Soy consumption, adhesion molecules, and pro-inflammatory cytokines: a brief review of the literature

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Given the interest in the vascular effects of both soyfoods and soy isoflavones, the purpose of this short review is to evaluate clinical trials that have examined the effects of isoflavone-rich soy products on the novel cardiovascular risk factors, cellular adhesion molecules, and pro-inflammatory cytokines. A total of 14 randomized clinical studies were assessed. From the data evaluated, evidence suggests that neither soyfoods nor soy isoflavones affect IL-6 or TNF-α expression. In contrast, the effects of soy on cellular adhesion molecules are mixed. Study design characteristics possibly contributing to the inconsistent data are discussed and recommendations for future research in this area are presented.

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INTRODUCTION

The soybean is a versatile legume that contains high-quality protein, minimal saturated fat, and is an essentially unique dietary source of isoflavones1 – a group of diphenolic compounds classified as phytoestrogens. Isoflavones bind to both estrogen receptors, although preferentially to estrogen receptor beta (ERβ),2 and in people who regularly consume soyfoods, serum isoflavone levels reach the low micromolar range.3 In soybeans, the three isoflavones genistein, daidzein, and glycitein comprise approximately 50%, 40%, and 10% of total isoflavone content, respectively.4 Of the three isoflavones, genistein has received the most attention.

In recent years these foods have been studied extensively for their ability to reduce the risk of several chronic diseases, particularly cardiovascular disease (CVD). To date, more than 100 clinical studies have examined the effects of soy protein on blood cholesterol levels. Although initial estimates3 of the hypocholesterolemic effects of soy protein are now known to be too high, recent meta-analyses indicate soy protein directly lowers blood low-density-lipoprotein cholesterol (LDL-C) levels by 3–5%.6,7 Over a period of many years, even this modest reduction can, in theory, reduce coronary heart disease (CHD) risk by as much as 10%.8

Interestingly, in animal models, both soy protein and soybean isoflavones have been shown to reduce the development of atherosclerosis independent of effects on LDL-C.9,10 Further, several Asian epidemiologic studies have found higher soy intake to be associated with substantial reductions (30–86%) in the risk of developing CVD and/or having coronary events.11,12 Such protective effects are far beyond that which can be attributable to cholesterol lowering alone, even when considering the additional reduction in cholesterol that occurs when soyfoods displace foods high in saturated fat from the diet. These epidemiologic observations coupled with evidence from animal models have led to the concept that soy favorably affects one or more of the lipid-independent CVD risk factors.

In this regard, there is evidence that soy protein lowers blood pressure13 and that soybean isoflavones enhance endothelial function, as measured by changes in flow mediated dilation (FMD) and systematic arterial compliance, although the data are inconsistent.14 Several mechanisms have been proposed by which isoflavones might improve endothelial function, these include
increasing endothelial nitric oxide synthase gene expression and nitric oxide production and calcium-channel antagonism. In 2002, Squadrito et al. reported that in postmenopausal women, the diameter of the brachial artery increased significantly in subjects given genistein (54 mg/d) for 6 months, whereas no change was noted in the placebo group. More recently, in a 12-week study from Singapore, Chan et al. reported that 80 mg/d isoflavones increased FMD by approximately 50% in primary or recurrent ischemic stroke patients. Although, as noted, the effects of isoflavones on FMD are inconsistent, recent data suggests that to demonstrate efficacy a threshold serum genistein level be reached in subjects and may be more apparent in those with somewhat impaired endothelial function.

In addition to endothelial function, there is recent interest in understanding the impact of soy and especially isoflavones on the inflammatory process. Certainly there is a biological basis for thinking that isoflavones impact inflammation, since isoflavones possess estrogen-like properties and in animal models estrogen treatment has been shown to decrease tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6). In fact, in animals, isoflavones have been shown to affect adhesion molecules and pro-inflammatory cytokines in vitro and in vivo. However, the authors of a recently published review that included 13 clinical studies concluded there was little evidence to suggest either soy protein or isoflavones favorably affects C-reactive protein (CRP) levels. Studies published subsequent to this review, with one exception, support this conclusion.

