Soyfoods, glycemic control and diabetes

ENSA Scientific Advisory Committee Position Paper

Introduction

Diet is thought to play a key role in preventing the onset of type 2 diabetes mellitus (DM) and in helping to mitigate the risk of chronic diseases for which people with DM are at an increased risk. For example, a meta-analysis by Lee et al.[1] that included 14 observational studies found that the pooled odds ratio (OR) for DM in vegetarians compared with non-vegetarians was 0.726 (95% confidence interval [CI]: 0.608, 0.867). Furthermore, subgroup analysis indicated that vegans had a much lower risk than vegetarians overall (0.596 vs 0.726). Importantly, the observed inverse association between a vegetarian diet and the risk of DM exists even after adjusting for body mass index (BMI).[2,3]

There are many components of a vegetarian diet that may contribute to lower risk of developing DM among vegetarians. For example, vegetarians consume higher amounts of whole grains and less refined grain compared to nonvegetarians; observational studies show that these food groups are associated with lower and higher risks, respectively, of developing DM. Another component common to vegetarian that may reduce DM risk is soy.[4] Interestingly, more than 100 years ago Friedenwald and Ruhrah[5] concluded that "The soy bean in some way causes a reduction in the percentage and total quantity of sugar passed in diabetic subjects on the usual dietary restrictions." Much more recently, Bhathena and Velasquez[6] concluded that emerging evidence suggests that diets rich in soy protein, at least in part because of the isoflavones it contains, can have beneficial effects on several aspects of DM.

The purpose of this review is to examine the role of soyfoods and soybean components in the management of glycemic control and DM risk.

Soy/Isoflavone Exposure and Risk of Diabetes: Epidemiology

A recently published meta-analysis by Tian et al.,[7] which included seven cohort studies, found that when comparing high vs. low soy intake the summary relative risk (RR) for developing DM was 0.87 (95% CI: 0.74–1.01) in all participants and 0.74 (95% CI: 0.56, 0.93) in women only. However, this analysis included a British[8] and Indian study,[9] that reported legume intake but not soy intake; furthermore, the former was published only as an abstract. Also included in the meta-analysis was a pooled analysis of three US cohort studies; the Nurses' Health Study (NHS, 1998-2012), the Nurses' Health Study II (NHSII, 1999-2013) and the Health Professionals Follow-Up Study (2002-2010).[10] For reasons noted below, this pooled analysis,[10] and previously published related research[11] by this group, is of dubious value for providing insight about the relationship between soy and DM.

The pooled analysis found that when comparing extreme quintiles of isoflavone intake, the hazard ratio (HR) was 0.89 (95% CI: 0.83, 0.96; P for trend = 0.009).[10] In addition, a nested case-control study among 1,111 type 2 diabetic pairs participating in the NHS and NHSII found that when comparing extreme tertiles of urinary isoflavones, the odds ratio (OR) of DM were 0.71 (95% CI: 0.55, 0.93) for daidzein and 0.74 (95% CI: 0.56, 0.97) for genistein, although the test for linear trend was not significant for genistein (P trend=0.03 and 0.15, respectively).[11] The inverse association of daidzein with DM risk was stronger among postmenopausal women who did not use hormone replacement therapy.

Although these US results generally suggest soyfoods are protective against DM, there is an important caveat to consider. Of the >163,000 participants in the three cohorts, only about 5% consumed at least one serving of soyfoods per week. Furthermore, the mean isoflavone intake of this group was only about 10-13 mg/d. Although causality cannot be ruled out, it is unlikely that soy/isoflavone intake at this level could affect the development of DM. Concern about the inability of Western epidemiologic studies involving the general population to provide meaningful insight into the health effects of soyfoods, because soy intake is so minimal, was first expressed more than a decade ago.[12]

In contrast to these particular US results, soyfood intake was not protective against DM in the Hawaii component of the Multiethnic Cohort.[13] Among the 29,719 Caucasian, 35,141 Japanese American and 10,484 native Hawaiian men and women, 8,564 incident DM cases were identified during 14 years of follow-up. However, this analysis suffers from the same limitation of low soy intake noted previously. Even among Japanese Americans, mean soyfood intake was only 14.5 g/d. The authors of study highlighted this limitation as a possible reason for their failure to find protective effects of soyfoods and compared intake in their study to a Japanese study that found soyfood intake was indeed protective against DM among overweight women.[14]

Mean soy product and isoflavone intake in the Japanese study was about 90 g/d and about 45 mg/d, respectively,[14] which is about 6 times higher than the intake reported for Japanese Americans.[12] In this Japanese cohort study by Nanri et al.,[14] although soy intake was unrelated to risk among men and women overall, among overweight women (BMI ≥ 25) there were trends toward higher intakes of soy products and isoflavone intakes being associated with lower risks.

Participants included 25,872 men and 33,919 women aged 45-75 y who were part of the second survey of the Japan Public Health Center-Based Prospective Study. A total of 1,114 new cases of type 2 DM were self-reported.

Interestingly, in contrast to the results of Nanri et al.,[14] in the Saku cohort study, soy intake was protective among overweight Japanese men (BMI ≥23.6), but not normal-weight men or women.[15] In comparison to low soy-consumers (0-1x/wk), high soy-consumers (≥4x/wk) were 60% less likely to develop DM, fasting hyperglycemia or

postload hyperglycemia (95% CI: 0.18, 0.92) over the 4-year follow period.[15] This cohort involved 1,738 men and 1,301 women, aged 30–69 years.

The first prospective study to examine the relationship between soy intake and DM risk was the Shanghai Women's Health Study (SWHS), a population-based cohort of more than 64,000 middle-aged Chinese women.[16] Dietary intake was assessed with a validated food-frequency questionnaire at the baseline survey and at the first follow-up survey administered 2-3 y after study recruitment. The multivariate-adjusted RR for DM for the upper quintile compared with the lowest quintile was 0.62 (95% CI: 0.51, 0.74) for total legumes (peanuts, soybeans and other legumes) and 0.53 (95% CI: 0.45, 0.62) for soybeans. However, the association between soy products (other than for soy drink) and soy protein consumption with DM was not significant although not surprisingly, the trend was in that direction (P for trend = 0.13 for both food categories).

Another large Asian cohort to examine the soy-DM connection is the Singapore Chinese Health Study (SCHS), which includes 43,176 Chinese men and women aged 45-74 y.[17] During an average follow-up of 5.7 y, 2,252 participants developed DM. After adjustment for potential confounders and BMI, consumption of unsweetened soy was inversely associated with DM risk. HRs and 95% CI for DM across unsweetened soy intake categories (none, 1-4/month, 1-2/week, 3-4/week, ≥5/week) were: 1.00 (reference), 0.81 (0.67, 0.97), 0.76 (0.63, 0.91), 0.76 (0.63, 0.92), and 0.72 (0.59, 0.89), respectively (P for trend, 0.015). Conversely, in multivariate models, consuming sweetened soybean drink was positively associated with DM risk. After full adjustment, there was also a marginally significant inverse association between isoflavone intake and DM (HR for the fifth compared to the first quintile: 0.76; 95% CI: 0.58, 1.00; P for trend, 0.08).

