

## Review

# Nuts, inflammation and insulin resistance

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The beneficial effects of nut consumption on cardiovascular disease (CVD) have been widely documented. These protective effects are mainly attributed to the role of nuts in the metabolism of lipids and lipoproteins. As chronic inflammation is a key early stage in the atherosclerotic process that predicts future CVD events and is closely related to the pathogenesis of insulin resistance, many recent studies have focused on the potential effect of nut consumption on inflammation and insulin resistance. Through different mechanisms, some components of nuts such as magnesium, fiber,  $\alpha$ -linolenic acid, L-arginine, antioxidants and MUFA may protect against inflammation and insulin resistance. This review evaluates the epidemiologic and experimental evidence in humans demonstrating an association between nut consumption and these two emergent cardio-protective mechanisms.

**Key Words:** nuts, inflammation, insulin resistance, type 2 diabetes, cardiovascular disease

## INTRODUCTION

A large body of evidence from epidemiological studies and controlled clinical trials demonstrates the multiple beneficial effects of nut consumption on CVD and other chronic conditions. In the past two decades, the favorable effect of nut consumption on plasma lipids and lipoproteins appeared to be one of the main mechanisms accounting for the cardiovascular benefits observed.<sup>1,2</sup> In recent years, however, researchers have primarily focused on studying other novel cardio-protective mechanisms of nuts, including decreasing susceptibility to LDL oxidation, decreasing inflammation processes, improving endothelial function and decreasing insulin resistance.<sup>3</sup> The purpose of this article is to review the epidemiologic and experimental evidence in human studies that show an association between nut consumption, inflammation and insulin resistance.

Chronic inflammation is a key early stage in the atherosclerotic process that predicts future CVD events.<sup>2,4</sup> Several inflammatory markers have been identified as independent predictors of diabetes or CVD in different human prospective studies.<sup>5,6</sup> In fact, it has been suggested that chronic low-grade inflammation is closely related to the pathogenesis of insulin resistance.<sup>7</sup> For example, plasma concentrations of interleukin 6 (IL-6), an important mediator of the acute-phase response, are associated with insulin resistance and its complications.<sup>8</sup> Its role favoring insulin resistance can be mediated by the activation of tyrosine phosphatase<sup>9</sup> or an interaction between a suppressor of cytokine signaling proteins and the insulin receptor.<sup>10,11</sup> Thus, circulating levels of inflammatory markers such as C Reactive Protein (CRP), interleukin 6 or tumor necrosis factor (TNF) have been related

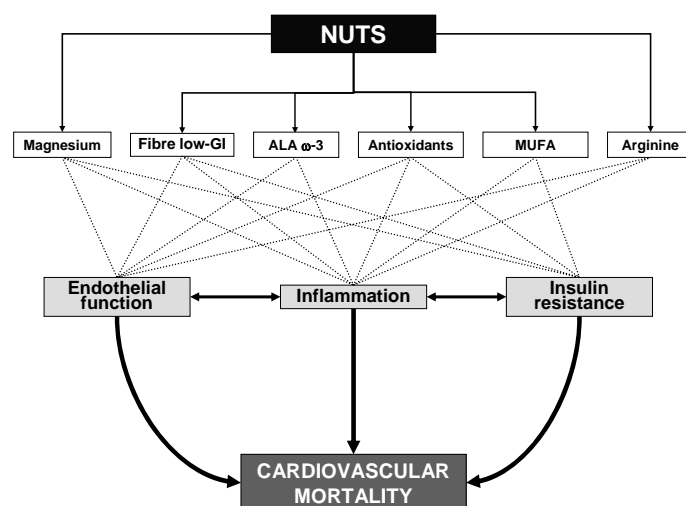
to insulin resistance and its complications.<sup>5</sup> In this scenario, because several components of nuts have been shown to be able to modulate inflammation *in vivo*, the regular consumption of nuts could protect against the possible consequences of low-grade inflammation, *i.e.* insulin resistance and diabetes.

