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Basic study

Soyfoods, glycemic control and diabetes

Soja, contrôle glycémique et diabète

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ABSTRACT

Soy is characterised by a higher content of specific proteins and isoflavones. The question is to know if incorporation of soy foods in the diet may have a favourable effect, or not, on the risk of diabetes, on glycaemic index and insulinemic response, and which are the components involved in these effects. This literature review analyses the epidemiological, clinical and experimental data for that question. Studies are in favour of a beneficial effect of soy on glycaemia, type 2 diabetes risk, and probably on complications of this disease. Its place in the diet should be examined.

Mots clés :
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RÉSUMÉ

Le soja est caractérisé par une teneur élevée en protéines spécifiques et en isoflavones. La question est de savoir dans quelle mesure l'incorporation d'aliments à base de soja peut avoir un effet favorable ou non sur le risque de survenue du diabète, sur l'indice glycémique et sur la réponse insulinémique et, quels sont les constituants qui pourraient en être responsables. Cette revue de la littérature analyse les données épidémiologiques, cliniques et mécanistiques relatives à cette question. Les études sont en faveur d'un bénéfice du soja sur la glycémie et le risque de diabète, voire les complications du diabète. Sa place dans l'alimentation mérite d'être examinée.

1. Introduction

The role of soy in diabetes mellitus prevention and glycemic control has emerged through many facts since more than twenty years [1]: animal studies, epidemiological studies and mechanistic data on the stimulatory action of genistein on glucose uptake in vitro and in vivo [2] and on insulin secretory function of pancreatic β-cells [3]. Moreover genistein has been considered for many years as a potent agent against diabetic retinopathy through an inhibition of retinal neovascularization [4] and an anti-inflammatory effect [5].

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. [6] that included

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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) [7,8].

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 diet that may reduce DM risk is soy [9]. More than 100 years ago Friedenwald and Ruhrah [10] 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 [1] 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.

2. Soy/Isoflavone exposure and risk of diabetes: epidemiology

2.1. Dietary soyfoods intake or isoflavones exposure

2.1.1. Multi ethnic studies

A meta-analysis [11], which included seven cohort studies, found that 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 when comparing high vs. low soy intake. However, this analysis included a British [12] and Indian study [13], that reported legumes 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) [14]. For reasons noted below (low consumption of soy), this pooled analysis [14] and another previously published [15] is questionable for providing insight about the relationship between soy and DM. The pooled analysis found that when comparing extreme quintiles of isoflavones intake, the hazard ratio (HR) was 0.89 (95% CI: 0.83, 0.96; *P* for trend = 0.009) [14].

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/day. 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 [16].

In contrast to these particular US results, soyfood intake was not protective against DM in the Hawaii component of the Multiethnic Cohort which is a prospective study (14 years of follow-up) performed among 29 141 Caucasian, 35 141 Japanese American and 10 484 Native Haiwaiian subjects [17]. Furthermore, 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 this 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 [18].

2.1.2. Asian populations

Indeed in this Japanese study, soyfood intake was protective against DM among overweight women [18]. Mean soy products and isoflavones intake in the Japanese study was about 90 g/d and about 45 mg/d, respectively [18], which is about six times higher than the intake reported for Japanese Americans [16]. Among the 59 791 participants (43% men, 57% women, aged 45–75 y) a total of 1,114 new cases of type 2 DM were self-reported. In this Japanese cohort study [18], although soy intake was unrelated to risk of DM 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 risk.

Interestingly, in contrast to the results of Nanri et al. [18], in the Saku cohort study [19], soy intake was protective among overweight Japanese men (BMI ≥ 23.6), but not among normal-weight men or women. In comparison to low soy-consumers (0–1 ×/wk), high soy-consumers (≥ 4 ×/wk) were 60% less likely to develop DM, fasting hyperglycemia or postload hyperglycemia (95% CI: 0.18, 0.92) over the 4-years follow period [19]. 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 [20]. 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 of DM for the upper quintile of 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 the trend was in that direction (*P* for trend = 0.13 for both food categories).

Another large Asian cohort that examined the soy-DM connection is the Singapore Chinese Health Study (SCHS), which includes 43,176 Chinese men and women aged 45–74 y [21]. During an average follow-up of 5.7 years, 2,252 participants developed DM. After adjustment for potential confounders and BMI, consumption of unsweetened soy was inversely associated with DM risk. HRs 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 (95% CI: 0.67, 0.97), 0.76 (95% CI: 0.63, 0.91), 0.76 (95% CI: 0.63, 0.92), and 0.72 (95% CI: 0.59, 0.89), respectively (*P* for trend, 0.015). Conversely, in multivariate models, consuming sweetened soybean drinks was positively associated with DM risk. After full adjustment, there was also a marginally significant inverse association between isoflavones 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).