Once regarded largely as a disorder of lipid accumulation, atherosclerosis is now generally viewed as an inflammatory disease. Inflammation plays a key role in all stages of atherothrombosis, the underlying cause of approximately 80% of all sudden cardiac deaths. Inflammation occurs in the vasculature as a response to injury and lipid peroxidation. Various risk factors are amplified by the harmful effects of oxidized LDL-C, initiating a chronic inflammatory reaction, the result of which is a vulnerable plaque prone to rupture and thrombosis. The process begins with endothelial dysfunction caused, for example, by modified LDL, or free radicals. Post-insult endothelial changes include increased leukocyte adhesion and migration into the arterial wall, increased permeability to lipoproteins, a switch from anticoagulant to procoagulant activity, and formation of cytokines. As the inflammatory process continues, circulating monocytes and lymphocytes migrate into the subendothelial space, and macrophages ingest oxidized LDL and are transformed into foam cells. The resulting fatty streak is augmented by smooth muscle cells and platelets to form an intermediate atherosclerotic lesion. Eventually, a fibrous cap, which represents a healing response, forms over the mixture of leukocytes, lipid, and debris to wall off the lesion from the lumen. However, the core of such an advanced lesion can become necrotic and subsequent thinning and rupture of the fibrous cap appears to be the principal cause of acute coronary syndrome.

Increased inflammation, as determined by elevated levels of CRP, cytokines, and adhesion molecules, have been shown to predict cardiovascular morbidity and mortality. CRP is an acute-phase reactant that is synthesized in the liver. While numerous epidemiologic studies have demonstrated correlations between elevations in CRP and CVD risk, the evidence implicating CRP as a potent stimulus of atherogenesis lies predominantly in experiments that show CRP to be present within the atheroma and that CRP administration in animals leads to inflammatory changes, such as increased expression of IL-6, TNF-α, and soluble cellular adhesion molecules (sCAMs). However, the predictive value of adding CRP to standard risk assessments such as the Framingham-based risk score is unclear. Although less well studied, the pro-inflammatory cytokines TNF-α and IL-6 are known to activate sCAMs which promote early adhesion of leukocytes to the arterial endothelium. Selectin molecules (such as P-selectin and E-selectin) have also been shown to contribute significantly to leukocyte recruitment.

Given the interest in the coronary effects of both soyfoods and isoflavones, the purpose of this short review is to assess and provide perspective on those clinical studies that have evaluated the effects of isoflavone-containing products on select soluble adhesion molecules and pro-inflammatory cytokines. Note that because the relationship between soy and CRP has been summarized elsewhere, it will not be discussed here.

**SEARCH CRITERIA**

To identify appropriate research, the PubMed database (National Library of Medicine, Bethesda, MD) was searched inclusively through July 1, 2008 using the following key words: soy, inflammation, cardiovascular, isoflavones, genistein, cytokine, interleukin, IL-6, TNF-α, adhesion molecule, VCAM, ICAM, and selectin. References within identified papers as well as papers that came to the attention of the authors through other means were also examined for appropriateness of fit.

**PERTINENT FINDINGS FROM REVIEWED ARTICLES**

A total of 14 randomized clinical studies were identified as suitable; six addressing pro-inflammatory cytokines, seven addressing adhesion molecules,
and one addressing both. Relevant details of all studies are presented in Tables 1 and 2.

**Proinflammatory cytokines and soy**

Of the seven applicable studies, two were composed entirely of women,\(^{31,51}\) one of men,\(^{42}\) and four contained both genders.\(^{38–40,43}\) The intervention products used in these trials were isolated soy protein (ISP),\(^{39,40,42,43}\) which is, by definition, at least 90% soy protein, and soy protein coming from other soy foods.\(^{38,41,51}\) Soy protein and isoflavone exposure ranged from 17 to 52 g/d and 10–102 mg/d, respectively. Only two of the seven studies, which are discussed below, found statistically significant changes in pro-inflammatory cytokines.\(^{38,51}\)