## BIOACTIVE COMPONENTS OF NUTS THAT MODULATE INFLAMMATION AND INSULIN SENSITIVITY

Nuts comprise a complex food group containing diverse macro and micronutrients and other bioactive components. By means of different mechanisms some components of nuts such as magnesium, fiber,  $\alpha$ -linolenic acid, L-arginine, antioxidants and MUFA may protect against inflammation and/or insulin resistance (Figure 1). For instance, cross-sectional epidemiologic studies have shown that magnesium intake is significantly associated with systemic inflammation and endothelial dysfunction,<sup>12</sup> possibly due to the link between magnesium homeostasis and insulin resistance.<sup>13,14</sup> In fact, as recently reviewed, lower intakes of magnesium and lower serum magnesium concentrations are associated with and may lead to metabolic syndrome,

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**Figure 1.** Different mechanisms by which some components of nuts may protect against inflammation and insulin resistance.

insulin resistance, and/or type 2 diabetes mellitus.<sup>15</sup> Nuts are also rich in fiber,<sup>16</sup> which lowers postprandial glycemia levels, thereby possibly inhibiting inflammation.<sup>17-19</sup> Galisteo et al.<sup>20</sup> recently suggested that portal short-chain fatty acids produced through the fermentation of fiber may also contribute to decreased inflammation.  $\alpha$ -linolenic acid, an important component of walnuts, also appears to elicit anti-inflammatory effects via activation of the peroxisome-proliferator activated receptor  $\gamma$ .<sup>21-23</sup> Finally, nuts contain considerable amounts of L-arginine, a precursor of nitric oxide, which might have a positive effect on endothelium-dependent vasomotion.<sup>24</sup>

The type of fat contained in nuts could also play a role in the modulation of insulin resistance. Nuts are high in unsaturated fat, specifically walnuts are rich in polyunsaturated fatty acids (PUFA) whereas almonds and hazelnuts have high levels of monounsaturated fatty acids (MUFA) and PUFA. Some epidemiological evidence suggests that dietary saturated fatty acids (SFA) and trans fatty acids are related to an increased risk of developing insulin resistance and diabetes, whereas dietary MUFA and PUFA protect against these conditions.<sup>25-27</sup> For example, baseline serum SFA levels were higher and PUFA concentrations were lower in men who developed insulin resistance.<sup>28</sup> Diets rich in MUFA and low in SFA also improve insulin sensitivity<sup>29</sup> and glycemic control in people with diabetes.<sup>30</sup> Moreover, replacing SFA with MUFA positively affects plasma lipid profile and improves insulin sensitivity.<sup>26,31</sup> Although the mechanisms by which some types of fatty acids may affect insulin sensitivity are not clearly understood, it is well known that the fatty acid composition of the skeletal muscle cell membrane is directly related to insulin sensitivity in humans.<sup>32</sup> In addition, MUFA are also known to improve beta cell efficiency by enhancing the secretion of glucagon-like peptide-1, a molecule that helps in the regulation of postprandial glucose clearance and insulin sensitivity.<sup>33</sup>

Because nuts are very rich in soluble and insoluble fiber and fat, changing to a diet which includes the regular consumption of nuts could induce a decrease in the glucose and insulin response to the diet. In fact, nuts de-

crease the glycemic index (GI) and the glycemic load of the diet. The intake of high GI foods has been found to cause a rapid increase in blood glucose and insulin concentrations, and a subsequent decrease in glycemia, which leads to hunger and reduced fat oxidation.<sup>3</sup> The intake of low GI foods has been shown to decrease levels of LDL-cholesterol, serum CRP and hemoglobin A<sub>1c</sub> in diabetic patients.<sup>34</sup> Thus, a decrease in the GI of the diet could be a simple strategy for increasing insulin sensitivity and ameliorating various cardiovascular risk factors for chronic diseases.<sup>35</sup> Therefore, the consumption of nuts and other vegetables with high fiber contents might prevent the development of diabetes.<sup>36</sup>

