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Review Article

Soy and cardio-metabolic abnormalities: an update

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Abstract

Soy protein contains beneficial components like complex carbohydrates, unsaturated fatty acids, vegetable protein, soluble fiber, oligosaccharides, vitamins, minerals, inositol-derived substances and phytoestrogens**,** particularly the isoflavones genistein, diadzein, and glycitein**,** which might affect different cardio-metabolic abnormalities. Soy consumption has been reported to beneficially affect features of the metabolic syndrome in animal models and also in humans to some extent. There are inconsistent reports regarding the hypothesis of the effectiveness of soy protein on obesity. While some studies have shown that soy consumption can improve the features of the metabolic syndrome without affecting body weight, others showed that soy consumption has beneficial role in weight management and might improve the metabolic syndrome by affecting body weight control. Several studies have consistently reported the effects of soy on cardiovascular risks. Beneficial role of soy intake on diabetes is another aspect of soy inclusion in the diet. The present study discusses the effects of soy consumption on different cardio-metabolic abnormalities and provides information regarding the possible mechanisms by which soy protein might exert its beneficial roles.

KEYWORDS: Soy, cardiovascular disease, diabetes, obesity, metabolic syndrome.

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The prevalence of chronic diseases such as metabolic syndrome, obesity and diabetes is growing rapidly both in developing and developed world [1-4]. These heterogeneous diseases are the results of interaction between genetic and environmental factors, especially the diet [5,6]. It has been proposed that different components of the diet especially unsaturated fatty acids [7], omega-3 fatty acids [8], dairy products [9], and whole grains [10] might influence the prevalence of the syndrome, either positively or negatively. Numerous studies have also assessed the effects of dietary intakes on glycemic control and insulin resistance in type 2 diabetes [11-13]. Soy, as a component of the diet, has received considerable attention in this regard. Several studies have reported the beneficial effects of soy consumption on insulin resistance and glycemic control [14,15]. Recently, some studies have reported the effects of soy consumption on the metabolic syndrome in animals [16-18], and humans [19-21]. Soy consumption could reduce risk of the metabolic syndrome through its beneficial components including complex carbohydrates, unsaturated fatty acids, vegetable protein, soluble fiber, oligosaccharides, vitamins, minerals, inositol-derived substances like lipintol, pinitol and phytoestrogens**,** particularly the isoflavones genistein, diadzein, and glycitein [22-24]. Some investigators have shown that soy consumption can improve features of the metabolic syndrome without affecting body weight [19]. Others reported that soy consumption has

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beneficial role in weight management and may improve the metabolic syndrome by affecting insulin resistance and weight control [25]. The aim of the current study was to review the effects of soy protein consumption on different cardio-metabolic abnormalities and to look for possible mechanisms of action.

Soy consumption and features of the metabolic syndrome

Animal studies have suggested beneficial effects of soy protein on development of the metabolic syndrome in obese rats [16-18]. A recent clinical trial among humans has shown that soy nut consumption in a framework of Dietary Approaches to Stop Hypertension (DASH) protocol for 8-week period improved fasting blood glucose, C-peptide level, HOMA-IR, and serum insulin concentrations (P<0.01 for all). Furthermore, when soy nut was compared with soy protein, it was demonstrated that soy nut could have more beneficial effects on glycemic control than soy protein (difference in percent change for HOMA-IR: -7.4 ± 0.8, P<0.01; difference in percent change for fasting plasma glucose: -5.3 ± 0.5, P<0.01). These effects were independent of changes in anthropometric measures [19]. Such finding may support a direct pharmacological effect of soy constituents. The hypothesis that soy isoflavones modulate glycemic control has not been confirmed yet. It has been assumed that higher level of isoflavones joint with polyunsaturated fatty acids, pinitol and protein might affect glycemic control. Most studies have indicated no significant effects of consuming soy protein containing isoflavones on blood pressure [24,26,27]. However, more longitudinal studies are required to come to conclusion in this regard. In a longitudinal study of soy food intake and blood pressure among middle-aged and elderly Chinese women, soy protein intake was inversely associated with both systolic blood pressure (P for trend = 0.01) and diastolic blood pressure (P for trend = 0.009) after adjustment for age, body mass index, lifestyle and other dietary factors [28]. In the Framingham Offspring Study of 939 post-menopausal US women, no significant relationship was found between isoflavone intake and blood pressure [29]. A small cross-sectional study in Japan reported a significant inverse association of blood pressure with soy food intake in men but not in women [30]. Atherogenic dyslipidemia is a major component of the metabolic syndrome. A meta-analysis of twenty-three randomized controlled trials published between 1995 and 2002 demonstrated that soy consumption could significantly increase serum HDL cholesterol levels (by 0.04 mmol/L, or 3.03%). Improvements in HDL cholesterol were only observed in studies with the duration of >12 weeks [31]. The mechanisms by which soy isoflavones affect lipid profiles may be related to the characteristic of the isoflavones, natural selective estrogen receptor modulator and its similarities to estrogens [32,33]. A meta-analysis assessing the effects of soy consumption on serum triglyceride levels suggested that soy protein containing isoflavones reduce serum triglyceride levels as compared to the corresponding control group in 23 (70%) out of 33 clinical trials [31]. Only 2 (6%) comparisons showed that the upper limit of the 95% CI was less than zero [31].