In a crossover study by Azadbakht et al.,\(^{51}\) 42 postmenopausal women with metabolic syndrome consumed in random order one of three diets: the Dietary Approaches to Stop Hypertension (DASH) diet, the DASH diet in which one serving of red meat was replaced with soy flour, or one in which one serving of red meat was replaced by soy nuts. The soy flour and soy nuts provided 15 and 11 g protein and about 50 and 60 mg isoflavones, respectively. As shown in Table 1, final TNF-\(\alpha\) but not IL-6 levels were significantly lower in the soy nut group compared to the soy protein and control groups (\(P < 0.01\)). However, the actual decrease (\(-13\%)\) from baseline in the soy nut group was almost identical to the decrease in the control group. Furthermore, in direct contrast to these findings, are those from a 4-week study by Jenkins et al.,\(^{38}\) in which the effects of high and low isoflavone-containing soy foods on pro-inflammatory cytokines were assessed in hypercholesterolemic men and women. Although there was no treatment effect on IL-6 or TNF-\(\alpha\), a significant interaction was noted between diet and gender. In women on the high isoflavone diet, final serum IL-6 values were significantly higher than those of the control group (\(P = 0.013\)).

Finally, findings from one other study are noteworthy. In subjects with end-stage renal disease,\(^{43}\) although there were no effects on TNF-\(\alpha\), IL-6 concentrations decreased about 40% in response to a diet that included isoflavone-rich soy products, whereas there was a nearly 50% increase in the control group; however, the difference between groups was not statistically significant.

**Adhesion molecules and soy**

A total of eight clinical studies, all of which involved postmenopausal women (one also included men\(^{50}\)), were identified that addressed the relationship between soy/ isoflavone intake and adhesion molecule expression,\(^{44–51}\) four used isoflavones,\(^{44,45,46,49}\) three used isoflavone-rich ISP,\(^{47,48,50}\) and one used soy foods.\(^{51}\) Of the eight studies, the three described below found statistically significant reductions in at least one of the adhesion molecules assayed.\(^{44,45,51}\) In these studies, isoflavone intake ranged from 54 to 120 mg/d.

In a 2-year study, Atteritano et al.\(^{41}\) found that among postmenopausal Italian women, genistein (54 mg/d) intake resulted in approximately 10% decreases in sVCAM-1 and sICAM-1 levels when compared to placebo (\(P < 0.05\)). However, despite the statistical significance, a cautionary note is warranted because in the analysis of the results, the investigators imputed missing data for patients who began but did not complete the 2-year study by carrying the last observation forward (\(n = 48\) in treatment and \(n = 37\) in placebo groups). Also, it is not clear whether the statistical analysis accounted for multiple comparisons. Nevertheless, these findings concur with those from another Italian study by Colacurci et al.\(^{45}\)

In this second study,\(^{45}\) postmenopausal women were given a placebo or 120 mg/d isoflavones for 6 months, an amount that would provide approximately the amount of genistein used in the study by Atteritano et al.\(^{41}\) Women in the isoflavone group experienced approximately 20%, 10%, and 40% reductions in concentrations of sICAM-1, sVCAM-1, and E-selectin, respectively, with all values reaching statistical significance (\(P < 0.05\)). There was also a 20% reduction in plasma levels of P-selectin, but this finding was not statistically significant (\(P = 0.07\)). These two studies agree with those from the previously described study by Azadbakht et al.,\(^{51}\) in which women were asked to consume either the DASH diet or a diet in which soy nuts or soy flour replaced one serving of red meat. Vascular adhesion molecules and E-selectin were found to be reduced in response to both soy diets when compared with the control (\(-11.4\%, P < 0.01\) and \(-4.7\%, P = 0.19\), respectively).

Two additional studies are worthy of mention. In a study by Nikander et al.,\(^{45}\) over a 3-month period, although soy isoflavones (114 mg/d) did not significantly lower plasma E-selectin (the only adhesion molecule assayed) levels in the treatment group, serum concentrations of daidzein (\(=861\) versus >861 nM/L) and genistein (\(=363\) versus >363 nM/L) were directly related to reductions in E-selectin levels (\(r = 0.392, P = 0.003; r = 0.382, P = 0.004\), respectively). Importantly, although the total isoflavone amount given to women in this study equaled that given to the women in the study by Colacurci et al.,\(^{45}\) Nikander et al.\(^{46}\) used a low-genistein supplement such that genistein exposure was only about 6 mg/d.