However, a subsequently published nested case control study within the SCHS that included 564 DM cases and 564 matched controls failed to show that urinary isoflavone levels were related to DM risk.[18] More specifically, the multivariate-adjusted OR for DM were 1.00 (reference), 0.76 (95% CI: 0.52, 1.11), 0.78 (95% CI: 0.53, 1.14) and 0.79 (95% CI: 0.54, 1.15) across quartiles of urine isoflavones (P for trend=0.54). The mean age of the participants at the time of urine collection was 59.8 years, and the average interval between urine collection and DM diagnosis was 4.0 years. A possible caveat about this study is that because the half-life of isoflavones is only about 6-8 hours, morning urinary isoflavone excretion can be greatly affected by the timing of prior isoflavone intake and therefore, may not be a good measure of overall long-term exposure.[19]

Finally, there are two case control studies, one from Korea[20] and one from Vietnam,[21] both of which provide some support for the protective effects of soyfoods, but the former comes with an important caveat. A nested case-control study comprised of 693 cases (316 women and 377 men) and 698 matched controls (317 women and 381 men) within the Korean Genome and Epidemiology Study found that in women, compared with the lowest quartile of plasma concentration of genistein, the highest quartile exhibited a significantly decreased risk of DM (OR 0.58, 95% CI: 0.35, 0.95).[20]

However, when stratified by equol-producing status in women, genistein was protective only among equol producers and in men isoflavone concentrations were not associated with risk of DM, regardless of equol-producing status.

In Vietnam, a hospital-based case-control study involving 599 newly diagnosed diabetic cases (age 40-65 years) and 599 hospital-based controls found higher intake of total soyfoods was significantly associated with a lower risk of DM.[21] The adjusted OR for the highest versus the lowest intake was 0.31 (95% CI: 0.21, 0.46; P<0.001). An inverse dose-response relationship of similar magnitude was also observed for total isoflavone intake (OR: 0.35; 95% CI: 0.24, 0.49; P<0.001). In addition, inverse associations of specific soyfoods (soydrink, tofu and mung bean sprout) and major isoflavones (daidzein, genistein and glycitein) with the DM risk were evident.

Summary for epidemiologic data

Case control and/or cohort studies examining the relationship between soy and DM have been conducted in China,[16] Singapore,[17,18] Japan,[14,15] Vietnam,[21] Korea[20] and the United States.[10,11,13] The US data provide some support for the protective effects of soy against the development of DM but as noted, they are of doubtful relevance because of the low soy intake of Americans. When limiting interpretation to the Asian studies, it is clear the data are inconsistent.

Among the ethnic Chinese, soy intake was protective against DM in a Shanghainese cohort[16] whereas a Singaporean cohort, this was true for unsweetened but not sweetened soy[17] and urinary isoflavones were found to be unrelated to risk in a nested case control study from this cohort.[22] One Japanese cohort found that soy intake was protective among overweight women but not men or normal-weight women[14] whereas another found just the opposite, soy intake was protective against overweight men but not among women or normal-weight men.[15] Finally, a Korean case-control study found soy intake was protective only among equol producers[20] whereas a Vietnamese study found soy intake was markedly protective in both men and women.[21]

There is no obvious explanation for the discrepant findings. In Singapore, the finding that unsweetened but not sweetened soy was associated with a reduction in the risk of DM suggests that the naturally-low carbohydrate content of the soybean could be a factor. Another point to consider is whether the differing amounts of soy consumed among the populations studied could be one key. For example, in the Shanghainese cohort, which found soy intake to be very protective, median soy protein intake among those in the 5th quintile was 15.3 g/d,[16] whereas in the Singaporean cohort, the 5th quintile consumed only 10.9 g/d.[17] At this point while there is some suggestive epidemiologic evidence that soyfood intake is protective against DM the data are too mixed to reach conclusions.

Importance of maintaining healthy glucose levels

Maintaining a blood glucose level within a normal range by lowering postprandial hyperglycemia is effective at preventing diabetic complications, such as neuropathy, renal failure, blindness, and heart failure.[23] Several dietary therapies for preventing postprandial hyperglycemia have been proposed including plant-based diets.[24]

Clinical trials show that the adoption of a vegetarian diet leads to a reduction in glycosylated hemoglobin (HbA1C),[25] an important measure of long-term glucose control.[26] In fact, very recently, it was found that after just three days, the adoption of a vegan diet that included soy protein led to marked reductions in glucose levels and insulin resistance in comparison to the consumption of an omnivore diet even though carbohydrate intake was higher on the latter.[27]

Two of the main medical complications of DM are cardiovascular disease (CVD) and renal failure.[8,15] As is the case for DM, vegetarian diet is associated with a lower risk of CVD although it warrants emphasizing that the reduction in risk is more pronounced for men than it is for women.[28] Less is known about the potential benefits of vegetarian diets for those at risk of developing, and for those with existing, kidney disease. Plant-based diets may offer a number of advantages in this regard but some concerns about these diets have also been expressed.[29] Reduced urinary albumin excretion and lower glomerular filtration rates although still within the normal range, have been demonstrated in vegans and vegetarians compared to nonvegetarians.[30] These effects suggest vegetarian diets place less stress on renal function.

Soyfoods: Glycemic index and load

Unlike most beans which derive the majority (~70%) of their calories from carbohydrate, only about 30% of the energy from soybeans comes from this macronutrient.[31,32] This distinction is important because after a recent comprehensive review of the literature, Feinman et al.[33] concluded that "The benefits of carbohydrate restriction in DM are immediate and well documented." Although very recently published research provides only very modest support for the benefits of low-carbohydrate diets over low-fat diets, at the very least these data show the former are viable options for patients with DM.[34,35]

Furthermore, not only are soybeans low in carbohydrate, but about half of the carbohydrate in soybeans is comprised of oligosaccharides (primarily stachyose and raffinose) which are very poorly absorbed,[36] and which were recently shown to favorably affect insulin and glucose levels in pregnant women with gestational diabetes mellitus.[37]

Not surprisingly, many soyfoods have a very low glycemic index (GI). Even before Jenkins et al.[38] coined this term in 1981, this research group had established that soybeans had a low GI.[39] In fact, of the 24 foods they tested, which included eight legumes, soybeans had the lowest GI.[39] It was soon determined that a number of factors could contribute to the low GI of soybeans unrelated to carbohydrate

content.[40,41] For example, Thompson et al.[40] showed a strong inverse correlation between the intake of polyphenols from foods and the GI when tested in both healthy and diabetic individuals. Of the foods they examined, legumes in general and soybeans in particular had the highest polyphenol concentration.

Soy fiber may also play a role in the low GI of soybeans[42-47] although not all studies suggest this is the case.[48,49] Soy fiber is less effective than gel-forming fibers such as guar gum and pectin which is not surprising because soy polysaccharide is mostly insoluble fiber.[50] On the other hand, insoluble fiber has been linked with increased insulin sensitivity and decreased risk of DM.[51] The low GI of soybeans was emphatically illustrated in 1995 when the first comprehensive list of the GI of foods was published.[52] However, that list also included a tofu-based dessert with a high GI because of the amount of sugar that had been added to it.[53]

As a metric the GI actually underestimates the advantages of soybeans and soy products for controlling glucose levels because it fails to consider the low carbohydrate content of soybeans. A superior measure is arguably the glycemic load (GL) which is a reflection of the GI and carbohydrate content of foods. In 2002, Foster-Powell et al.[54] published a comprehensive list of the GI and GL of foods. Soybeans had a GL of 1, indicating it was both low in carbohydrates and the carbohydrates in it had a low GI. In comparison, the GL for other beans ranged from 2 (boiled peas) to 19 (pressure cooked Haricot and navy beans).