Finally, nuts also contain different types of antioxidants such as flavonoids, polyphenols and tocopherols.<sup>37</sup> Dietary antioxidants in nuts may play an important role in modulating inflammation<sup>38,39</sup> through both their antioxidant action and the modulation of signal transduction pathways, such as the nuclear transcription factor  $\kappa$ B, and as a consequence regulate inflammatory genes in macrophages and endothelial cells.<sup>40</sup> Furthermore, antioxidant intake could modulate insulin resistance by restoring the plasma ratio of oxidized glutathione to reduced glutathione (GSSG/GSH) to a more appropriate concentration<sup>41</sup> and improving  $\beta$ -cell response to glucose and insulin action.<sup>42</sup>

### EFFECT OF NUT CONSUMPTION ON INFLAMMATION

The effect of nut consumption on inflammation has been studied in several cross-sectional and prospective epidemiologic studies including different population groups such as healthy people, individuals with type 2 diabetes and subjects at high cardiovascular risk. Nut consumption was inversely associated with peripheral concentrations of CRP, IL-6 and fibrinogen in the Multi-Ethnic Study of Atherosclerosis.<sup>43</sup> A cross-sectional analysis of diabetic women from the Nurses Health Study shows that greater adherence to a Mediterranean diet was associated with higher concentrations of plasma adiponectin, a potent anti-inflammatory cytokine originating in adipose tissue.

Among the components of the Mediterranean diet, alcohol, whole grains, and nuts showed the strongest associations. The association between frequency of nut consumption and adiponectin was attenuated after adjustment for several covariates.<sup>44</sup> Recently, in a cohort of participants at high risk for coronary heart disease, our group reported that subjects in the highest tertiles of nut consumption showed the lowest vascular cell adhesion molecule-1 (VCAM-1), intracellular adhesion molecule-1 (ICAM-1), CRP and IL-6 serum concentrations, although this association was only significant for ICAM-1.<sup>45</sup>

The results of these epidemiological studies are consistent with several clinical trials. To the best of our knowledge, one acute and seven chronic clinical trials analyzing the effect of nut consumption on inflammatory markers have been published. Cortés et al<sup>46</sup> showed that postprandial increases in plasma inflammation markers were similarly blunted after the intake of two meals, one enriched with walnuts or another enriched with olive oil (80 g of fat and 35% saturated fatty acids, both meals), except for E-selectin which was lower after the consumption of the walnut meal than after the olive oil meal.

Four of the chronic studies report a protective effect of nuts against inflammation, whereas three show no effect. For instance, two crossover studies with hypercholesterolemic subjects receiving two doses of almonds<sup>47</sup> or a single dose of walnuts, representing 18% of total energy intake,<sup>24</sup> failed to observe any effect on serum CRP concentrations, an accepted measure of chronic inflammation. Mukkudem-Petersen et al.<sup>48</sup> also showed no improvement in serum CRP concentrations after investigating the effect of a high walnut diet and a high unsalted cashew nut diet compared to a control diet (without nuts) for eight weeks in subjects with metabolic syndrome. However, a recently published four-week clinical trial demonstrated that regular macadamia nut consumption (40-90 g/day), equivalent to 15% of total daily energy intake, significantly decreases plasma concentrations of leukotriene and LTB(4) in hypercholesterolemic subjects,<sup>49</sup> suggesting that the regular consumption of nuts ameliorates the inflammatory response in vivo. Our group conducted a randomized parallel interventional study over 12 weeks in patients with metabolic syndrome. We found similar decreases in plasma MCP-1 and interleukin-18 concentrations after the consumption of a healthy diet compared to the consumption of the same diet supplemented with 30 g/day of mixed nuts, while leukocyte counts and serum IL-6 only significantly decreased in subjects who ate the nut-enriched diet.<sup>50</sup> However, the decrease observed in these two classic markers for inflammation may be in part explained by the greater weight loss experienced by the subjects who consumed nuts. Furthermore, compared to a Mediterranean diet, a four-week pistachio enriched diet (representing 20% of the total energy intake as monounsaturated fat) decreased serum IL-6 concentrations in healthy men living in a controlled environment.<sup>51</sup>