Finally, in another 3-month study by Hall et al.,\(^{49}\) no effects of isoflavones (50 mg/d) on plasma E-selectin or sVCAM-1 and sICAM-1 concentrations were noted in participants overall. However, sVCAM-1 concentrations were significantly decreased in participants with the
<table>
<thead>
<tr>
<th>Reference</th>
<th>Design duration</th>
<th>N (M:F)/age (years)</th>
<th>Intervention used</th>
<th>IL-6 (pg/mL) Initial</th>
<th>Final</th>
<th>TNF-α (pg/mL) Initial</th>
<th>Final</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azadbakht et al. (2007)</td>
<td>xo/8 wk</td>
<td>42 (0:42)/postmenopausal</td>
<td>30 g soy nut: 102 mg isoflavone</td>
<td>1.8 (1.7–2.0)†</td>
<td>1.8 (1.6–2.0)</td>
<td>1.5 (1.4–1.6)†</td>
<td>1.3 (1.2–1.4) (P &lt; 0.01 versus control and soy protein)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>30 g soy protein: 84 mg isoflavone</td>
<td>1.7 (1.5–1.9)</td>
<td>1.8 (1.6–2.0)</td>
<td>1.5 (1.4–1.6)</td>
<td>1.4 (1.3–1.5)</td>
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<td></td>
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<td>DASH diet</td>
<td>1.7 (1.5–1.9)</td>
<td>1.7 (1.5–1.8)</td>
<td>1.6 (1.5–1.7)</td>
<td>1.4 (1.3–1.5)</td>
</tr>
<tr>
<td>Hermansen et al. (2005)</td>
<td>p/24 wk</td>
<td>49 (23:26)/60.6 ± 3.4</td>
<td>30 g ISP + 100 mg isoflavones</td>
<td>–</td>
<td>–</td>
<td>4.7 ± 1.8†</td>
<td>4.9 ± 2.6</td>
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<td></td>
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<td>40 g total milk protein</td>
<td>1.6 (1.5–1.9)</td>
<td>1.7 (1.5–1.8)</td>
<td>1.6 (1.5–1.7)</td>
<td>1.4 (1.3–1.5)</td>
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<tr>
<td>Hilpert et al. (2005)</td>
<td>xo/6 wk</td>
<td>17 (14:18)/57.9 ± 3.4</td>
<td>25 g ISP + 90 mg isoflavones</td>
<td>99.4 (30.4–517.6)††</td>
<td>61.6 (43.9–554.6)</td>
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<td></td>
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<td>25 g milk protein isolate</td>
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<tr>
<td>Fanti et al. (2006)</td>
<td>p/8 wk</td>
<td>15 (9:6)/60.7 ± 3.4</td>
<td>17 g ISP + 38 mg isoflavone</td>
<td>140 (6.4–23.2)††</td>
<td>103 (8.0–14.0)</td>
<td>7.6 (6.5–13.7)††</td>
<td>7.5 (6.6–8.1)</td>
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<td></td>
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<td>17 g casein</td>
<td>22.2 (14.2–48.9)</td>
<td>32.7 (14.5–86.4)</td>
<td>12.5 (7.1–23.5)</td>
<td>9.0 (7.3–17.6)</td>
</tr>
<tr>
<td>Jenkins et al. (2002)</td>
<td>xo/4 wk</td>
<td>41 (23:18)/62 ± 2</td>
<td>17 g casein</td>
<td>0.9 ± 0.3³</td>
<td>0.88 ± 0.47</td>
<td>2.01 ± 0.38³</td>
<td>2.2 ± 0.6</td>
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<td>50 g soy protein + 73 mg isoflavone</td>
<td>0.72 ± 0.16 (P = 0.013 versus control)</td>
<td>Women: 1.4 ± 0.1</td>
<td>1.5 ± 0.1</td>
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<td>52 g soy protein + 10 mg isoflavone</td>
<td>Men: 1.1 ± 0.4</td>
<td>1.0 ± 0.5</td>
<td>Men: 1.8 ± 0.3</td>
<td>1.7 ± 0.2</td>
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<td></td>
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<td>NCEP diet</td>
<td>Women: 0.4 ± 0.1</td>
<td>0.4 ± 0.1</td>
<td>Women: 1.4 ± 0.1</td>
<td>1.4 ± 0.1</td>
</tr>
<tr>
<td>Ryan-Borchers et al. (2006)</td>
<td>p/16 wk</td>
<td>18 (0:18)/56.1 ± 4.4</td>
<td>18 g SP + 71.6 mg isoflavones</td>
<td>0.9 ± 0.4</td>
<td>0.9 ± 0.4</td>
<td>2.1 ± 0.6</td>
<td>2.1 ± 0.5</td>
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<td></td>
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<td></td>
<td>15 (0:15)/55.9 ± 3.5</td>
<td>0.6 ± 0.2</td>
<td>0.34 ± 0.06</td>
<td>Women: 1.5 ± 0.1</td>
<td>1.5 ± 0.1</td>
</tr>
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<td></td>
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<td>24 g milk protein</td>
<td>2.0 ± 1.1⁴</td>
<td>2.5 ± 1.2</td>
<td>2.5 ± 1.2</td>
<td></td>
</tr>
</tbody>
</table>