2.2. Plasma or urinary isoflavones concentration

A nested case-control study among 1,111 type 2 diabetic pairs participating in the NHSI 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* for trend = 0.03 and 0.15, respectively) [15]. The inverse association of daidzein with DM risk was stronger among postmenopausal women who did not use hormone replacement therapy.

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 [22]. 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 h, morning urinary isoflavones excretion can be greatly affected by the timing of prior isoflavones intake and therefore, may not be a good measure of overall long-term exposure [23].

Finally, there are two case control studies, one from Korea [24] and one from Vietnam [25], 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) [24]. However, when stratified by equol-producing status in women, genistein was protective only among equol producers and in men isoflavones 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 [25] 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 isoflavones intake (OR: 0.35; 95% CI: 0.24, 0.49; $P < 0.001$). In addition, inverse associations of specific soyfoods (soy drink, tofu and mung bean sprout) and major isoflavones (daidzein, genistein and glycitein) with the DM risk were evident.

Recently a cross-sectional study of 3 314 subjects aged 18–79 years, was performed in Beijing, China in 2019 [26]. After adjustment soy products consumption was inversely associated with type 2 diabetes risk: OR for DM was 1.00 (reference), 0.82 (95% CI: 0.63–1.07), 0.60 (95% CI: 0.39–0.94) respectively across soy products consumption frequencies (monthly, weekly, daily) (P for trend 0.033) and with impaired fasting glucose (IFG): OR for IFG 1.00 (reference), 0.87 (95% CI: 0.66–1.15), 0.62 (95% CI: 0.385–0.985) respectively (P for trend 0.046).

2.3. Summary of the epidemiologic data

Case-control and/or cohort studies examining the relationship between soy and DM have been conducted in China [20], Singapore [21,22], Japan [18,19], Vietnam [25], Korea [24] and the United States [14,15,17]. 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.

Among the ethnic Chinese, soy intake was protective against DM in a Shanghainese cohort [20] and in Beijing population [26] whereas a Singaporean cohort, this was true for unsweetened but not sweetened soy drink [21] 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 [18] whereas another found that, soy intake was protective against overweight men but not among women or normal-weight men [19]. Finally, a Korean case-control study found soy intake was protective only among equol producers [24] whereas a Vietnamese study found soy intake was markedly protective in both men and women [25].

The differing amounts of soy consumed among the populations studied could be 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 [20], whereas in the Singaporean cohort, the 5th quintile consumed only 10.9 g/d [21].

Although some results are discordant according to the weight status, globally there are no negative studies and almost all show a protective effect of soyfoods and isoflavones intake (or markers of isoflavones intake) against DM.

3. Glycemic index and glycemic load of soyfoods

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 [27,28]. This distinction is important because after a recent comprehensive review of the literature, Feinman et al. [29] 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 [30,31]. Recently a meta-analysis of randomized controlled trials on the effect of the amount of carbohydrate in the management of type 2 diabetes has shown that a moderate low-carbohydrate diet more beneficial on HbA_{1c} than a normal carbohydrate diet [32]. 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 [33], and which were recently shown to favorably affect insulin and glucose levels in pregnant women with gestational diabetes mellitus [34].

Not surprisingly, many soyfoods have a very low glycemic index (GI). Even before Jenkins et al. [35] coined this term in 1981, this research group had established that soybeans had a low GI [36]. In fact, of the 24 foods they tested, which included eight legumes, soybeans had the lowest GI [36]. It was soon determined that a number of factors could contribute to the low GI of soybeans unrelated to carbohydrate content [37,38]. For example, Thompson et al. [37] 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 polyphenols concentration.

Soy fiber may also play a role in the low GI of soybeans [39–44] although not all studies suggest this is the case [45,46]. Soy fiber is less effective in reducing GI than gel-forming fibers such as guar gum, beta glucans or pectin, which is not surprising because soy polysaccharide is mostly insoluble fiber. On the other hand, insoluble fiber [47] has been linked with increased insulin sensitivity and decreased risk of DM [48]. The low GI of soybeans was emphatically illustrated in 1995 when the first comprehensive list of the GI of foods was published [49]. 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 [50].

As a metric the GI 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 reflects both the GI and carbohydrate content of foods. In 2002, Foster-Powell et al. [51] 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). Glycemic index should be considered at the level of the food and not as a characteristic of a type-isolated carbohydrate. Indeed, consumers eat foods, not carbohydrates; and foods containing the same type of carbohydrates can have different glycemic index, depending on their content in other nutrients, the structure of the matrix, the process they are submitted to.