Quite a few other soy-containing products were included in the list but were part of a mixed food or beverage so it is difficult to gleam specific information about soy per se in these cases. Several flavored soy drinks were listed as having GLs between 6 and 8 and a soy yogurt and tofu-based frozen desert had GLs of 13 and 10, respectively.[54] Not surprisingly, as shown by Torres y Torres et al.[55] in the case of soy beverages the non-soy components, especially the addition of sugars, will greatly influence the GI and GL. These authors found that soy beverages had a low or moderate GI, depending upon the presence of other compounds like carbohydrates and fiber. Consumption of soy beverages with low concentrations of carbohydrates produced the lowest insulin secretion. Therefore, these products can be recommended in obese and diabetic patients. More recently, Serrano et al.[56] attributed the very low GI of soy drink (2.7 g sugar/100 ml) partly to a a relatively low carbohydrate absorption and partly to components in soy increasing incretin levels. Incretins are hormones that are released from the gut into the bloodstream in response to ingestion of food that modulates insulin response.[57]

Effects of co-ingestion protein source on glycemic response

Several studies have examined the impact of soy on the glycemic response of other foods, which is an important consideration since foods are rarely eaten in isolation. Recently, Law et al.[58,59] conducted two studies comparing the effects of different beverages on the glycemic response of cereal. In the first study, in response to 250 ml of the test beverages, the area under the curve (AUC, mmol/min/L) for glucose

120 minutes post ingestion was lowest following the soy beverage compared with all treatments ($p = 0.0002$) but was not significantly different from milk (97.4 ± 9.7 vs 120.4 ± 10.0) although it was lower than in comparison to almond milk and yogurt.[58] The AUC insulin was lowest for almond milk and the soy drink, the values for both of which differed significantly from milk and yogurt.

In the second study, participants received in random order 250 mL of 2% fat milk and soy beverage, 175 g of 2% Greek yogurt, and 30 g of Cheddar cheese consumed as part of an isocaloric (380 kcal) meal with bread and jam.[59] Water alone served as the energy-free control Cheese and yogurt resulted in lower post-treatment blood glucose than milk and soy beverage when consumed with carbohydrate ($p < 0.0001$), but no differences among any treatments were observed postmeal (after consuming a meal 3 hours later) and the treatments led to similar insulin concentrations.

In a study by Veldhorst et al.,[60] 500 ml 2% fat milk lowered the glucose response following a meal more than soy drink even though the former had a higher sugar content although it also had a slightly higher protein content (18 vs. 14 g). The lower glucose response could have been because milk protein may be more insulinotropic than soy protein.[60] On the other hand, although Sun et al.[61] found that soy drink and cow's milk similarly affected the glycemic response to bread; co-ingesting soy drink with bread increased insulin response and insulinemic index significantly compared to co-ingestion of dairy milk and preload treatments. Cow's milk may have influenced glycemic control by delaying gastric emptying. Evidence suggests that soy drink and cow's milk may be equally good at favorably impacting glycemic regulation although through different mechanisms.[62]

Finally, other studies have found little difference in the glucose response to a meal when comparing soy protein with animal protein including milk protein[63,64] although one study found that a casein-enriched lunch delayed glucose and insulin responses for 1.5 h, compared with soy protein, probably due to a lag in gastric emptying.[65] In summary, it appears that the ingestion of soy protein with a food with a high GI will favorably impact the glycemic response. Some studies show that soy protein has advantages over milk protein in this regard but the evidence is too mixed to reach definitive conclusions.

Effects of soybean components on insulin and glucose levels

Isoflavones

Four meta-analyses (or subsets within the analyses), which in total included 25 studies, that evaluated the impact of isoflavones on glycemic control have been published. The specific analyses included 7,[66] 9,[67] 10,[68] and 17,[69] studies. The publication date combined with the different inclusion criteria account for the differences in the number of studies included in each analysis. For example, the analysis by Liu et al.[66] included only studies that intervened with the isoflavone genistein whereas Ricci et al.[67] included only studies involving non-Asian women.

As can be seen from the table I nearly all studies involved postmenopausal women and only seven of the 25 studies involved women with abnormal glycemic control including women with elevated fasting glucose, insulin resistance, metabolic syndrome or DM. The vast majority of the isoflavones were administered in tablet form and compared to placebo whereas three studies intervened with soy protein containing different amounts of isoflavones,[70-72] one study used a cereal bar fortified with isoflavones[73] and one compared soy protein containing isoflavones with casein,[74] even though this experimental design does not allow outcome differences between groups to be attributed to isoflavones.

The dosage of isoflavones ranged from a low of 40 mg[75] to a high of 132 mg/d.[72] Seven trials intervened with genistein only, 11 trials intervened with a mixed isoflavones wherein the supplement contained an amount of genistein similar to or greater than that of daidzein, in five trials daidzein was the predominant isoflavone and genistein was present in lower amounts than glycitein, in one glycitein was the predominant isoflavone and in one study the composition of the isoflavone was not identified.

In the first published meta-analysis which included 9 studies and involved 405 treated women and 389 controls, Ricci et al.[67] concluded that isoflavones overall had no effect on glycemic control but based on the results of three studies concluded that genistein alone likely favorably did.[76-78] In agreement, in the 2011 meta-analysis by Liu et al.,[68] which included 696 participants and 10 studies, no effect of isoflavones on glycemic control was noted. However, it should be emphasized that because the three genistein-only studies[76-78] cited above in the analysis by Ricci et al.,[67] led to significant heterogeneity in fasting glucose concentrations, they were excluded from this analysis. Not surprisingly, in the 2017 analysis by Liu et al.,[66] which involved 670 participants all of which were involved in studies intervening with genistein only, it was found that genistein significantly lowered elevated glucose levels and increased insulin sensitivity in postmenopausal women.