† Data presented as means (95% CI).
† Data presented as mean ± SE.
³ Data presented as mean ± SD.
⁴ Baseline gender breakdown reported.
†† Data presented as medians (25th–75th percentile).
Abbreviations: NCEP, National Cholesterol Education Program; mg, milligram; g, gram; pg, picogram; xo, cross over; p, parallel; IL-6, interleukin 6; TNF-α, tumor necrosis factor alpha.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Design duration</th>
<th>N (M/F) age (years)</th>
<th>Intervention used</th>
<th>sICAM-1 (ng/mL)</th>
<th>sVCAM-1 (ng/mL)</th>
<th>E-selectin (ng/mL)</th>
<th>P-selectin (ng/mL)</th>
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<td>Initial</td>
<td>Final</td>
<td>Initial</td>
<td>Final</td>
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<tr>
<td>Azadbakht et al. (2007)</td>
<td>xo/8 wk</td>
<td>42 (0:42)/postmenopausal</td>
<td>30 g soy nut: 102 mg isolavones</td>
<td>289 (280–297)</td>
<td>280 (270–289)</td>
<td>498 (488–507)</td>
<td>485 (477–496)</td>
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<tr>
<td></td>
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<td>30 g soy protein: 84 mg isolavones</td>
<td>293 (285–303)</td>
<td>282 (274–291)</td>
<td>505 (495–513)</td>
<td>492 (484–502)</td>
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<td></td>
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<td>DASH diet</td>
<td>299 (291–308)</td>
<td>286 (278–293)</td>
<td>502 (494–510)</td>
<td>488 (480–495)</td>
</tr>
<tr>
<td>Atterisano et al. (2007)</td>
<td>p/24 mo</td>
<td>198 (0:198)/54.7 ± 0.25</td>
<td>54 mg genistein</td>
<td>28.15 ± 3.3¹</td>
<td>25.3 ± 3.2² (p &lt; 0.001 versus placebo)</td>
<td>352.6 ± 4.9³</td>
<td>317.7 ± 4.7 (p &lt; 0.001 versus placebo)</td>
</tr>
<tr>
<td>Blum et al. (2003)</td>
<td>xo/6 wk</td>
<td>24 (0:24)/55 ± 5</td>
<td>25 g ISP: isoflavones</td>
<td>2769 ± 3.1</td>
<td>288.7 ± 3.1</td>
<td>363.2 ± 4.8</td>
<td>373.1 ± 4.8</td>
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<td></td>
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<td>25 g milk protein</td>
<td>–</td>
<td>2660 ± 8.13¹</td>
<td>–</td>
<td>4027 ± 10.2¹²</td>
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<tr>
<td>Golucci et al. (2005)</td>
<td>p/6 mo</td>
<td>29 (0:29)/55.4 ± 3.7</td>
<td>120 mg isolavones</td>
<td>34.3 ± 9.6⁴⁵</td>
<td>262.6 ± 8.2⁶</td>
<td>590.2 ± 163.6²²</td>
<td>5291 ± 167.5⁶⁶</td>
</tr>
<tr>
<td>Hail et al. (2005)</td>
<td>xo/8 wk</td>
<td>111–111²/59–111/57.7 ± 5.4⁶</td>
<td>placebo</td>
<td>336.6 ± 80.5</td>
<td>334.0 ± 87.3</td>
<td>605.3 ± 159.4</td>
<td>6180 ± 152.7</td>
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<td></td>
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<td>50 mg isolavones</td>
<td>2150.6 ± 51.6⁴⁶</td>
<td>220.4 ± 52.8</td>
<td>504.8 ± 134.4⁴⁷</td>
<td>503.5 ± 146.7</td>
</tr>
<tr>
<td>Nikander et al. (2003)</td>
<td>xo/3 mo</td>
<td>56 (0:56)/54 ± 6</td>
<td>114 mg isolavones</td>
<td>–</td>
<td>217.8 ± 48.3</td>
<td>498.1 ± 129.0</td>
<td>4998 ± 135.9</td>
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<td></td>
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<td>placebo</td>
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<tr>
<td>Steenbergen et al. (2003)</td>
<td>xo/6 wk</td>
<td>28 (0:28)/54.9 ± 1.0</td>
<td>25 g ISP: 107 mg isolavones</td>
<td>–</td>
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<td>placebo</td>
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<td>25 g total milk protein</td>
<td>–</td>
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<td>–</td>
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</tr>
<tr>
<td>West et al. (2005)</td>
<td>xo/6 wk</td>
<td>32 (14:18)/men age: 57.36 ± 1.43</td>
<td>25 g ISP: 90 mg isolavones</td>
<td>–</td>
<td>–</td>
<td>Men 711.9 ± 35.6⁶</td>
<td>Men 725.4 ± 35.6</td>
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<td>HRT+: 638.6 ± 52.6</td>
<td>HRT+: 660.7 ± 52.6</td>
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<td>25 g milk protein</td>
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<td>–</td>
<td>HRT+: 552.2 ± 39.0</td>
<td>HRT+: 553.4 ± 39.0</td>
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<td></td>
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<td>HRT+: women age: 57.17 ± 2.18</td>
<td>–</td>
<td>–</td>
<td>Men 687.2 ± 35.6</td>
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<td>HRT+: women age: 59.0 ± 1.54</td>
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<td>HRT+: 655.5 ± 52.6</td>
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<td>HRT+: 20% whey</td>
<td>–</td>
<td>–</td>
<td>HRT+: 540.3 ± 39.0</td>
<td>–</td>
</tr>
</tbody>
</table>

