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REVIEW ARTICLE

Effects of soy isoflavones and genistein on glucose metabolism in perimenopausal and postmenopausal non-Asian women: a meta-analysis of randomized controlled trials

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Abstract

Objective: Several randomized controlled trials (RCTs) have examined the role of soy isoflavones on cardiovascular risk factors in perimenopausal and postmenopausal women and have yielded inconsistent results. This meta-analysis aimed to assess the overall effect of soy isoflavones on glucose metabolism: fasting blood glucose, insulin, and insulin resistance.

Methods: We searched for all articles published in English and indexed in Medline from January 1990 to December 2009. We included RCTs for soy isoflavone supplementation in perimenopausal and postmenopausal women not taking hormone therapy, selecting non-Asian women only. The main outcomes were fasting blood glucose changes from baseline.

Results: We identified 10 eligible RCTs containing blood glucose data of 794 women. The main result was that soy isoflavones did not affect fasting blood glucose significantly. Under a random-effects model, the average difference in fasting blood glucose values between women assigned to isoflavones and women assigned to placebo was −2.16 mg/dL (95% CI, −5.21 to 0.89 mg/dL; $P = 0.17$). In genistein studies, the mean difference was −7.15 mg/dL (95% CI, −11.47 to −2.82). However, the effects on insulin and homeostasis model assessment insulin resistance were significant: −1.37 μIU/mL (95% CI, −1.92 to −0.81 μIU/mL) and −0.39 (95% CI, −0.65 to −0.14), respectively. Subgroup analyses did not show a significant effect of isoflavone dose, whereas isoflavone mixtures and genistein had a different effect on fasting blood glucose.

Conclusions: This meta-analysis of RCTs showed that isoflavone use was not associated with a significant glycemia reduction in perimenopausal and postmenopausal non-Asian women. However, the few studies that reported insulin and homeostasis model assessment insulin resistance changes suggested that soy isoflavones and genistein alone had a beneficial effect on glucose metabolism.

Key Words: Glucose metabolism – Menopause – Soy – Isoflavones – Meta-analysis.

In recent years, great attention has been paid to evaluating the effect of phytoestrogens (PEs) as a treatment for climacteric symptoms. Furthermore, several studies have evaluated the effect of PEs on bone mass and cholesterol levels. Limited data are available about their effect on glycemic homeostasis. Notably, blood glucose values are important determinants of cardiovascular disease risk in women.

Epidemiological studies have suggested that Japanese women have lower insulin levels than Japanese-American women do. Furthermore, soy supplements improve insulin concentration and resistance in healthy and diabetic men and women.[1-7]

Further observational studies have suggested that estrogens may have beneficial effects on glucose homeostasis,[8-10] and animal studies in mice and rats on soy-derived diets and soy protein have shown a reduction in plasma glucose concentration and increased glucose tolerance and/or insulin sensitivity.[11-17]

In biological terms, it has been suggested that the potential benefit of isoflavones on glucose levels may be due to the inhibition of α-glucosidase, intestinal glucose uptake and

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tyrosine kinase,[18-20] changes in insulin receptor numbers and affinity, intracellular phosphorylation, and increased insulin receptor mRNA concentration in the liver and adipose tissue.[11-14,18] Recently, a study[21] compared rats fed with high-isoflavone soy protein or low-isoflavone soy protein or casein; the beneficial effects of soy isoflavones were attributed to reduced production of methylglyoxal, a glucose metabolite correlated to glucose levels, and increased glutathione antioxidant protection. This led to improved insulin secretion and better glycemic control than in low-isoflavone or control rats.

Clinical studies have shown controversial results. Some researchers have suggested a reduction in fasting blood glucose levels in women taking PEs,[22-24] but others do not confirm this finding.[25,26]

We thought that it would be of interest to analyze the effect of PE supplementation on non-Asian women, whose diet, unlike Asian women's, is lacking in these substances, mainly found in soy-derived foods.