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 [51]. Not surprisingly, as shown by Torres y Torres et al. [52] 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 for obese and diabetic patients. More recently, Serrano et al. [53] attributed the very low GI of soy drink (2.7 g sugar/100 mL) partly to 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 [54].

4. Effects of co-ingestion of soy and carbohydrate 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. [55,56] conducted two studies comparing the effects of different beverages on the glycemic response of cereal. In the first study, thirty six healthy males and females consumed non isocaloric amounts (250 mL) of four test beverages (almond beverage, soy beverage, 1% fat milk, yoghurt beverage): the area under the curve (AUC, mmol/min/L) for glucose 120 min post ingestion was lowest following the soy beverage compared with all treatments but was not significantly different from milk [55]. The AUC insulin was lowest for almond milk and the soy drink and the values for both differed significantly from milk and yoghurt. In the second study, thirty participants received in random order 250 mL of 2% fat milk and soy beverage, 175 g of 2% Greek yoghurt, and 30 g of Cheddar cheese consumed as part of an isocaloric (380 kcal) meal with bread and jam [56] providing respectively 64 g, 71 g, 60 g, 55 g of carbohydrate for each meal. Water alone served as the energy-free control. Cheese and yoghurt 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 post-meal (after consuming a meal 3 h later) and the treatments led to similar insulin concentrations.

In a study with twenty five healthy subjects in a randomized trial by Veldhorst et al. [57], 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 and also 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 [57]. On the other hand, although Sun et al. [58] found in a cross-over study with twelve healthy male that soy drink and cow's milk similarly affected the glycemic response to bread; but co-ingesting soy drink with bread increased insulin response and insulinemic index significantly compared to co-ingestion of dairy milk. A randomized study on twelve healthy male has shown that soy drink and cow's milk might be equally on glycemic regulation although through different mechanisms [59]. Plasma amino acid and incretins such as GIP may be involved in the hyperinsulinemia observed after soymilk meals. However higher plasma branched chain amino acid concentration and GLP_1 release may be responsible for the reduced glycaemia after cow milk consumption and delaying gastric emptying.

Finally, other studies have found little difference in the glucose response to a meal when comparing soy protein with animal protein including milk protein [60,61] 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 [62].

In summary, some data suggest there is a favorable effect of soy beverage on glycemic response. However there is still a gap due to the lack of studies comparing food with high GI only to food with high GI plus soy food.

5. Effects of soybean components on insulin and glucose levels

5.1. Isoflavones

Four meta-analysis (or subsets within the analysis), which in total included 25 studies, that evaluated the impact of isoflavones on glycemic control have been published. The specific analysis included 7 [63], 9[64], 10 [65] and 17 studies [66], which do not have the same design. For example, the analysis by Liu et al. [63] included only studies that intervened with the isoflavone genistein (10 studies, 696 participants) whereas Ricci et al. [64] included only studies involving non-Asian women (9 studies, 405 women and 389 controls). Moreover in the same meta-analysis, some studies are performed with total isoflavones, other with genistein or a mixture (Table 1).

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 [67–69], one study used a cereal bar fortified with isoflavones [70] and one compared soy protein containing isoflavones with casein [67], 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 [68] to a high of 132 mg/day [69]. Seven trials intervened with genistein only, eleven 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.

Ricci et al. [64] 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. In agreement, in the 2011 meta-analysis by Liu et al. [65], no effect of isoflavones on glycemic control was noted.

However, it should be emphasized that because the three genistein-only studies cited above in the analysis by Ricci et al. [64], led to significant heterogeneity in fasting glucose concentrations, they were excluded from this analysis. Not surprisingly, in the 2017 analysis by Liu et al. [63], which involved 670 participants all of which were involved in studies intervening with genistein only,