Table 1. Studies included in meta-analyses evaluating the effects of isoflavones on long-term glycemic control

Author/year/reference	Location	Isoflavone composition[a]	Dose (mg/day)	Participants	Diabetic, MetS,[b] ↑ FG[c] or IR[d]	Meta-analyses			
						Ricci, 2010[67]	Liu, 2011[68]	Fang, 2016[69]	Liu, 2017[66]
Atteritano, 2007[78]	Italy	G	54	Postmenopausal	No	x		x	x
Aubertin-Leheudre, 2008[79]	Italy	D>Gly>G	70	Postmenopausal	No	x	x	x	
Bakhtiary, 2011[80]	Iran	G>D>Gly	117	Older	Yes			x	
Chan, 2008[81]	Hong Kong	NI	80	Older men/women	~50%		x		
Charles, 2009[70] ISP	USA	G=D>Gly	96	Postmenopausal	No	x	x	x	
Choquette, 2011[82]	Canada	D>Gly>G	70	Postmenopausal	No			x	

Colacurci, 2005[83]	Italy	G=D	120	Postmenopausal	No	x		x	
Crisafulli, 2005[77]	Italy	G	54	Postmenopausal	No			x	x
Duncan, 1999[71]	USA	G>D>Gly	10, 64, 128	Premenopausal	No		x		
Duncan, 1999[72]	USA	G>D>Gly	7, 65, 132	Postmenopausal	Yes		x		
Garrido, 2006[84]	Chile	D>Gly>G	100	Postmenopausal	No	x	x	x	
Gonzalez, 2007[85]	UK	G>D>Gly	132	Postmenopausal	Yes		x		
Hall, 2006[73] bars	Europe	G>D>Gly	50	Postmenopausal	No		x		
Han, 2002[86]	South Korea	G>D>Gly	100	Postmenopausal	No	x		x	
Ho, 2007[87]	Hong Kong	D>Gly>G	40, 80	Postmenopausal	No		x	x	
Irace, 2013[88]	Italy	G	54	Postmenopausal	Yes			x	x
Kaygusuz, 2010[89]	Turkey	G	50	Postmenopausal	No				x
Khaodhiar, 2008[75]	USA	D>Gly>G	40, 60	Postmenopausal	No	x		x	
Llaneza, 2010[90]	Spain	G>D>Gly	40	Postmenopausal	Yes			x	
Llaneza, 2012[91]	Spain	G>D>Gly	80	Postmenopausal	No			x	
Marini, 2010[92]	Italy	G	54	Postmenopausal	No			x	x
Nikander, 2004[93]	Finland	Gly>D>G	114	Postmenopausal	No		x	`	
Sites, 2007[74]	USA	G=D>Gly	96	Postmenopausal	No	x			
Squadrito, 2013[94]	Italy	G	54	Postmenopausal	Yes			x	x
Villa, 2009[76]	Italy	G	54	Postmenopausal	Yes	x		x	x

[a]Relative proportion of isoflavones [b]MS metabolic syndrome [c]fasting glucose [d]IR, insulin resistance

Finally, there is the meta-analysis by Fang et al.,[69] which included 17 studies. The results showed that overall in response to isoflavones blood glucose and insulin levels were lower in comparison to the placebo group. However, it was concluded that "genistein alone played an important role in improving glucose metabolism …" These findings are not surprising because of the 17 studies, six intervened with genistein only. Compared to the analysis by Liu et al.[66] only the Turkish study by Kaygusuz et al.[89] was not included in the analysis by Fang et al.[69]

In conclusion, the evidence shows that genistein favorably affects glycemic control. With one exception these studies were conducted in Italy by one research group and involved the use of 54 mg genistein delivered in aglycone form.[89] No obvious explanation for the striking performance of these genistein-only studies has been offered. It may be that when presented in aglycone form Cmax genistein levels are higher in comparison to when this isoflavone is ingested in glycoside form and as a result, biological processes related to glycemic control are favorably affected.

Soy protein

Two meta-analyses were identified that evaluated the effects of soy protein on glycemic control over a period of many weeks. One of these included eight studies and involved 183 patients with DM.[95] However, of the eight studies only four reported serum fasting glucose concentration in a way that permitted pooling of data. The pooled weighted mean differences for fasting glucose, insulin and HbA1C were -0.68 mmol/L (95% CI: -1.78, 0.42), -0.77 pmol/L (95% CI: -4.16, 2.62) and -0.09% (95% CI: -0.50% to 0.31%). Not surprisingly, given that none of these findings were statistically significant, the authors concluded that soy wouldn't affect glycemic control although parenthetically, they concluded soy would favorably affect lipids.

Table 2. Studies included in meta-analyses evaluating the effects of soy protein on long-term glycemic control

Author/year/(reference)	Soy protein dose (g/d)	Yang et al., 2011 (all diabetics) [95]	Zhang et al., 2016[96]
Anderson, 1998[97]	111	X	
Azadbakht, 2003[98]	20	X	
Azadbakht, 2007[99]	30		X
Azadbakht, 2008[100]	20	X	X
Gobert, 2010[101]	40	X	
Hermansen, 2001[102]	50	X	
Jayagopal, 2002[103]	30	X	
Kwak, 2010[104]	4.5		X
Liu, 2010[105]	15		X
Pipe, 2009[106]	40	X	
Teixeira, 2004[107]	0.5 g/kg bw	X	X

In contrast to the conclusions by Yang et al.,[95] on the basis of their 2016 meta-analysis, Zhang et al.[96] concluded that soy protein favorably affects fasting plasma glucose [weighted mean difference (WMD), -0.207; 95% CI, -0.374 to -0.040; p=0.015], fasting serum insulin (WMD, -0.292; 95% CI, -0.496 to -0.088; p=0.005) and homeostasis model of assessment for insulin resistance index (WMD, -0.346; 95% CI, -0.570 to -0.123; p=0.002) compared with a placebo control group, in patients with DM or the metabolic syndrome. However, their analysis included only 5 studies. Furthermore, one of the five trials intervened with peptides derived from black soybeans[104] and two intervened with soynuts in place of red meat.[99,100] Obviously, the latter two studies don't allow the outcome differences to be attributed specifically to soy protein and the results of the former are not necessarily applicable to the ingestion of soy protein.

In summary, relatively few studies have compared the effects of soy protein with a control protein on glycemic control. Based on the available data soy protein may favorably affect glucose levels but the effect is modest and the data too limited to draw definitive conclusions.

Effects of soyfoods on diabetes-related complications

As noted at the onset two of the main medical complications of DM are CVD and renal failure.[8,15] It is far beyond the scope of this review to address the impact of soyfoods on these two diseases. it would be an oversight not to at least mention that intriguing data suggest soy can help to reduce risk of developing, and possibly be useful in the management of CVD and renal disease.

For example, the most recently published meta-analysis of the clinical data shows that soy protein statistically significantly lowers low-density lipoprotein cholesterol (LDL-C) and that whole soyfoods lower LDL-C more than isolated soy protein.[108] Soyfoods can also lower cholesterol levels when they replace sources of protein commonly consumed by Westerners because of the favorable change in the fatty acid content of the diet.[109] Whole soyfoods provide ample amounts of linoleic acid,[110] which, when replacing saturated fat in the diet, reduces risk of developing CVD.[111] There may be other components of soybeans, such as the isoflavones, that favorably affect non-lipid CVD risk factors.[112-115] Thus, soyfoods potentially reduce risk of developing CVD through multiple mechanisms.

In addition, some evidence suggests that soy protein places less stress on renal function in comparison to animal protein.[116] Furthermore, meta-analyses of the clinical data indicate that soy protein helps to maintain favorable serum creatinine and phosphorus levels,[117,118] and possibly also decreases inflammation (as assessed by C-reactive protein) and proteinuria.[118] All of these effects are to the benefit of individuals at risk of developing, and those with existing kidney disease, the incidence of which has increased dramatically over the past 20 years as a result of the increased prevalence of DM.[119]

Overall conclusions

Several lines of evidence suggest soyfood may be especially healthful for people at risk of developing DM and for those with existing disease. Several observational studies show that higher soy intake is associated with a lower risk of developing DM. In the Asian studies soyfoods are consumed in their traditional form, principally as tofu, miso and soy drink. In addition, clinical works indicates soy protein may favorably affect glycemic control although the data are very inconsistent. More intriguing data exist in support of the isoflavone genistein increasing insulin sensitivity and lowering elevated glucose levels.