We therefore conducted a systematic review and meta-analysis to assess the effects of soy PEs on fasting blood glucose levels in perimenopausal and postmenopausal non-Asian women. Our aim was to identify all published randomized controlled trials (RCTs) comparing soy PEs to placebos, conducted on perimenopausal and postmenopausal non-Asian women.

METHODS

Search and selection

Medline (January 1990-December 2009) was searched to retrieve articles that described RCTs investigating the effects of soy isoflavones on fasting blood glucose levels and insulin levels. Before 1990, no RCT on isoflavones involving perimenopausal and postmenopausal women was published.

The following key words (as subject headings and as free text in titles and abstracts) were used to search the databases: *phytoestrogen*, *isoflavone*, *genistein*, *daidzein*, *soy*, *soya*, *menopause*, *menopausal*, *climacteric*, *older women*, and *random*. Then we added *humans* and *English* as limits.

We included studies if they had a parallel design, were placebo controlled, enrolled women without breast cancer and not taking hormone therapy, did not involve Asian populations, and reported fasting blood glucose level or insulin or homeostasis model assessment of insulin resistance (HOMA-IR) as outcome measures.

The articles were initially scanned by two authors (F.C. and S.C.) based on titles and abstracts. Selected articles were retrieved in full and were assessed for eligibility by two authors (F.C. and S.C.). Discrepancies were resolved by consensus.

References of selected articles and reviews on the issue were hand-searched to retrieve further relevant articles.

Methodological quality

Two reviewers (E.R. and S.C.) independently evaluated each trial for internal validity, as indicated in the Cochrane Handbook.[27] Four potential sources of bias were considered: sequence generation, allocation concealment, blinding, data incompleteness, selective reporting.

Data collection

Data were independently extracted by two researchers (E.R. and S.C.). Descriptive data were collected: participant characteristics, dose and formulation of isoflavones, placebo, duration of treatment, and concurrent diet. Baseline and outcome data were entered in a standard form.

Analysis

The inverse variance (IV) method was used to pool the mean difference. Estimates of the average effect of soy isoflavones on fasting blood glucose and 95% CIs were calculated by using both fixed-effect and random-effect models. If the test for heterogeneity (apparent diversity in mean differences across studies) was significant, we presented the results of the random-effect model. Otherwise, estimated results based on a fixed-effect model were presented. To avoid duplication of data derived from the same participants from studies with multiple time points, only the endpoints for the longest duration were used. If a study had two or more treatment groups, one pooled measure was calculated with and without the lower dose group: if the estimate was significantly different, the lower dose group was excluded from the overall calculation.

To remove possible bias due to baseline differences, correlation coefficients for imputing change-from-baseline SD were calculated, using data from the study of Villa et al[28] as indicated in the *Cochrane Handbook*.[27] We calculated the correlation coefficient for treated and placebo groups and used it for calculating and imputing the SD of the mean change where data were reported only as final means. A funnel plot was performed to detect publication bias.

Subgroup analyses

To explore the possible influence of covariates on fasting blood glucose change, we conducted a series of prespecified subgroup analyses stratified by isoflavone mixture use or isolated isoflavone, by total dose of isoflavones (>median or ≤median, considered as aglycone units), by baseline value of glycemia, by concurrent diet, by duration of treatment (<6 or ≥6 mo), and by the country where the study was conducted (Europe vs North America). Review Manager (RevMan; computer program, version 5.0; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2008) was used to analyze the available data.

RESULTS

A total of 403 studies were identified. Abstracts were read to perform a first selection based on study design and the population involved; then, all potentially relevant articles were retrieved for detailed evaluation. Hand-searching the references of these articles, we did not identify other potentially relevant articles. The results of this search are detailed in Table 1.

TABLE 1. *Results of search for eligible studies*

403 RCTs were identified
307 were excluded because of the following:
66 were reviews or commentaries.
13 involved ipriflavone.
31 included women with a history of breast cancer.
101 had a crossover design.
24 included Asian women.
7 included fertile women.
30 did not use soy IFs.
3 did not have a placebo arm.
23 were observational or phase I studies.
6 were animal studies.
3 used IFs as topical treatment.
96 articles were extensively read
83 did not present data nor statements about glycemia.
13 RCTs met the inclusion criteria; 3 did not report data.[35,36,39]
10 RCTs were included in the meta-analysis

RCT, randomized controlled trial; IF, isoflavone.