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	Liu, 2011	Fang, 2016	Liu, 2017
Atteritano, 2007/[98]	Italy	G	54	Postmenopausal	No	x		x	x
Aubertin-Leheudre, 2008/[68]	Italy	D > Gly > G	70	Postmenopausal	No	x	x	x	
Bakhtiary, 2011/[99]	Iran	G > D > Gly	117	Older	Yes			x	
Chan, 2008/[100]	Hong Kong	NI	80	Older men/women	~50%		x		
Charles, 2009/[101]	USA	G = D > Gly	96	Postmenopausal	No	x	x	x	
Choquette, 2011/[102]	Canada	D > Gly > G	70	Postmenopausal	No			x	
Colacurci, 2005/[103]	Italy	G = D	120	Postmenopausal	No	x		x	
Crisafulli, 2005/[104]	Italy	G	54	Postmenopausal	No			x	x
Duncan, 1999/[105]	USA	G > D > Gly	10, 64, 128	Premenopausal	No		x		
Duncan, 1999/[69]	USA	G > D > Gly	7, 65, 132	Postmenopausal	Yes		x		
Garrido, 2006/[106]	Chile	D > Gly > G	100	Postmenopausal	No	x	x	x	
Gonzalez, 2007/[107]	UK	G > D > Gly	132	Postmenopausal	Yes		x		
Hall, 2006/[108]	Europe	G > D > Gly	50	Postmenopausal	No		x		
Han, 2002/[109]	South Korea	G > D > Gly	100	Postmenopausal	No	x		x	
Ho, 2007/[110]	Hong Kong	D > Gly > G	40, 80	Postmenopausal	No		x	x	
Irace, 2013/[91]	Italy	G	54	Postmenopausal	Yes			x	x
Kaygusuz, 2010/[70]	Turkey	G	50	Postmenopausal	No				x
Khaodhiar, 2008/[111]	USA	D > Gly > G	40, 60	Postmenopausal	No	x		x	
Llaneza, 2010/[112]	Spain	G > D > Gly	40	Postmenopausal	Yes			x	
Llaneza, 2012/[113]	Spain	G > D > Gly	80	Postmenopausal	No			x	
Marini, 2010/[114]	Italy	G	54	Postmenopausal	No			x	x
Nikander, 2004/[115]	Finland	Gly > D > G	114	Postmenopausal	No		x		
Sites, 2007/[67]	USA	G = D > Gly	96	Postmenopausal	No	x			
Squadrito, 2013/[84]	Italy	G	54	Postmenopausal	Yes			x	x
Villa, 2009/[116]	Italy	G	54	Postmenopausal	Yes	x		x	x

[a] Relative proportion of isoflavones.
[b] MS: metabolic syndrome.
[c] Fasting glucose.
[d] IR: insulin resistance.

it was found that genistein significantly lowered elevated glucose levels and increased insulin sensitivity in postmenopausal women.

Finally, there is the meta-analysis by Fang et al. [66], 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. [63] only the Turkish study by Kaygusuz et al. [70] was not included in the analysis by Fang et al. [66].

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 [70]. 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.

5.2. Soy protein

Two meta-analyses were identified that evaluated the effects of soy protein on glycemic control over a period of many weeks (Table 2). One of these included eight studies and involved 183 patients with DM [71]. 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 HbA_{1C} 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.

In contrast to the conclusions by Yang et al., [71] on the basis of their 2016 meta-analysis, Zhang et al. [83] 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 [79] and two intervened with soynuts in place of red meat [74,75]. 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.

5.3. Soy peptides

Soy is also an interesting source of bioactive peptides, which are able to have physiologic actions against glucose homeostasis and insulin metabolism. A recent review [84] has summarized the in vitro and in vivo studies of soy hydrolysates peptides. In vitro results show that soy hydrolysates peptides obtained after hydrolysis by specific enzymes and some identified peptides can improve insulin sensitivity, inhibit DPP-IV, increase glucose intake in muscle and liver, and reduce lipid accumulation and inflammation

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) [77]	Zhang et al., 2016 [89]
Anderson, 1998/[72]	111	X	
Azadbakht, 2003/[73]	20	X	
Azadbakht, 2007/[74]	30		X
Azadbakht, 2008/[75]	20	X	X
Gobert, 2010/[76]	40	X	
Hermansen, 2001/[77]	50	X	
Jayagopal, 2002/[78]	30	X	
Kwak, 2010/[79]	4.5		X
Liu, 2010/[80]	15		X
Pipe, 2009/[81]	40	X	
Teixeira, 2004/[82]	0.5 g/kg bw	X	X

in adipose tissue. In vivo results, although scarce, show that soy hydrolysates and soy peptides can potentially reduce tissue fat accumulation and increase fat excretion. Moreover the soy peptides aglycin is resistant to gastrointestinal digestion and can be absorbed intact in mice. Nevertheless, only a few studies were performed to test soy hydrolysates and peptides as antidiabetic agents.