In general, many soyfoods fit well within the diet of people with DM because of their low GI and low GL. However, the extent to which this is true varies among products because of their differing composition. This point is most evident for soy beverages because of differences in the amount of added sugar they contain.

There may be a number of components of soyfoods that function individually, collectively or interactively to affect risk of DM. For example, as noted, soybeans, as

well as many soyfoods are relatively high in the essential omega-6 polyunsaturated linoleic acid. Clinical data show that linoleic acid favorably affects glycemic control and reduces insulin resistance[120] and epidemiologic data show that endogenous levels of this essential omega-6 fatty acid are inversely related to DM risk.[121] In support of the importance of whole soyfoods are data from a previously cited meta-analysis of the clinical data by Liu et al.,[68] which found that there was no significant overall effect of soy intake on fasting glucose and insulin concentrations, but there was a favorable change in fasting glucose concentrations in response to whole soyfoods.

Finally, as briefly discussed, independent of their effects on glycemic control and DM risk, soyfoods may be of help in alleviating common medical complications of DM such as CVD and renal disease. Therefore, there are several reasons for people with DM or at risk of developing DM to consider incorporating soyfoods into their diet.

References

1. Lee Y, Park K. Adherence to a vegetarian diet and diabetes risk: A systematic review and meta-analysis of observational studies. Nutrients. 2017;9.

2. Tonstad S, Butler T, Yan R, Fraser GE. Type of vegetarian diet, body weight, and prevalence of type 2 diabetes. Diabetes Care. 2009;32:791-6.

3. Tonstad S, Stewart K, Oda K, Batech M, Herring RP, Fraser GE. Vegetarian diets and incidence of diabetes in the Adventist Health Study-2. Nutrition, Metabolism, and Cardiovascular diseases: 2013;23:292-9.

4. Rizzo NS, Jaceldo-Siegl K, Sabate J, Fraser GE. Nutrient profiles of vegetarian and nonvegetarian dietary patterns. Journal of the Academy of Nutrition and Dietetics. 2013;113:1610-9.

5. Friedenwald J, Ruhrah J. The use of the soybean as a food in diabetes. Am J Med Sci. 1910;140:793-803.

6. Bhathena SJ, Velasquez MT. Beneficial role of dietary phytoestrogens in obesity and diabetes. Am J Clin Nutr. 2002;76:1191-201.

7. Tian S, Xu Q, Jiang R, Han T, Sun C, Na L. Dietary protein consumption and the risk of type 2 diabetes: A systematic review and meta-analysis of cohort studies. Nutrients. 2017;9.

8. Aldwairji M, Orfila C, Burley VJ. Legume intake and risk of type 2 diabetes in British women. Proc Nutr Soc. 2013;72:E275.

9. Agrawal S, Ebrahim S. Association between legume intake and self-reported diabetes among adult men and women in India. BMC Public Health. 2013;13:706.

10. Ding M, Pan A, Manson JE, et al. Consumption of soy foods and isoflavones and risk of type 2 diabetes: a pooled analysis of three US cohorts. Eur J Clin Nutr. 2016;70:1381-7.

11. Ding M, Franke AA, Rosner BA, et al. Urinary isoflavonoids and risk of type 2 diabetes: a prospective investigation in US women. Br J Nutr. 2015;114:1694-701.

12. Messina M. Western soy intake is too low to produce health effects. Am J Clin Nutr. 2004;80:528-9.

13. Morimoto Y, Steinbrecher A, Kolonel LN, Maskarinec G. Soy consumption is not protective against diabetes in Hawaii: the Multiethnic Cohort. Eur J Clin Nutr. 2011;65:279-82.

14. Nanri A, Mizoue T, Takahashi Y, et al. Soy product and isoflavone intakes are associated with a lower risk of type 2 diabetes in overweight Japanese women. J Nutr. 2010;140:580-6.

15. Tatsumi Y, Morimoto A, Deura K, Mizuno S, Ohno Y, Watanabe S. Effects of soybean product intake on fasting and postload hyperglycemia and type 2 diabetes in Japanese men with high body mass index: The Saku Study. Journal of diabetes investigation. 2013;4:626-33.

16. Villegas R, Gao YT, Yang G, et al. Legume and soy food intake and the incidence of type 2 diabetes in the Shanghai Women's Health Study. Am J Clin Nutr. 2008;87:162-7.

17. Mueller NT, Odegaard AO, Gross MD, et al. Soy intake and risk of type 2 diabetes in Chinese Singaporeans. Eur J Nutr. 2012;51:1033-40.

18. Talaei M, Lee BL, Ong CN, et al. Urine phyto-oestrogen metabolites are not significantly associated with risk of type 2 diabetes: the Singapore Chinese health study. Br J Nutr. 2016;115:1607-15.

19. Setchell KD, Faughnan MS, Avades T, et al. Comparing the pharmacokinetics of daidzein and genistein with the use of 13C-labeled tracers in premenopausal women. Am J Clin Nutr. 2003;77:411-9.

20. Ko KP, Kim CS, Ahn Y, et al. Plasma isoflavone concentration is associated with decreased risk of type 2 diabetes in Korean women but not men: results from the Korean Genome and Epidemiology Study. Diabetologia. 2015;58:726-35.

21. Nguyen CT, Pham NM, Do VV, et al. Soyfood and isoflavone intake and risk of type 2 diabetes in Vietnamese adults. Eur J Clin Nutr. 2017.

22. American Diabetes Association: Nutrition recommendations and principles for people with diabetes mellitus (Position Statement). Diabetes Care.20 (Suppl. 1):S14-S7.

23. Guideline for management of postmeal glucose in diabetes. Diabetes Res Clin Pract. 2014;103:256-68.

24. O'Keefe JH, Gheewala NM, O'Keefe JO. Dietary strategies for improving post-prandial glucose, lipids, inflammation, and cardiovascular health. J Am Coll Cardiol. 2008;51:249-55.

25. Yokoyama Y, Barnard ND, Levin SM, Watanabe M. Vegetarian diets and glycemic control in diabetes: a systematic review and meta-analysis. Cardiovasc Diagn Ther. 2014;4:373-82.

26. Inada M, Oishi M, Nishikawa M, Kurata S, Imura H. Clinical evaluation of measuring glycosylated hemoglobin levels for assessing the long-term blood glucose control in diabetics. Endocrinol Jpn. 1980;27:411-5.

27. Fogarty Draper C, Vassallo I, Di Cara A, et al. A 48-Hour Vegan Diet Challenge in Healthy Women and Men Induces a BRANCH-Chain Amino Acid Related, Health Associated, Metabolic Signature. Mol Nutr Food Res. 2017.

28. Kwok CS, Umar S, Myint PK, Mamas MA, Loke YK. Vegetarian diet, Seventh Day Adventists and risk of cardiovascular mortality: a systematic review and meta-analysis. Int J Cardiol. 2014;176:680-6.