1 Same study cited in Table 1.
2 Data presented as means (95% CI).
3 Data presented as mean ± SE.
4 Unspecified isoavone amount used.
5 Data presented as mean ± SD.
6 Sample size varied by biomarker and timepoint, ranging from 111 to 117.

Abbreviations: mg, milligrams; xo, crossover; p, parallel; wk, week; mo, month; DASH, dietary approaches to stop hypertension; HRT+, positive for hormone replacement therapy; HRT-, negative for hormone replacement therapy; g, gram; ng, nanogram; sVCAM-1, soluble vascular cell adhesion molecule 1; sICAM-1, soluble intercellular adhesion molecule 1.
estrogen receptor (ER) α/β ALu1 genotype (P < 0.05) but not in those with the GG or GA genotypes. Hall et al. speculated that variation in the function of the estrogen receptor may influence the expression of sVCAM-1 in response to estrogen receptor-binding ligands, such as phytoestrogens.

**DISCUSSION**

There is evidence that soyfoods, likely at least in part because they contain isoflavones, exert lipid-independent vascular benefits. In vitro and some animal data indicate one such benefit may be a decrease in circulating levels of cytokines and soluble adhesion molecules, elevated levels of which are associated with development of atherosclerosis. The inflammatory cytokines are known to induce the expression of sCAMs, which mediate the adhesion of leukocytes to the vascular endothelium, thereby initiating the cascade of the atherosclerotic process.

The cytokines IL-6 and TNF-α are pleiotropic molecules that play major roles in the inflammatory process and have been linked to cardiovascular morbidity and mortality. However, it is quite clear from the clinical data that neither soyfoods nor isoflavones affect these two cytokines. In only two of the seven studies was a statistically significant effect of soy isoflavones observed on either TNF-α or IL-6, and in one of these the reduction in TNF-α was very modest while in the other, there was actually an increase (not a decrease) in IL-6 levels.