6. 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. 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 [85]. Recently a meta-analysis of 46 controlled trials identified by the Food and Drug Administration demonstrates that soy protein reduces LDL concentration by approximately 3–4% in adults [86]. Soyfoods can also lower cholesterol levels when replacing sources of protein commonly consumed by Westerners because of the favorable change in the fatty acid content of the diet [87]. Whole soyfoods provide ample amounts of linoleic acid [88] which, when replacing saturated fat in the diet, reduces risk of developing CVD [89]. There may be components of soybeans, such as the isoflavones, that favorably affect other non-lipid CVD risk factors [90–93]. Recently a randomized controlled clinical trial on 75 subjects with type 2 diabetes has analyzed the effect of the substitution of red meat with soybean or not-soy legumes on inflammatory and oxidative stress markers [94]. In these 8 weeks parallel trial, two servings red meat a day, three days/week were substituted by one cup of soybeans or one cup of legumes. Soy bean but not non-soy legumes reduce significantly serum CRP with no effect on oxidative marker (serum malondialdehyde). 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 [95]. Furthermore, meta-analyses of the clinical data indicate that soy protein helps to maintain favorable serum creatinine and phosphorus levels [96,97] and possibly also decreases inflammation (as assessed by C-reactive protein) and proteinuria in chronic kidney disease. 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.

7. Overall conclusions

Some epidemiological data show that higher soy foods consumption and isoflavones intake is associated with a lower risk of developing type 2 diabetes. The mechanism is discussed and may involve the low glycemic index of soyfoods. Some data exist in support of the isoflavones genistein increasing insulin sensitivity and lowering elevated glucose levels. The role of soy protein on glucose metabolism is inconsistent, but some data suggest that soy bioactive peptides may have a favorable role on glucose homeostasis. But one must take account firstly the specificity of the traditional form of consumed soyfoods in Asian populations principally as fermented tofu and miso, secondly the fact that soy beverages in western countries contain added sugar, thirdly the complexity of soyfoods and so the importance of whole soyfoods [65] because several components of soyfoods may affect the risk of type 2 diabetes or of glucose tolerance.

Moreover it is important to consider that a part of the beneficial effect of soyfoods consumption may be due to the global diet: indeed in western countries soyfoods are very often included in a vegetarian diet.

Finally, as briefly discussed, independent of their potential 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.

Disclosure of interest

All authors are member of ENSA (European Natural Soyfoods Association).

References

[1] Bhathena SJ, Velasquez MT. Beneficial role of dietary phytoestrogens in obesity and diabetes. Am J Clin Nutr 2002;76:1191–201.
[2] Ha BG, Nagaoka M, Yonezawa T, Tanabe R, Woo JT, Kato H, et al. Regulatory mechanism for the stimulatory action of genistein on glucose uptake in vitro and in vivo. J Nutr Biochem 2012;23:501–9.
[3] Fu Z, Liu D. Long-term exposure to genistein improves insulin secretory function of pancreatic beta-cells. Eur J Pharmacol 2009;616:321–7.
[4] Wang B, Zou Y, Li H, Yan H, Pan J-S, Yuan Z-L. Genistein Inhibited Retinal Neovascularization and Expression of Vascular Endothelial Growth Factor and Hypoxia Inducible Factor 1α in a Mouse Model of Oxygen-Induced Retinopathy. J Ocul Pharmacol Ther 2005;21:107–13.
[5] Ibrahim AS, El-Shishtawy MM, Peña A, Liou GI. Genistein attenuates retinal inflammation associated with diabetes by targeting of microglial activation. Mol Vis 2010;16:2033–42.
[6] Lee Y, Park K. Adherence to a Vegetarian Diet and Diabetes Risk: A Systematic Review and Meta-Analysis of Observational Studies. Nutrients 2017;9:603.
[7] 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.
[8] Tonstad S, Stewart K, Oda K, Batech M, Herring RP, Fraser GE. Vegetarian diets and incidence of diabetes in the Adventist Health Study-2. Nutr Metab Cardiovasc Dis 2013;23:292–9.
[9] Rizzo NS, Jaceldo-Siegl K, Sabate J, Fraser GE. Nutrient profiles of vegetarian and nonvegetarian dietary patterns. J Acad Nutr Diet 2013;113:1610–9.