Zhao et al.<sup>52</sup> evaluated the effects of a diet high in linoleic and  $\alpha$ -linolenic acid (derived from walnuts, walnut oil and flaxseed oil) on serum proinflammatory cytokine concentrations and cytokine production in cultured peripheral blood mononuclear cells (PBMCs) compared to an average American diet in hypercholesterolemic sub-

jects. They found that the diet high in  $\alpha$ -linolenic acid inhibited the PBMC production of IL-6, IL-1 $\beta$  and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and decreased serum TNF- $\alpha$  concentrations, compared to an average American diet. Using an in vitro study, the same group also showed that  $\alpha$ -linolenic, linoleic, and docosahexaenoic acid reduced the *Escherichia coli* lipopolysaccharide stimulated production of IL-6, interleukin-1 $\beta$  and TNF- $\alpha$  in a dose dependent manner in THP-1 cells compared to palmitic acid.<sup>21</sup> Recently, a significant lower postprandial response in the RNA expression of IL-6 was found in PBMCs in healthy subjects after consuming a walnut breakfast (4%  $\alpha$ -linolenic acid) compared to a butter breakfast with a fat content of 60% each.<sup>53</sup> The beneficial effect on inflammation observed in this study might have been due to SFA replacement rather than  $\alpha$ -linolenic acid walnut content. Therefore, replacing SFA with nuts and other possible sources of  $\alpha$ -linolenic acid in the diet is an appropriate measure for decreasing inflammation and cardiovascular risk.<sup>21,52</sup>

The beneficial effect of nut consumption on inflammatory biomarkers has also been studied in the context of a Mediterranean diet. In the PREDIMED (PREvencion con DIeta MEDiterranea) study, Estruch et al.<sup>54</sup> found a decrease in plasma IL-6, ICAM-1, and VCAM-1 concentrations in subjects randomized into two Mediterranean diet groups (one supplemented with nuts and the other with olive oil) compared to subjects in a low-fat diet group after three months of intervention. In recent results from the PREDIMED trial, subjects who after three months increased adherence to the two Mediterranean diets showed reduced immune cell activation and decreased concentrations of plasma inflammatory biomarkers related to atherogenesis compared to participants advised to consume a low-fat diet. Specifically, the Mediterranean diet supplemented with nuts reduced serum IL-6 and soluble ICAM-1 levels, but no differences in changes in serum CRP concentration were found compared to a low-fat diet.<sup>55</sup> To analyze the influence of genetic variability in the modulation of inflammation after the consumption of a Mediterranean diet, Corella et al.<sup>56</sup> studied the effect of the -765G>C polymorphism in the cyclooxygenase-2 gene and the -174G>C polymorphism in the IL-6 gene on several serum inflammatory biomarkers and their influence on the response to a nutritional intervention with the two Mediterranean diets after a three-month intervention period. The IL-6-147G>C polymorphism was associated with higher (CC vs. G-carriers) serum ICAM-1 concentrations in both men and women and with higher serum IL-6 concentrations in men, although no significant gene x dietary interactions were found.

Because it has been suggested that oxidized LDL plays a key role in the generation of inflammatory processes in atherosclerotic lesions at all stages,<sup>57</sup> our group conducted a systematic review in order to analyze the possible effect of nut consumption on oxidative stress status.<sup>37</sup> We concluded that although the beneficial effect of nut consumption on oxidation is not consistent in the published studies, no deleterious effect on oxidation has been reported in any of the published studies performed in humans.<sup>37</sup>

In summary, nut intake seems to be associated with lower concentrations of inflammatory biomarkers, espe-

cially IL-6. The capacity of nuts to ameliorate inflammation could partly explain the reduced risk of diabetes and CVD associated with the frequency of nut consumption. Further research is needed to pinpoint the role of nut intake in this important field.