Ten articles were included in the meta-analysis: 9 reported baseline and posttreatment glucose values,[24-26,28-33] 7 reported insulin values,[24,28-30,32-34] and 4 reported HOMA-IR values.[24,28,30,32] In two articles,[35,36] glucose was analyzed, but data were not reported; however, the authors stated that isoflavone treatment had no effect on glucose.

Trial characteristics

A total of 794 participants (405 in active treatment and 389 in the placebo group) were included in this meta-analysis on blood glucose. Characteristics of the selected studies are reported in Table 2. Concerning the quality of the selected studies, we found that they were all properly randomized and double blinded. Selective reporting was unlikely to occur, but a common problem was a high although similar proportion of women who stopped both treatments. This was mainly due to adverse gastrointestinal effects or low liking of either soy- and placebo-containing foods. If the article did not report the number of women interrupting treatment, we assumed that there was a data incompleteness problem. Because the quality scores were similar across studies, a subgroup analysis for quality score was not necessary.

Isoflavone doses ranged from 54 to 120 mg/day of aglycone units, and treatment duration ranged from 3 to 24 months. Six studies[28,30-34] enrolled healthy women, two studies enrolled women with vasomotor symptoms,[25,26] one study enrolled obese women,[29] and one study enrolled osteopenic women.[24]

In the study of Khaodhiar et al,[26] the same control group was repeatedly compared with two active treatment arms. Treating each arm as an independent study in the overall estimation might have led to an overestimation of statistical difference; thus, we considered only the higher-dose group in the analysis.

Effect on glycemia

Fasting blood glucose values at baseline did not show any heterogeneity ($P = 0.93$).

Final values are affected by a statistically significant heterogeneity ($P < 0.001$). Under a random-effects model, the

TABLE 2. *Description of studies included in the meta-analysis of isoflavones on glycemia*

Study	Country	No. of women who completed the study (treated/placebo)	Age of women (treated/placebo), mean (range), y	Postmenopausal women	Length of treatment	Diet (fat restricted)	Intervention	Total daily dose[a]	Single isoflavones, mg	Formulation
Atteritano et al (2007)[24]	Italy	178/172	54.7/54.2 (49-67)	Osteopenic	2 y	Yes	Genistein	54	54	Tablets
Aubertin-Lehudre et al (2007)[29]	Canada	22/21	57/58 (50-70)	Obese	6 mo	No	Genistein + daidzein + glycitein	70	10 + 44 + 16	Capsules
Charles et al (2009)[30]	United States	32/43	57.3/56.1 (46-74)	Healthy	12 wk	No	Genistein + daidzein + glycitein	96	64 + 63 + 34	Powder
Colacurci et al (2005)[31]	Italy	29/28	55.4/54.9 (NA)	Healthy	6 mo	Yes	Genistein + daidzein	120	60 + 60	Tablets
Crisafulli et al (2005)[32]	Italy	30/30	54/57 (52-60)	Healthy	6 mo	Yes	Genistein	54	54	Tablets
Garrido et al (2006)[34]	Chile	15/14	54/53 (45-60)	Healthy	3 mo	No	Genistein + daidzein	94	48 + 46	Capsules
Han et al (2002)[25]	Brazil	40/40	48/49 (45-55)	Vasomotor symptoms	4 mo	No	Genistein + daidzein + glycitein	100	70 + 18 + 12	Capsules
Khaodhiar et al (2008)[26]	United States	49/45	53.2/53.8 (38-60)	Vasomotor symptoms	3 mo	No	Genistein + daidzein + glycitein	60	6 + 42 + 12	Capsules
Sites et al (2007)[33]	United States	9/6	55.0/57.8 (NA)	Healthy	3 mo	No	Isoflavones NS	96	NS	Shakes
Villa et al (2009)[28]	Italy	28/15	54.3/53.5 (NA)	Healthy	6 mo	No	Genistein	54	54	Tablets

[a]Aglycone units.
NA, not available; NS, not specified.