29. Cupisti A, D'Alessandro C, Gesualdo L, et al. Non-traditional aspects of renal diets: Focus on fiber, alkali and vitamin K1 intake. Nutrients. 2017;9.

30. Gluba-Brzozka A, Franczyk B, Rysz J. Vegetarian diet in chronic kidney disease-A friend or foe. Nutrients. 2017;9.

31. Messina MJ. Legumes and soybeans: overview of their nutritional profiles and health effects. Am J Clin Nutr. 1999;70:439S-50S.

32. US Department of Agriculture, Agricultural Research Service, Nutrient Data Laboratory. USDA National Nutrient Database for Standard Reference, Release 28. Version Current: September 2015. Internet: http://www.ars.usda.gov/nea/bhnrc/ndl

33. Feinman RD, Pogozelski WK, Astrup A, et al. Dietary carbohydrate restriction as the first approach in diabetes management: critical review and evidence base. Nutrition. 2015;31:1-13.

34. Tay J, Luscombe-Marsh ND, Thompson CH, et al. Comparison of low- and high-carbohydrate diets for type 2 diabetes management: a randomized trial. Am J Clin Nutr. 2015;102:780-90.

35. Snorgaard O, Poulsen GM, Andersen HK, Astrup A. Systematic review and meta-analysis of dietary carbohydrate restriction in patients with type 2 diabetes. BMJ Open Diabetes Research & Care. 2017;5:e000354.

36. Grieshop CM, Kadzere CT, Clapper GM, et al. Chemical and nutritional characteristics of United States soybeans and soybean meals. J Agric Food Chem. 2003;51:7684-91.

37. Fei BB, Ling L, Hua C, Ren SY. Effects of soybean oligosaccharides on antioxidant enzyme activities and insulin resistance in pregnant women with gestational diabetes mellitus. Food Chem. 2014;158:429-32.

38. Jenkins DJ, Wolever TM, Taylor RH, et al. Glycemic index of foods: a physiological basis for carbohydrate exchange. Am J Clin Nutr. 1981;34:362-6.

39. Jenkins DJ, Wolever TM, Taylor RH, Barker HM, Fielden H. Exceptionally low blood glucose response to dried beans: comparison with other carbohydrate foods. Br Med J. 1980;281:578-80.

40. Thompson LU, Yoon JH, Jenkins DJ, Wolever TM, Jenkins AL. Relationship between polyphenol intake and blood glucose response of normal and diabetic individuals. Am J Clin Nutr. 1984;39:745-51.

41. Yoon JH, Thompson LU, Jenkins DJ. The effect of phytic acid on in vitro rate of starch digestibility and blood glucose response. Am J Clin Nutr. 1983;38:835-42.

42. Madar Z. Effect of brown rice and soybean dietary fiber on the control of glucose and lipid metabolism in diabetic rats. Am J Clin Nutr. 1983;38:388-93.

43. Librenti MC, Cocchi M, Orsi E, Pozza G, Micossi P. Effect of soya and cellulose fibers on postprandial glycemic response in type II diabetic patients. Diabetes Care. 1992;15:111-3.

44. Tsai AC, Vinik AI, Lasichak A, Lo GS. Effects of soy polysaccharide on postprandial plasma glucose, insulin, glucagon, pancreatic polypeptide, somatostatin, and triglyceride in obese diabetic patients. Am J Clin Nutr. 1987;45:596-601.

45. Tsai AC, Mott EL, Owen GM, Bennick MR, Lo GS, Steinke FH. Effects of soy polysaccharide on gastrointestinal functions, nutrient balance, steroid excretions, glucose tolerance, serum lipids, and other parameters in humans. Am J Clin Nutr. 1983;38:504-11.

46. Lo GS, Goldberg AP, Lim A, Grundhauser JJ, Anderson C, Schonfeld G. Soy fiber improves lipid and carbohydrate metabolism in primary hyperlipidemic subjects. Atherosclerosis. 1986;62:239-48.

47. Munoz JM, Sandstead HH, Jacob RA, et al. Effects of some cereal brans and textured vegetable protein on plasma lipids. Am J Clin Nutr. 1979;32:580-92.

48. Mahalko JR, Sandstead HH, Johnson LK, et al. Effect of consuming fiber from corn bran, soy hulls, or apple powder on glucose tolerance and plasma lipids in type II diabetes. Am J Clin Nutr. 1984;39:25-34.

49. Thomas BL, Laine DC, Goetz FC. Glucose and insulin response in diabetic subjects: acute effect of carbohydrate level and the addition of soy polysaccharide in defined- formula diets. Am J Clin Nutr. 1988;48:1048-52.

50. Riccardi G, Rivellese AA. Effects of dietary fiber and carbohydrate on glucose and lipoprotein metabolism in diabetic patients. Diabetes Care. 1991;14:1115-25.

51. Weickert MO, Pfeiffer AF. Metabolic effects of dietary fiber consumption and prevention of diabetes. J Nutr. 2008;138:439-42.

52. Foster-Powell K, Miller JB. International tables of glycemic index. Am J Clin Nutr. 1995;62.

53. Bukar J, Mezitis NH, Saitas V, Pi-Sunyer FX. Frozen desserts and glycemic response in well-controlled NIDDM patients. Diabetes Care. 1990;13:382-5.

54. Foster-Powell K, Holt SH, Brand-Miller JC. International table of glycemic index and glycemic load values: 2002. Am J Clin Nutr. 2002;76:5-56.

55. Torres y Torres N, Palacios-Gonzalez B, Noriega-Lopez L, Tovar-Palacio AR. [Glycemic, insulinemic index, glycemic load of soy beverage with low and high content of carbohydrates]. Rev Invest Clin. 2006;58:487-97.

56. Serrano JC, Martin-Gari M, Cassanye A, Granado-Serrano AB, Portero-Otin M. Characterization of the post-prandial insulinemic response and low glycaemic index of a soy beverage. PloS one. 2017;12:e0182762.

57. Kim W, Egan JM. The role of incretins in glucose homeostasis and diabetes treatment. Pharmacol Rev. 2008;60:470-512.

58. Law M, Huot PSP, Lee YT, Vien S, Luhovyy BL, Anderson GH. The effect of dairy and nondairy beverages consumed with high glycemic cereal on subjective appetite, food intake, and postprandial glycemia in young adults. Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme. 2017:1-9.

59. Law M, Lee YT, Vien S, Luhovyy BL, Anderson GH. The effect of dairy products consumed with high glycemic carbohydrate on subjective appetite, food intake, and postprandial glycemia in older adults. Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme. 2017:1-7.

60. Veldhorst MA, Nieuwenhuizen AG, Hochstenbach-Waelen A, et al. Dose-dependent satiating effect of whey relative to casein or soy. Physiol Behav. 2009;96:675-82.

61. Sun L, Tan KWJ, Han CMS, Leow MK, Henry CJ. Impact of preloading either dairy or soy milk on postprandial glycemia, insulinemia and gastric emptying in healthy adults. Eur J Nutr. 2017;56:77-87.

62. Sun L, Tan KW, Siow PC, Henry CJ. Soya milk exerts different effects on plasma amino acid responses and incretin hormone secretion compared with cows' milk in healthy, young men. Br J Nutr. 2016:1-6.