Soy and obesity

Protein intake has an important role in the pathogenesis of the obesity due to its satiating and thermogenic effects [34,35]. It have been shown that high protein diets are the most effective ones in weight reduction [36,37]. However, both the amount and the source of the protein intake are important in reducing body fat. Vegetable proteins like soy protein can stimulate satiety and prevent weight gain, which is already reported from some experimental investigations [38,39], but it has not been confirmed by clinical trials [40,41]. A twelve-week clinical trial by Anderson et al [41] showed beneficial effects of soy meal replacement, as part of a low-energy diet for weight loss. Others have also come to the same conclusion [42], while recent clinical trials have not found any significant difference between the effects of soy protein and casein on body weight [43,44]. Isoflavones, fatty acids, saponin and phospholipids content of soy might have beneficial effects on weight

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loss [45]. Soy protein might also affect lipid absorption, insulin resistance, fatty acid metabolism, and other hormonal, cellular, or molecular changes associated with adiposity [46]. An in-vivo study has suggested that soy protein may influence lipogenesis in the liver via reducing the concentrations of triglycerides in plasma and liver [47]. Furthermore, soy protein improves insulin resistance and lipid levels by activating peroxisome-proliferator activated receptors (PPARs), which are nuclear transcription factors that regulate the expression of genes involved in glucose homeostasis, lipid metabolism, and fatty acid oxidation [48,49]. Other possible mechanisms by which soy consumption might exert its beneficial effects in body weight management is stimulating adiponectin, which has an important role in the adipocyte differentiation and secretory function, and in enhancing insulin sensitivity [50-52]. Other components of soy have also been suggested for its mechanism of action [53-56].

Soy and cardiovascular risks

Beneficial effects of soy consumption on blood lipids are the most consistently reported findings. In a meta-analysis of 38 controlled clinical trials, Anderson et al [57] showed significant reductions in total cholesterol (9%), LDL cholesterol (13%) and triglycerides (11%) with a consumption on average of 47 g/d of soy protein. Two recent meta-analyses concluded that the isoflavones content of soy might be responsible for its lipid-lowering effect [58,59]. Controversy still exists in this field regarding the relative contribution of potential mechanisms of action of soy protein, isoflavones and other soy components on blood lipids and lipoproteins. Some investigators attribute this to the isoflavones content of soy. The isoflavones are structurally similar to estrogen and bind to the estrogen receptor, so it is biologically plausible that they protect against atherosclerosis development as estrogen agonists. Genistein is also a tyrosine kinase inhibitor, and some of the cardiovascular protection might be mediated by this mechanism. Some of the potential mechanisms have only reported from in vitro studies while others have been seen in vivo [60]. Findings on the effect of soy protein on serum apolipoproteins levels are inconsistent. Some reported no significant changes in circulating apo B [61,62] and apo A-I [63,64] in hyperlipidemic men following soy intake while others reported a significant decrease in apo B [64]. Inconsistent findings have also been reported on the effects of soy consumption on apolipoproteins among normolipidemic or healthy subjects. No significant changes in apo A or Apo B [65], significant reduction in apo-B/apo-A-I ratio [66] and no significant change in apo B but a significant increase in apo A have been reported among healthy individuals [67].

Soy and inflammatory markers

Soy contains fiber, polyunsaturated fat and phytoestrogens, which are individually associated with lower levels of inflammatory markers and improved endothelial function [68-70]. There are conflicting data in literature about the effect of soy components on inflammatory markers and endothelial function in humans [71-77]. Several trials have evaluated the effect of soy consumption on endothelial function; most of them assessed endothelial function by flow-mediated vasodilatation [78-81] and few focused on the biochemical markers of endothelial function such as soluble adhesion molecules and endothelial metabolites [71,74,76]. Some studies have assessed the effect of soy on inflammatory markers in healthy [71-73,75-77] or hypercholesterolemic postmenopausal women [74]. Nikander et al showed a neutral effect of phytoestrogen tablet consumption on the concentration of CRP, NO and E-selectin in postmenopausal women [75]. Isolated soy protein consumption caused no significant effect on the biochemical markers of endothelial function in healthy postmenopausal women [76] or vascular inflammation in hypercholesterolemic ones [74]. Decreased circulating levels of TNF-α were reported with the consumption of soymilk containing isoflavone in postmenopausal women [72]. There is only one study that examines the effect of soy protein or soy nut consumption on markers of inflammation and endothelial function in individuals with the metabolic syndrome in the frame work of us-