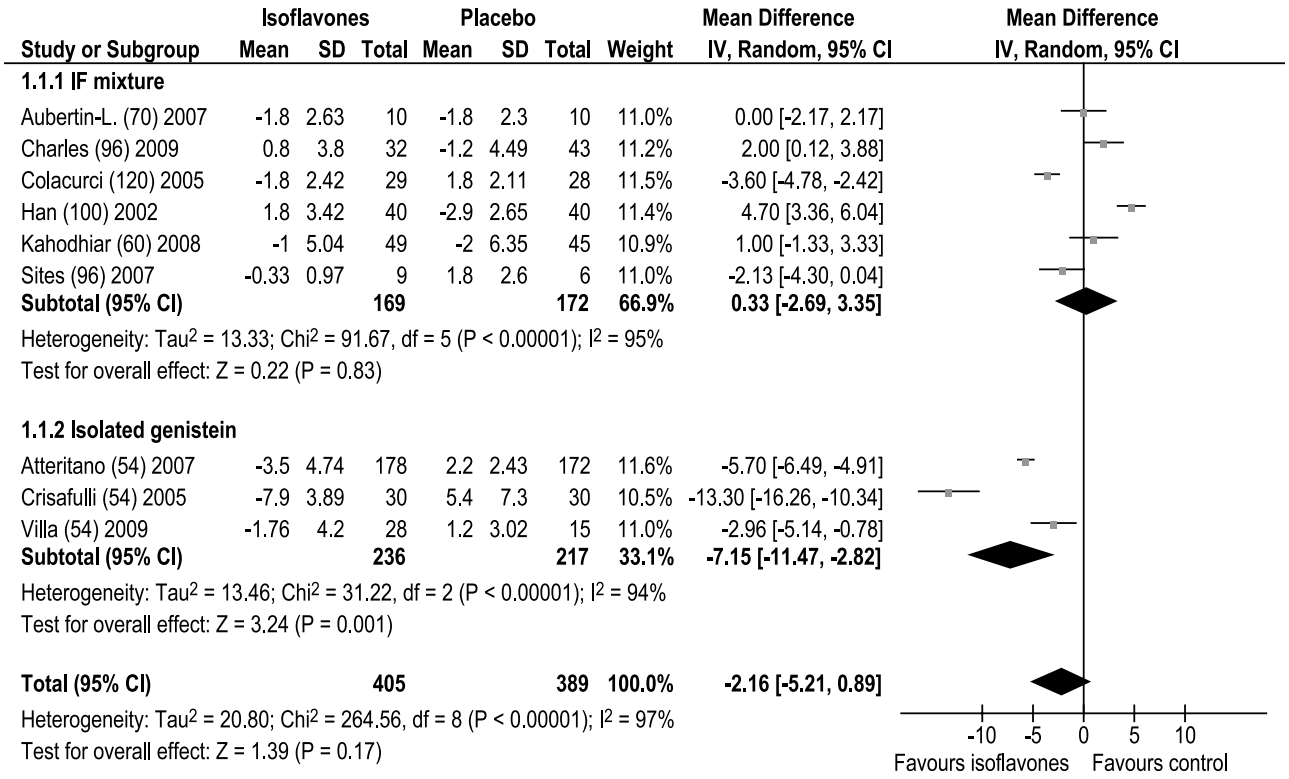

FIG. 1. Effects of soy IFs on fasting blood glucose (mg/dL; change from baseline). The horizontal lines denote the 95% CIs. IF, isoflavone; IV, inverse variance.

average difference in fasting blood glucose values between women assigned to isoflavones and women assigned to placebo was −2.16 mg/dL (95% CI, −5.21 to 0.89 mg/dL; $P = 0.17$).

No relation emerged between the isoflavone dose and the effect on fasting blood glucose values.