[10] Friedenwald, Julius, Ruhrah J. The use of the soy bean as a food in diabetes. Am J Med Sci 1910;140:793.
[11] 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;9:982.
[12] Aldwairji M, Orfila C, Burley VJ. Legume intake and risk of type 2 diabetes in British women. Proc Nutr Soc 2013;72:E275.
[13] 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.
[14] Ding M, Pan A, Manson JE, Willett WC, Malik V, Rosner B, 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.
[15] Ding M, Franke AA, Rosner BA, Giovannucci E, van Dam RM, Tworoger SS, et al. Urinary isoflavonoids and risk of type 2 diabetes: a prospective investigation in US women. Br J Nutr 2015;114:1694–701.
[16] Messina M. Western soy intake is too low to produce health effects. Am J Clin Nutr 2004;80:528–9 [author reply 529-30].
[17] 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.
[18] Nanri A, Mizoue T, Takahashi Y, Kirii K, Inoue M, Noda M, 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.
[19] 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. J Diabetes Investig 2013;4:626–33.
[20] Villegas R, Gao Y-T, Yang G, Li H-L, Elasy TA, Zheng W, 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.
[21] Mueller NT, Odegaard AO, Gross MD, Koh W-P, Yu MC, Yuan J-M, et al. Soy intake and risk of type 2 diabetes mellitus in Chinese Singaporeans. Eur J Nutr 2012;51:1033–40.
[22] Talaei M, Lee BL, Ong CN, van Dam RM, Yuan JM, Koh WP, et al. Urine phytoestrogen metabolites are not significantly associated with risk of type 2 diabetes: the Singapore Chinese health study. Br J Nutr 2016;115:1607–15.
[23] Setchell KDR, Faughnan MS, Avades T, Zimmer-Nechemias L, Brown NM, Wolfe BE, et al. Comparing the pharmacokinetics of daidzein and genistein with the use of 13C-labeled tracers in premenopausal women. Am J Clin Nutr 2003;77:411–49.
[24] Ko K-P, Kim C-S, Ahn Y, Park S-J, Kim Y-J, Park JK, 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.
[25] Nguyen CT, Pham NM, Do VV, Binns CW, Hoang VM, Dang DA, et al. Soyfood and isoflavone intake and risk of type 2 diabetes in Vietnamese adults. Eur J Clin Nutr 2017;71:1186–92.
[26] Zhu Z, He H, Zhou J, Zhang T, Zhou G, Zhuang G, et al. Soy product consumption and type 2 diabetes among adults in Beijing, China. Asia Pac. J Clin Nutr 2019;28:150–6.
[27] Messina MJ. Legumes and soybeans: overview of their nutritional profiles and health effects. Am J Clin Nutr 1999;70:439S–50S.
[28] Agricultural research Service, Nutrient Data Laboratory. USDA National Nutrient Database for Standard Reference, release 28. Version Current. US Department of Agriculture; 2015 http://www.ars.usda.gov/nea/bhnrc/ndl [INTERNET/. 2015].
[29] Feinman RD, Pogozelski WK, Astrup A, Bernstein RK, Fine EJ, Westman EC, et al. Dietary carbohydrate restriction as the first approach in diabetes management: critical review and evidence base. Nutrition 2015;31:1–13.
[30] Tay J, Luscombe-Marsh ND, Thompson CH, Noakes M, Buckley JD, Wittert GA, 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.
[31] 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 Res Care 2017;5:e000354.
[32] Huntriss R, Campbell M, Bedwell C. The interpretation and effect of a low-carbohydrate diet in the management of type 2 diabetes: a systematic review and meta-analysis of randomised controlled trials. Eur J Clin Nutr 2018;72:311–25.
[33] Grieshop CM, Kadzere CT, Clapper GM, Flickinger EA, Bauer LL, Frazier RL, et al. Chemical and nutritional characteristics of United States soybeans and soybean meals. J Agric Food Chem 2003;51:7684–91.