### EFFECT OF NUT CONSUMPTION ON INSULIN RESISTANCE AND TYPE 2 DIABETES

Nuts are very rich in fat and energy, which has given rise to a certain amount of controversy regarding the safety of regular nut consumption in relation to insulin sensitivity and diabetes control. Data from two prospective studies, the Nurses' Health Study<sup>58</sup> and the Shanghai Women's Health Study,<sup>59</sup> indicate that frequent nut and peanut consumption is associated with a reduced risk of developing diabetes, whereas results from the Iowa Women's Health Study reports either no association or a weak association.<sup>60</sup> As the three previous studies were performed in women, it is unknown whether nut consumption is associated with a reduced risk of diabetes in men.

To the best of our knowledge, no deleterious effects of nut consumption on glucose homeostasis have been reported to date. Using a 24-week randomized dietary interventional trial, subjects with metabolic syndrome following an almond-based hypocaloric diet showed a 54% decrease in fasting insulin levels from baseline compared to the 32% reduction observed in the high complex carbohydrate diet group.<sup>61</sup> In the same study, insulin resistance as measured by the HOMA-IR was significantly decreased in both diet groups, but improved beta cell function was only observed in the almond diet group. In keeping with these results, we also observed that after consuming a healthy diet supplemented with nuts, insulin response decreased by 22% from the initial value with the effect of treatment differing significantly from that of the control diet.<sup>59</sup> In the same study, insulin sensitivity changes measured by the HOMA-IR were also more favorable after the supplemented nut diet compared to the control. Moreover, in a randomized crossover design, the effect of four diets: a) high fat, high almond, b) low fat, high almond, c) high fat control and d) low fat control, on glucose and insulin concentrations were examined in subjects with type 2 diabetes. However, in this study, no significant effect of fat source (almond compared to oil) or fat level (high compared to low fat) on glucose, insulin response or levels of hemoglobin A<sub>1c</sub> was observed.<sup>62</sup> It has been suggested that the short duration of this study and the small increase in body weight observed in the subjects could explain why no changes in diabetes control were observed.<sup>63</sup> Finally, the effect of a high walnut and cashew diet (20% of total energy intake) on several markers of metabolic syndrome, such as the von Willebrand factor antigen, fibrinogen, factor VII coagulant activity, plasminogen activator inhibitor 1 activity, tissue plasminogen activator activity and thrombin activatable fibrinolysis inhibitor, was studied without observing any significant changes in HOMA-IR that could be attributed to the consumption of nuts.<sup>64</sup>

### CONCLUSIONS

Nuts are complex food matrices with many bioactive components that may favorably act on inflammation and

decrease the risk of insulin resistance. More and more evidence suggests that oxidative stress and inflammation are associated with insulin resistance. Therefore, the potential effect of nut consumption on inflammation and insulin resistance as well as oxidative stress status is an essential topic for future study. The evidence summarized in this review indicates that introducing nuts into one's diet has protective or, at least, no deleterious effects on inflammation and insulin response in healthy people or individuals with hypercholesterolemia, metabolic syndrome or diabetes.

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### AUTHOR DISCLOSURES

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## Review

# Nuts, inflammation and insulin resistance

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## 核果類與發炎作用及胰島素抗性

食用核果類對於心血管疾病的益處已被廣泛的證實。這些保護的效應主要歸因於核果類在脂質和脂蛋白代謝上所扮演的角色。慢性發炎是動脈粥狀硬化進程的早期關鍵階段，將預測未來心血管疾病的發生，並且與胰島素抗性的致病密切相關，因此很多近期的研究專注於核果類的食用對於發炎及胰島素抗性的影響。經由不同的機制，一些核果類的成分，例如鎂、纖維、 $\alpha$ -亞麻油酸、L-精胺酸、抗氧化物及單元不飽和脂肪酸，可能對於發炎及胰島素抗性有保護的作用。本文回顧人類流行病學的研究及人體實驗的證據來論證核果類的攝取與此兩種新興的心血管保護機制之間的關係。

**關鍵字：**核果類、發炎、胰島素抗性、第 II 型糖尿病、心血管疾病