The studies of Atteritano et al,[24] Crisafulli et al,[32] and Villa et al,[28] which used genistein alone (instead of isoflavone

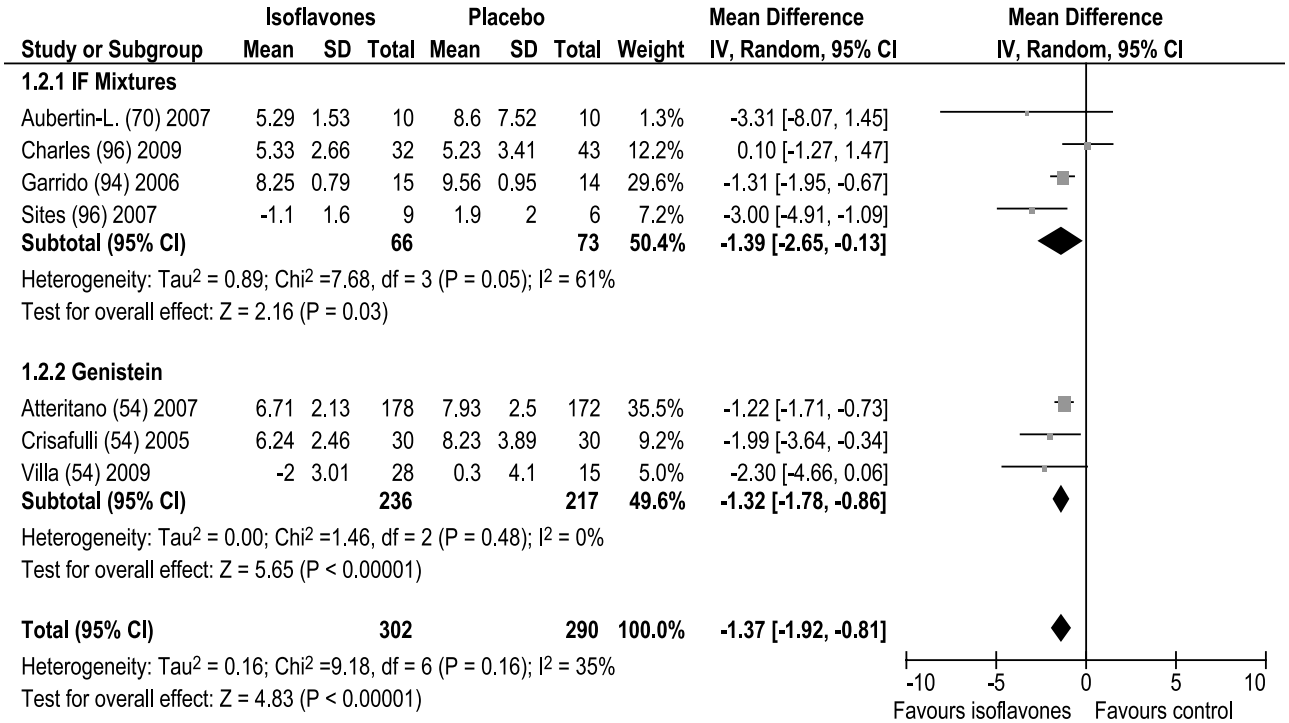

FIG. 2. Effects of soy IFs compared with placebo on fasting blood insulin (mIU/mL; posttreatment levels). IF, isoflavone; IV, inverse variance.

mixtures), showed the most marked effect (−7.15 mg/dL; 95% CI, −11.47 to −2.82 mg/dL; $P = 0.001$).

Isoflavone mixture treatment was not more effective than placebo in lowering fasting blood glucose (pooled estimate, 0.33 mg/dL; 95% CI, −2.69 to 3.35 mg/dL; $P = 0.83$; Fig. 1).