[34] Fei B, Ling L, Hua C, Ren S. Effects of soybean oligosaccharides on antioxidant enzyme activities and insulin resistance in pregnant women with gestational diabetes mellitus. Food Chem 2014;158:429–32.
[35] Jenkins DJ, Wolever TM, Taylor RH, Barker H, Fielden H, Baldwin JM, et al. V Glycemic index of foods: a physiological basis for carbohydrate exchange. Am J Clin Nutr 1981;34:362–6.
[36] 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.
[37] 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.
[38] 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.
[39] Madar Z. Effect of brown rice and soybean dietary fiber on the control of glucose and lipid metabolism in diabetic rats. Am Clin Nutr 1983;38:388–93.
[40] 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.
[41] 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.
[42] 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.
[43] 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.
[44] Munoz JM, Sandstead HH, Jacob RA, Logan GM, Reck SJ, Klevay LM, et al. Effects of some cereal brans and textured vegetable protein on plasma lipids. Am J Clin Nutr 1979;32:580–92.
[45] Mahalko JR, Sandstead HH, Johnson LK, Inman LF, Milne DB, Warner RC, 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.
[46] 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.
[47] Riccardi G, Rivellese AA. Effects of dietary fiber and carbohydrate on glucose and lipoprotein metabolism in diabetic patients. Diabetes Care 1991;14:1115–25.
[48] Weickert MO, Pfeiffer AFH. Metabolic effects of dietary fiber consumption and prevention of diabetes. J Nutr 2008;138:439–42.
[49] Foster-Powell K, Miller JB. International tables of glycemic index. Am J Clin Nutr 1995;62:871S–90S.
[50] 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.
[51] Foster-Powell K, Holt SHA, Brand-Miller JC. International table of glycemic index and glycemic load values: 2002. Am J Clin Nutr 2002;76:5–56.
[52] Torres y Torres N, Palacios-González B, Noriega-López 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.
[53] Serrano JC, Martín-Gari M, Cassanye A, Granado-Serrano AB, Portero-Otín M. Characterization of the post-prandial insulinemic response and low glycaemic index of a soy beverage. PLoS One 2017;12:e0182762.
[54] Kim W, Egan JM. The role of incretins in glucose homeostasis and diabetes treatment. Pharmacol Rev 2008;60:470–512.
[55] 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. Appl Physiol Nutr Metab 2017;42:1201–9.
[56] 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. Appl Physiol Nutr Metab 2017;42:1210–6.
[57] Veldhorst MAB, Nieuwenhuizen AG, Hochstenbach-Waelen A, van Vught AJAH, Westerterp KR, Engelen MPKJ, et al. Dose-dependent satiating effect of whey relative to casein or soy. Physiol Behav 2009;96:675–82.
[58] Sun L, Tan KWJ, Han CMS, Leow MK-S, 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.
[59] Sun L, Tan KWJ, 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;116:1216–21.
[60] Bos C, Metges CC, Gaudichon C, Petzke KJ, Pueyo ME, Morens 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.
[61] 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.
[62] Lang V, Bellisle F, Alamowitch C, Craplet C, Bornet FR, Slama G, 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.
[63] 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.
[64] 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.
[65] Liu Z-M, Chen Y-M, Ho SC. Effects of soy intake on glycemic control: a meta-analysis of randomized controlled trials. Am J Clin Nutr 2011;93:1092–101.