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ing dietary approaches to stop hypertension (DASH). The results of the mentioned study showed that only soy nut could reduce E-selectin, interleukin-18, and C-reactive protein (difference from the control diet –11.4%, –9.2%, and –4.6%, respectively) but soy protein could not [20]. Several trials have evaluated the effect of soy consumption on endothelial function; most of them assessed endothelial function by flow-mediated vasodilatation [78-80] and few focused on the biochemical markers of endothelial function such as soluble adhesion molecules and endothelial metabolites [71,74,76]. It seems that the purified phytoestrogens or isolated soy protein alone are not as effective as the combination of soy protein, fatty acids and phytoestrogens together [76,82]. Most of studies in this field have used purified phytoestrogens in the form of tablets, or isolated soy protein, which appears to have not as favorable effects as whole soy. This has been reflected to some extent in the Azadbakht et al study [20]. Although both soy protein and soy nut regimens had high amount of phytoestrogens compared to the control diet, only soy nut diet improved the inflammatory markers. Thus, the favorable effect might be attributed to higher amount of unsaturated fat or the interaction of fat, phytoestrogens and other components in soy nut. The levels of several inflammatory and endothelial markers in soy protein period were between that in the control period and that in the soy nut period. So, phytoestrogens itself may have week effect on reducing the levels of inflammatory markers. However, the deletion of red meat from the diet in the study periods may play a role in decreased levels of inflammatory markers [20]. The mechanisms through which soy affects inflammatory state and endothelial function are largely unknown, but may be related to the effects of soy phytoestrogens [83,84], specific fatty acids [39-42] or fibers [16]. Soy phytoestrogens can enhance nitric oxide release and bioavailability, and so reduce ET-1 concentrations [37,38]. These phytoestrogens may resemble hormone replacement therapy regimens, so reduce cell adhesion molecules and inflammatory markers [76]. Furthermore, polyunsaturated fat intake especially the combination of both omega-6 and omega-3 fatty acids is associated with the lowest levels of inflammation [70] as even omega-6 fatty acids have anti-inflammatory properties [85]. Therefore, some beneficial effects of soy nut on inflammatory markers, which contains both omega 3 and omega 6 fatty acids, are likely to be mediated by its fatty acids content.

Soy and oxidative stress

Several studies have focused on the effect of diet on oxidative stress, especially the effect of soy consumption [86-90]. The antioxidant properties of the soy isoflavones may protect against lipid oxidation [86] and improve total antioxidant status [87]. Some studies have suggested an antioxidant action of soy isoflavones [88,89] but others demonstrated little or no effect of soy-derived isoflavones on the biomarkers of oxidative stress [87,90]. A report on patients with hypercholesterolemia [91] suggested a reduction in lipid peroxidation as estimated by TBARs, after 6 weeks of soy milk consumption. Another report on postmenopausal women with metabolic syndrome showed that both soy protein and soy nut could increase total antioxidant capacity and reduce malondialdehyde level [21]. Conflicting results in different studies may be due to subject selection, doses of isoflavones and even interindividual variation in the ability to metabolize diadzein to equol [89,90]. Investigators mentioned that the antioxidant activity of soy might be related to its phytoestrogens or phytic acid content [92,93]. The antioxidant effect of soy phytoestrogens may be due to donating hydrogen atoms to free radicals, so making them less reactive [94]. Another possible mechanism, shown in a mouse model [95], may be related to increase antioxidant enzyme concentrations. In other way, the phytate in soy may quench free radicals because of its metal chelating ability [92]. Nevertheless, Engelman et al [90] showed that neither phytate nor isoflavones in soy protein isolate had a significant effect in reducing oxidative damage. It seems that the absorption of phytate in human is very low [90].

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Soy and diabetes

It is reported that soy can have important role in reducing the complications in patients with type 2 diabetes [96]. Studies in diabetic rats showed that soy intake can reduce glucagons and plasma glucose levels, increase first-phase insulin [97-99] and improve intra-arterial glucose tolerance test [100]. It is also demonstrated that soy protein consumption reduces hyperinsulinemia by stimulating insulin secretion to a lower extent. Furthermore, lower insulin levels and pancreatic islet area were found in soy protein fed rats as compared to rats fed the casein diet [101]. Clinical trials in human also have shown beneficial effects of soy consumption for type 2 diabetes [96,102,103]. However, the exact mechanism remains unknown. Possible suggested mechanisms include a tyrosine kinase inhibitory action, changes in insulin receptor numbers and affinity, intracellular phosphorylation and alterations in glucose transport [104]. Participants in different studies are not in the same range of weight. Soy protein consumption seems to influence glycemic control and insulin resistance more efficiently among obese subjects than among normal weight ones. By the way, most available studies have concluded that soy consumption might have a positive role in the control of the hyperglycemia and insulin resistance.

Conclusions

The results of the studies showed that soy inclusion in the diets could have beneficial effects on the cardio-metabolic abnormalities in different chronic diseases such as metabolic syndrome, type 2 diabetes, obesity, hypercholesterolemia and lipid abnormalities. These effects may be contributed to the soy compounds like isoflavones, fiber, phospholipids, fatty acids, saponins and other unknown parts. However, there are numerous questions and inconsistencies which is better to be clear in the future researches.

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