63. Bos C, Metges CC, Gaudichon C, et al. Postprandial kinetics of dietary amino acids are the main determinant of their metabolism after soy or milk protein ingestion in humans. J Nutr. 2003;133:1308-15.

64. Gannon MC, Nuttall FQ, Neil BJ, Westphal SA. The insulin and glucose responses to meals of glucose plus various proteins in type II diabetic subjects. Metabolism. 1988;37:1081-8.

65. Lang V, Bellisle F, Alamowitch C, et al. Varying the protein source in mixed meal modifies glucose, insulin and glucagon kinetics in healthy men, has weak effects on subjective satiety and fails to affect food intake. Eur J Clin Nutr. 1999;53:959-65.

66. Liu Y, Li J, Wang T, Wang Y, Zhao L, Fang Y. The effect of genistein on glucose control and insulin sensitivity in postmenopausal women: A meta-analysis. Maturitas. 2017;97:44-52.

67. Ricci E, Cipriani S, Chiaffarino F, Malvezzi M, Parazzini F. Effects of soy isoflavones and genistein on glucose metabolism in perimenopausal and postmenopausal non-Asian women: a meta-analysis of randomized controlled trials. Menopause. 2010;17:1080-6.

68. Liu ZM, Chen YM, Ho SC. Effects of soy intake on glycemic control: a meta-analysis of randomized controlled trials. Am J Clin Nutr. 2011;93:1092-101.

69. Fang K, Dong H, Wang D, Gong J, Huang W, Lu F. Soy isoflavones and glucose metabolism in menopausal women: A systematic review and meta-analysis of randomized controlled trials. Mol Nutr Food Res. 2016;60:1602-14.

70. Charles C, Yuskavage J, Carlson O, et al. Effects of high-dose isoflavones on metabolic and inflammatory markers in healthy postmenopausal women. Menopause. 2009;16:395-400.

71. Duncan AM, Merz BE, Xu X, Nagel TC, Phipps WR, Kurzer MS. Soy isoflavones exert modest hormonal effects in premenopausal women. J Clin Endocrinol Metab. 1999;84:192-7.

72. Duncan AM, Underhill KE, Xu X, Lavalleur J, Phipps WR, Kurzer MS. Modest hormonal effects of soy isoflavones in postmenopausal women. J Clin Endocrinol Metab. 1999;84:3479-84.

73. Hall WL, Vafeiadou K, Hallund J, et al. Soy-isoflavone-enriched foods and markers of lipid and glucose metabolism in postmenopausal women: interactions with genotype and equol production. Am J Clin Nutr. 2006;83:592-600.

74. Sites CK, Cooper BC, Toth MJ, Gastaldelli A, Arabshahi A, Barnes S. Effect of a daily supplement of soy protein on body composition and insulin secretion in postmenopausal women. Fertil Steril. 2007;88:1609-17.

75. Khaodhiar L, Ricciotti HA, Li L, et al. Daidzein-rich isoflavone aglycones are potentially effective in reducing hot flashes in menopausal women. Menopause. 2008;15:125-32.

76. Villa P, Costantini B, Suriano R, et al. The differential effect of the phytoestrogen genistein on cardiovascular risk factors in postmenopausal women: relationship with the metabolic status. J Clin Endocrinol Metab. 2009;94:552-8.

77. Crisafulli A, Altavilla D, Marini H, et al. Effects of the phytoestrogen genistein on cardiovascular risk factors in postmenopausal women. Menopause. 2005;12:186-92.

78. Atteritano M, Marini H, Minutoli L, et al. Effects of the phytoestrogen genistein on some predictors of cardiovascular risk in osteopenic, postmenopausal women: a two-year randomized, double-blind, placebo-controlled study. J Clin Endocrinol Metab. 2007;92:3068-75.

79. Aubertin-Leheudre M, Lord C, Khalil A, Dionne IJ. Isoflavones and clinical cardiovascular risk factors in obese postmenopausal women: a randomized double-blind placebo-controlled trial. J Womens Health (Larchmt). 2008;17:1363-9.

80. Bakhtiary A, Yassin Z, Hanachi P, Rahmat A, al. e. Evaluation of the oxidative stress and glycemic control statusin response to soy in older women with the metabolic syndrome. Iran Red Crescent Med. 2011;13:795-804.

81. Chan YH, Lau KK, Yiu KH, et al. Reduction of C-reactive protein with isoflavone supplement reverses endothelial dysfunction in patients with ischaemic stroke. Eur Heart J. 2008;29:2800-7.

82. Choquette S, Riesco E, Cormier E, Dion T, Aubertin-Leheudre M, Dionne IJ. Effects of soya isoflavones and exercise on body composition and clinical risk factors of cardiovascular diseases in overweight postmenopausal women: a 6-month double-blind controlled trial. Br J Nutr. 2011;105:1199-209.

83. Colacurci N, Chiantera A, Fornaro F, et al. Effects of soy isoflavones on endothelial function in healthy postmenopausal women. Menopause. 2005;12:299-307.

84. Garrido A, De la Maza MP, Hirsch S, Valladares L. Soy isoflavones affect platelet thromboxane A2 receptor density but not plasma lipids in menopausal women. Maturitas. 2006;54:270-6.

85. Gonzalez S, Jayagopal V, Kilpatrick ES, Chapman T, Atkin SL. Effects of isoflavone dietary supplementation on cardiovascular risk factors in type 2 diabetes. Diabetes Care. 2007;30:1871-3.

86. Han KK, Soares JM, Haidar MA, Rodrigues de Lima G, Baracat EC. Benefits of soy isoflavone therapeutic regimen on menopausal symptoms. Obstet Gynecol. 2002;99:389-94.

87. Ho SC, Chen YM, Ho SS, Woo JL. Soy isoflavone supplementation and fasting serum glucose and lipid profile among postmenopausal Chinese women: a double-blind, randomized, placebo-controlled trial. Menopause. 2007;14:905-12.

88. Irace C, Marini H, Bitto A, et al. Genistein and endothelial function in postmenopausal women with metabolic syndrome. Eur J Clin Invest. 2013;43:1025-31.

89. Kaygusuz I, Turhan NO, Duvan CI, Koca C, Aydin M. Effect of genistein therapy on plasma levels of asymmetric dimethylarginine in healthy postmenopausal women: a randomized, placebo-controlled study. Fertil Steril. 2010;94:764-6.

90. Llaneza P, Gonzalez C, Fernandez-Inarrea J, et al. Soy isoflavones, Mediterranean diet, and physical exercise in postmenopausal women with insulin resistance. Menopause. 2010;17:372-8.

91. Llaneza P, Gonzalez C, Fernandez-Inarrea J, Alonso A, Diaz F, Perez-Lopez FR. Soy isoflavones improve insulin sensitivity without changing serum leptin among postmenopausal women. Climacteric : the journal of the International Menopause Society. 2012;15:611-20.

92. Marini H, Bitto A, Altavilla D, et al. Efficacy of genistein aglycone on some cardiovascular risk factors and homocysteine levels: A follow-up study. Nutrition, metabolism, and cardiovascular diseases : NMCD. 2010;20:332-40.