[66] 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.
[67] 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.
[68] 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.
[69] Duncan AM, Underhill KEW, 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.
[70] 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.
[71] Yang B, Chen Y, Xu T, Yu Y, Huang T, Hu X, et al. Systematic review and meta-analysis of soy products consumption in patients with type 2 diabetes mellitus. Asia Pac J Clin Nutr 2011;20:593–602.
[72] 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.
[73] 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.
[74] Azadbakht L, Kimiagar M, Mehrabi Y, Esmaillzadeh A, Padyab M, Hu FB, 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.
[75] 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.
[76] 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.
[77] Hermansen K, Søndergaard M, Høie 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.
[78] Jayagopal V, Albertazzi P, Kilpatrick ES, Howarth EM, Jennings PE, Hepburn DA, et al. Beneficial effects of soy phytoestrogen intake in postmenopausal women with type 2 diabetes. Diabetes Care 2002;25:1709–14.
[79] Kwak JH, Lee JH, Ahn C-W, Park S-H, Shim S-T, Song YD, 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.
[80] Liu Z, Chen Y, 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.
[81] Pipe EA, Gobert CP, Capes SE, Darlington GA, Lampe JW, Duncan AM, et al. 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.
[82] Teixeira SR, Tappenden KA, Carson L, Jones R, Prabhudesai M, Marshall WP, 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.
[83] Zhang X-M, Zhang Y-B, Chi M-H. Soy Protein Supplementation Reduces Clinical Indices in Type 2 Diabetes and Metabolic Syndrome. Yonsei Med J 2016;57:681–9.
[84] de Campos Zani SC, Wu J, Chan CB. Egg and soy-derived peptides and hydrolysates: a review of their physiological actions against diabetes and obesity. Nutrients 2018;10:549.
[85] Tokede OA, Onabanjo TA, Yansane A, Gaziano JM, Djoussé L. Soya products and serum lipids: a meta-analysis of randomised controlled trials. Br J Nutr 2015;114:831–43.
[86] Blanco Mejia S, Messina M, Li SS, Viguiliouk E, Chiavaroli L, Khan TA, et al. A Meta-Analysis of 46 Studies Identified by the FDA Demonstrates that Soy Protein Decreases Circulating LDL and Total Cholesterol Concentrations in Adults. J Nutr 2019;149:968–81.
[87] Jenkins DJA, Mirrahimi A, Srichaikul K, Berryman CE, Wang L, Carleton A, et al. Soy protein reduces serum cholesterol by both intrinsic and food displacement mechanisms. J Nutr 2010;140:2302S–11S.
[88] Slavin M, Kenworthy W, Yu L. (Lucy) Antioxidant Properties, Phytochemical Composition, and Antiproliferative Activity of Maryland-Grown Soybeans with Colored Seed Coats. J Agric Food Chem 2009;57:11174–85.
[89] Li Y, Hruby A, Bernstein AM, Ley SH, Wang DD, Chiuve SE, 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.
[90] 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.
[91] Li S-H, Liu X-X, Bai Y-Y, Wang X-J, Sun K, Chen J-Z, 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.
[92] Li Y, Zhang H. Soybean isoflavones ameliorate ischemic cardiomyopathy by activating Nrf2-mediated antioxidant responses. Food Funct 2017;8:2935–44.
[93] Liu XX, Li SH, Chen JZ, Sun K, Wang XJ, Wang XG, et al. Effect of soy isoflavones on blood pressure: a meta-analysis of randomized controlled trials. Nutr Metab Cardiovasc Dis 2012;22:463–70.
[94] Hematdar Z, Ghasemifard N, Phishdad G, Faghih S. Substitution of red meat with soybean but not non- soy legumes improves inflammation in patients with type 2 diabetes, a randomized clinical trial. J. Diabetes Metab Disord 2018;17:111–6.
[95] McGraw NJ, Krul ES, Grunz-Borgmann E, Parrish AR. Soy-based renoprotection. World J Nephrol 2016;5:233–57.
[96] 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.
[97] 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.
[98] Atteritano M, Marini H, Minutoli L, Polito F, Bitto A, Altavilla D, 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.
[99] Bakhtiari A, Yasin Z, Hanachi PRA, et al. Evaluation of the oxidative stress and glycemic control status in response to soy in older women with the metabolic syndrome. Iran Red Crescent Med 2011;13:795–804, e-Marefa. Available online: https://search.emarefa.net/detail/BIM-321739?index=3.
[100] Chan Y-H, Lau K-K, Yiu K-H, Li S-W, Chan H-T, Fong DY-T, 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.
[101] Charles C, Yuskavage J, Carlson O, John M, Tagalicud AS, Maggio M, et al. Effects of high-dose isoflavones on metabolic and inflammatory markers in healthy postmenopausal women. Menopause 2009;16:395–400.
[102] Choquette S, Riesco É, Cormier É, 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.
[103] Colacurci N, Chiàntera A, Fornaro F, de Novellis V, Manzella D, Arciello A, et al. Effects of soy isoflavones on endothelial function in healthy postmenopausal women. Menopause 2005;12:299–307.
[104] Crisafulli A, Altavilla D, Marini H, Bitto A, Cucinotta D, Frisina N, et al. Effects of the phytoestrogen genistein on cardiovascular risk factors in postmenopausal women. Menopause 2005;12:186–92.
[105] 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.
[106] 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.
[107] 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.
[108] Hall WL, Vafeiadou K, Hallund J, Bugel S, Reimann M, Koebnick C, 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.
[109] Han KK, Soares JM, Haidar MA, de Lima GR, Baracat EC. Benefits of soy isoflavone therapeutic regimen on menopausal symptoms. Obstet Gynecol 2002;99:389–94.
[110] Ho SC, Chen Y, Ho SSS, Woo JLF. Soy isoflavone supplementation and fasting serum glucose and lipid profile among postmenopausal Chinese women. Menopause 2007;14:905–12.
[111] Khaodhiar L, Ricciotti HA, Li L, Pan W, Schickel M, Zhou J, et al. Daidzein-rich isoflavone aglycones are potentially effective in reducing hot flashes in menopausal women. Menopause 2008;15:125–32.
[112] Llaneza P, Gonzalez C, Fernandez-Iñarrea J, Alonso A, Diaz-Fernandez MJ, Arnott I, et al. Soy isoflavones, Mediterranean diet, and physical exercise in postmenopausal women with insulin resistance. Menopause 2010;17:372–8.
[113] Llaneza P, González C, Fernández-Iñarrea J, Alonso A, Díaz F, Pérez-López FR. Soy isoflavones improve insulin sensitivity without changing serum leptin among postmenopausal women. Climacteric 2012;15:611–20.
[114] Marini H, Bitto A, Altavilla D, Burnett BP, Polito F, Di Stefano V, et al. Efficacy of genistein aglycone on some cardiovascular risk factors and homocysteine levels: A follow-up study. Nutr Metab Cardiovasc Dis 2010;20:332–40.
[115] 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.
[116] Villa P, Costantini B, Suriano R, Perri C, Macrì F, Ricciardi L, 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.