Adhesion of circulating leukocytes to vascular endothelial cells plays an important role in the early stages of atherosclerosis. This process appears to be influenced by adhesion molecules expressed on the surface of vascular endothelial cells, and among such mediators, sICAM-1, sVCAM-1, E- and P-selectin have been well studied. Moreover, these specific adhesion molecules appear to be modulated by estrogen; as such, there is a basis for speculating that, like the pro-inflammatory cytokines, isoflavones may affect these molecules as well.

Three of the eight studies reviewed here found statistically significant reductions in adhesion molecules. Two of these were conducted in Italy; in one study, the intervention product used was isolated genistein and in the other it was mixed isoflavones. The third study involved Iranian postmenopausal women with the metabolic syndrome. However, in that study, because the intervention products soy flour and soy nuts replaced red meat in the control diet, there were fiber and macronutrient intake differences among the groups. In comparison to the control, both soy diets were higher in fiber and lower in saturated fat, and the soy-nut diet was also higher in polyunsaturated fat. It is not clear if these dietary differences may have contributed to the reduction of adhesion molecules. Two other studies found at least partial support for an effect of isoflavones; one found that higher serum genistein and daidzein levels were associated with reductions in E-selectin levels, and in the other, a reduction in sVCAM-1 was limited to subjects with a specific ERβ phenotype.

**Examining inconsistencies and positing future directions**

Given the inconsistent data, it is useful to attempt to determine whether study design characteristics may account for the conflicting results. Certainly, gender is not a factor since all studies involved postmenopausal women. However, it is interesting to consider whether differences in results could be due to the intervention product used. In four of the five studies that found at least partial support for an effect of isoflavones on adhesion molecules, the intervention was with an isoflavone supplement. In contrast, in the three studies that failed to demonstrate effects on adhesion molecule expression, the intervention material was ISP. Thus, it is plausible that the effects of ISP differ from those of supplements at least in regard to adhesion molecules, although this supposition is quite speculative.

It is also interesting to speculate whether the differing health outcomes noted in this review resulted from the differing isoflavone supplements used in the studies. To this point, Atteritano et al. found that 54 mg/d of isolated genistein was efficacious, whereas no effects were noted in the studies by Steinberg et al. and West et al., even though the mixed isoflavone supplement used by these investigators would have provided approximately this amount of genistein. As a general observation, it is worth noting that there are marked intra-individual differences in isoflavone metabolism that lead to very pronounced differences in circulating levels of both parent isoflavones and metabolites. In studies with relatively small sample sizes, this variation could easily contribute to inconsistent clinical results. The importance of metabolism is supported by the findings of Nikander et al., who found that serum levels of daidzein and genistein were directly related to efficacy. Therefore, in future studies, the result of health outcomes in which subjects are exposed to isoflavones should be analyzed according to serum isoflavone level.

Finally, there is the issue of differences in subject characteristics and how these differences might affect response to soy. As noted, Hall et al. found that only those with the ERβ ALu1 genotype showed a decrease in adhesion molecules. It may also be that baseline inflammatory and health status of the participants are factors, and that isoflavones are efficacious only in those having...
significantly elevated inflammatory biomarkers at baseline. Unfortunately, none of the studies examined in this review specifically selected subjects according to inflammatory status, and thus definitive conclusions with regard to this factor cannot be drawn. Future research in this area, which is certainly justifiable on the basis of the existing data, should take this possibility into consideration.

**CONCLUSION**

Atherosclerosis, once regarded largely as a disorder of lipid accumulation, is now generally viewed as an inflammatory disease. Studies show that reducing inflammation is associated with improved clinical and intravascular outcomes in patients with established heart disease. Thus, identifying dietary factors and interventions that can help modulate the inflammatory process are highly relevant to CVD risk reduction. From the data evaluated, the evidence suggests that neither soyfoods nor soy isoflavones affect IL-6 or TNF-α, and more research is needed to elucidate the effect of isoflavones on sCAMS. Future study designs should address potential confounding factors such as the isoflavone profile of the intervention product, isoflavone dose, and subject characteristics such as genotype and inflammatory status. Despite the mixed findings, it is well known that the inclusion of soyfoods in a Western diet provides an excellent means by which to find the effects of soyfoods on adhesion molecules, their role in a heart-healthy diet is evident.

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**REFERENCES**


