in the intake of ALA from walnuts, walnut oil and flaxseed oil elicit anti-inflammatory effects by inhibiting IL-6, IL-1β, and TNF-α production in peripheral blood mononuclear cells.[31]

ARGININE

L-arginine is the substrate for nitric-oxide synthase in the production of nitric oxide and is essential to normal endothelium-dependent vasomotion. L-arginine is an important constituent in nuts that might have a positive effect on endothelium-dependent vasodilation.[32] Wells et al. studied the association between dietary arginine and CRP in a cross-sectional study. After adjusting for age, sex,

race, exercise, total caloric intake, body mass index, smoking status, diabetes, hypertension and fiber intake, it was observed that subjects with the highest level of arginine intake were 30% less likely to have a CRP above 3.0 mg/L than were subjects with a median arginine intake. They concluded that consumption of more arginine-rich foods such as nuts and fish may reduce their cardiovascular disease risk.[33]

TREE NUTS, INFLAMMATION AND ENDOTHELIAL FUNCTION

Some evidence suggests a protective role of nuts against inflammation. Jiang et al examined the association between nut and seed consumption and inflammation in a cross-sectional study of a well-characterized multiethnic population. After adjusting for different confounding factors (age, gender, race/ethnicity, site, education, income, smoking, physical activity, use of fish oil supplements, and other dietary factors), frequent nut and seed consumption was inversely related to peripheral concentrations of CRP, IL-6, and fibrinogen.[34] In the same way, recently, in a cross-sectional study we evaluated the association between components of the Mediterranean diet and circulating markers of inflammation in a large cohort of asymptomatic subjects with high risk of cardiovascular disease.[35] Subjects with the highest consumption of nuts and virgin olive oil showed the lowest concentrations of VCAM-1, ICAM-1, IL-6 and CRP; although this difference was statistically significant for ICAM-1 only in the case of nuts (p=0.003) and for VCAM-1 in the case of olive oil (p=0.02).

Furthermore, an improvement in inflammation and endothelial function has been reported in two clinical trials analyzing the effect of nut consumption. Using a crossover design, Cortés et al. analyzed the acute effect of the intake of two meals enriched with walnuts or olive oil, containing the same quantity of fat (80 g of fat and 35% saturated fatty acids) on postprandial endothelial function in healthy subjects and patients with hypercholesterolemia. Venupunctures and ultrasound measurements of brachial artery vasomotor function were performed in fasting and 4-h postprandial conditions. In both study groups, flow-mediated dilatation worsened after the olive oil meal and improved after the walnut meal (p=0.006, time-period interaction). Moreover, soluble inflammatory cytokines and adhesion molecules decreased (p<0.01) independently of the meal type, except for E-selectin, which decreased more (p=0.033) after the walnut meal.[36] Also, in a chronic randomized crossover study comparing the effect of two diets containing 33% of calories from fat (a Mediterranean-type cholesterol-lowering diet versus a walnut-enriched diet) an increase in ultrasound measured endothelium-dependent vasodilation and a decrease in VCAM-1 was observed after the walnut-enriched diet.[32] The results of this study suggest that walnut intake could reverse endothelial dysfunction in subjects with hypercholesterolemia.

Finally, high cardiovascular risk participants from the PREDIMED trial who improved their baseline Mediterranean diet after nutritional education and supplementation with virgin olive oil or mixed nuts showed lower blood pressure, improved lipid profiles, decreased insulin resistance, and reduced concentrations of inflammatory molecules compared with those allocated to a low-fat diet.[37]

In conclusion, nuts are complex food matrices containing diverse nutrients and other chemical constituents that may favourably influence human physiology. These substances may inhibit the activation of the innate immune system, probably by decreasing the production of proinflammatory cytokines such as CRP, IL-6, TNF-α or IL-18, and increase the production of anti-inflammatory cytokines such as adiponectin. This may improve the proinflammatory milieu, which in turn ameliorates endothelial dysfunction at the vascular level, and ultimately decreases the risk of insulin resistance, type 2 diabetes and coronary heart disease. The capacity of nuts to modulate inflammation may explain at least in part why frequent nut consumption is associated with reduced risk of diabetes and cardiovascular disease in epidemiological studies.

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AUTHOR DISCLOSURES

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