93. Nikander E, Tiitinen A, Laitinen K, Tikkanen M, Ylikorkala O. Effects of isolated isoflavonoids on lipids, lipoproteins, insulin sensitivity, and ghrelin in postmenopausal women. J Clin Endocrinol Metab. 2004;89:3567-72.

94. Squadrito F, Marini H, Bitto A, et al. Genistein in the metabolic syndrome: results of a randomized clinical trial. J Clin Endocrinol Metab. 2013;98:3366-74.

95. Yang B, Chen Y, Xu T, et al. Systematic review and meta-analysis of soy products consumption in patients with type 2 diabetes mellitus. Asia Pacific journal of clinical nutrition. 2011;20:593-602.

96. Zhang XM, Zhang YB, Chi MH. Soy protein supplementation reduces clinical indices in type 2 diabetes and metabolic syndrome. Yonsei Med J. 2016;57:681-9.

97. Anderson JW, Blake JE, Turner J, Smith BM. Effects of soy protein on renal function and proteinuria in patients with type 2 diabetes. Am J Clin Nutr. 1998;68:1347S-53S.

98. Azadbakht L, Shakerhosseini R, Atabak S, Jamshidian M, Mehrabi Y, Esmaill-Zadeh A. Beneficiary effect of dietary soy protein on lowering plasma levels of lipid and improving kidney function in type II diabetes with nephropathy. Eur J Clin Nutr. 2003;57:1292-4.

99. Azadbakht L, Kimiagar M, Mehrabi Y, et al. Soy inclusion in the diet improves features of the metabolic syndrome: a randomized crossover study in postmenopausal women. Am J Clin Nutr. 2007;85:735-41.

100. Azadbakht L, Atabak S, Esmaillzadeh A. Soy protein intake, cardiorenal indices, and C-reactive protein in type 2 diabetes with nephropathy: a longitudinal randomized clinical trial. Diabetes Care. 2008;31:648-54.

101. Gobert CP, Pipe EA, Capes SE, Darlington GA, Lampe JW, Duncan AM. Soya protein does not affect glycaemic control in adults with type 2 diabetes. Br J Nutr. 2010;103:412-21.

102. Hermansen K, Sondergaard M, Hoie L, Carstensen M, Brock B. Beneficial effects of a soy-based dietary supplement on lipid levels and cardiovascular risk markers in type 2 diabetic subjects. Diabetes Care. 2001;24:228-33.

103. Jayagopal V, Albertazzi P, Kilpatrick ES, et al. Beneficial effects of soy phytoestrogen intake in postmenopausal women with type 2 diabetes. Diabetes Care. 2002;25:1709-14.

104. Kwak JH, Lee JH, Ahn CW, et al. Black soy peptide supplementation improves glucose control in subjects with prediabetes and newly diagnosed type 2 diabetes mellitus. J Med Food. 2010;13:1307-12.

105. Liu ZM, Chen YM, Ho SC, Ho YP, Woo J. Effects of soy protein and isoflavones on glycemic control and insulin sensitivity: a 6-mo double-blind, randomized, placebo-controlled trial in postmenopausal Chinese women with prediabetes or untreated early diabetes. Am J Clin Nutr. 2010;91:1394-401.

106. Pipe EA, Gobert CP, Capes SE, Darlington GA, Lampe JW, Duncan AM. Soy protein reduces serum LDL cholesterol and the LDL cholesterol:HDL cholesterol and apolipoprotein B:APOLIPOPRotein A-I ratios in adults with type 2 diabetes. J Nutr. 2009;139:1700-6.

107. Teixeira SR, Tappenden KA, Carson L, et al. Isolated soy protein consumption reduces urinary albumin excretion and improves the serum lipid profile in men with type 2 diabetes mellitus and nephropathy. J Nutr. 2004;134:1874-80.

108. Tokede OA, Onabanjo TA, Yansane A, Gaziano JM, Djousse L. Soya products and serum lipids: a meta-analysis of randomised controlled trials. Br J Nutr. 2015;114:831-43.

109. Jenkins DJ, Mirrahimi A, Srichaikul K, et al. Soy protein reduces serum cholesterol by both intrinsic and food displacement mechanisms. J Nutr. 2010;140:2302S-11S.

110. Slavin M, Kenworthy W, Yu LL. Antioxidant properties, phytochemical composition, and antiproliferative activity of Maryland-grown soybeans with colored seed coats. J Agric Food Chem. 2009;57:11174-85.

111. Li Y, Hruby A, Bernstein AM, et al. Saturated fats compared with unsaturated fats and sources of carbohydrates in relation to risk of coronary heart disease: A prospective cohort study. J Am Coll Cardiol. 2015;66:1538-48.

112. Pase MP, Grima NA, Sarris J. The effects of dietary and nutrient interventions on arterial stiffness: a systematic review. Am J Clin Nutr. 2011;93:446-54.

113. Li SH, Liu XX, Bai YY, et al. Effect of oral isoflavone supplementation on vascular endothelial function in postmenopausal women: a meta-analysis of randomized placebo-controlled trials. Am J Clin Nutr. 2010;91:480-6.

114. Li Y, Zhang H. Soybean isoflavones ameliorate ischemic cardiomyopathy by activating Nrf2-mediated antioxidant responses. Food & Function. 2017.

115. Liu XX, Li SH, Chen JZ, et al. Effect of soy isoflavones on blood pressure: A meta-analysis of randomized controlled trials. Nutrition, Metabolism, and Cardiovascular Diseases: NMCD. 2012;22:463-70.

116. McGraw NJ, Krul ES, Grunz-Borgmann E, Parrish AR. Soy-based renoprotection. World J Nephrol. 2016;5:233-57.

117. Zhang J, Liu J, Su J, Tian F. The effects of soy protein on chronic kidney disease: a meta-analysis of randomized controlled trials. Eur J Clin Nutr. 2014;68:987-93.

118. Jing Z, Wei-Jie Y. Effects of soy protein containing isoflavones in patients with chronic kidney disease: A systematic review and meta-analysis. Clin Nutr. 2016;35:117-24.

119. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. JAMA. 2007;298:2038-47.

120. Imamura F, Micha R, Wu JH, et al. Effects of saturated fat, polyunsaturated fat, monounsaturated fat, and carbohydrate on glucose-insulin homeostasis: A systematic review and meta-analysis of randomised controlled feeding trials. PLoS Med. 2016;13:e1002087.

121. Wu JHY, Marklund M, Imamura F, et al. Omega-6 fatty acid biomarkers and incident type 2 diabetes: pooled analysis of individual-level data for 39 740 adults from 20 prospective cohort studies. The lancet Diabetes & endocrinology. 2017.

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About ENSA

Established in January 2003, the ENSA represents the interests of natural soyfood manufacturers in Europe. The term “natural” refers to the production process used by ENSA members to produce food using whole soybeans. Soy food products from ENSA members are produced without any use of GM (genetically modified) material or GM beans.

ENSA is an association of internationally operating companies, ranging from large corporations to small, family-owned businesses with an annual turnover of €0.8 billion. Since its establishment in 2003, ENSA has been raising awareness about the role of soy and a plant-based diet in moving towards more sustainable food production and consumption patterns.

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