Effect on insulin

Seven studies reported data on baseline and posttreatment levels of serum insulin: 592 women were included in the meta-analysis, 302 were actively treated and 290 were in the placebo arm. The baseline pooled estimate was not significantly different between studies, but one study[29] had a baseline significantly different level of insulin between treated and placebo participants. The analysis was conducted both including and excluding this result. The pooled estimate of insulin difference between groups did not change significantly: −1.37 μIU/mL (95% CI, −1.92 to −0.81 μIU/mL; $P < 0.00001$) including the study and −1.34 μIU/mL (95% CI, −1.92 to −0.77 μIU/mL; $P < 0.00001$) excluding it (Fig. 2).

Effect on HOMA-IR

A total of 528 participants were included in the meta-analysis of HOMA-IR, 268 in the treated group and 260 in the placebo group. The baseline values of HOMA-IR were homogeneously similar in the two groups (−0.00; 95% CI, −0.09 to 0.09). After 3 months to 2 years of treatment, the variation was statistically significant: a −0.39 average difference (95% CI, −0.65 to −0.14) in fasting HOMA-IR values was found between women assigned to isoflavones and women in the placebo arm. It was noteworthy that the only study not reporting a decrease in HOMA-IR[30] used an isoflavone mixture as treatment (Fig. 3).

Subgroup analysis

The results of the subgroup analysis are reported in Table 3. The effect of isoflavones was not analyzed in the strata of glycemic values at study entry because the average value of fasting blood glucose was between 80 and 90 mg/dL in almost all studies. Two studies with glycemia values greater than 90 mg/dL[24,25] showed inconsistent effects on blood glucose.

The preplanned subgroup analyses by country, duration, and dieting presented a significant between-group difference. It probably reflected the effects of genistein or isoflavone mixtures: three[24,28,32] of four studies conducted in Europe (Italy), three[24,28,32] of five longer studies, and two[24,32] of three studies prescribing a diet to enrolled women were genistein studies. Thus, it is probable that the effect of genistein masks any potentially different effect due to these factors. All three genistein only studies were conducted in Italy and had a minimum duration of at least 6 months; two[24,32] of them prescribed a diet.

TABLE 3. *Subgroup analyses of isoflavone effect on serum glucose in perimenopausal and postmenopausal women*

Subgroup	No. of studies	No. of women (treated/placebo)	Mean difference, mg/dL (95% CI)	Analysis model
All studies	9	405/389	−2.16 (−5.21 to 0.89)	Random
Isoflavone				
Genistein	3	236/217	−7.15 (−11.47 to −2.82)	Random
Mixture	6	169/172	0.33 (−2.69 to 3.35)	Random
Dose of isoflavones				
<70 mg	4	285/262	−5.16 (−9.44 to −0.87)	Random
≥70 mg	5	120/127	0.20 (−3.32 to 3.72)	Random
Duration of treatment				
<6 mo	4	130/134	2.36 (1.46 to 3.26)	Random
≥6 mo	5	275/255	−4.85 (−5.44 to −4.26)	Random
Country				
America	5	140/144	1.54 (−0.67 to 3.76)	Random
Europe	4	265/245	−6.09 (−8.82 to −3.36)	Random
Diet				
No	6	168/159	0.66 (−1.88 to 3.19)	Random
Yes	3	237/230	−7.13 (−10.45 to −3.81)	Random
BMI[a]				
<26 kg/m^2	3	248/242	−4.68 (−13.18 to 3.82)	Random
≥26 kg/m^2	5	125/107	−1.60 (−3.60 to 0.41)	Random

BMI, body mass index; IF, isoflavone.
[a]One study[30] was excluded from the analysis because BMI was <26 kg/m^2 in the placebo group and ≥26 kg/m^2 in the IF group.

DISCUSSION

This meta-analysis of RCTs showed that isoflavone use was not associated with a significant glycemia reduction in perimenopausal and postmenopausal non-Asian women. However, when analyzed in subgroups, the effectiveness of genistein alone emerged, whereas it is improbable that ingesting a daily dose of isoflavone mixtures ranging from 40 to 120 mg affects the serum levels of glucose. This difference may be due to a more marked effect of genistein or, conversely, to the different composition of isoflavone mixtures

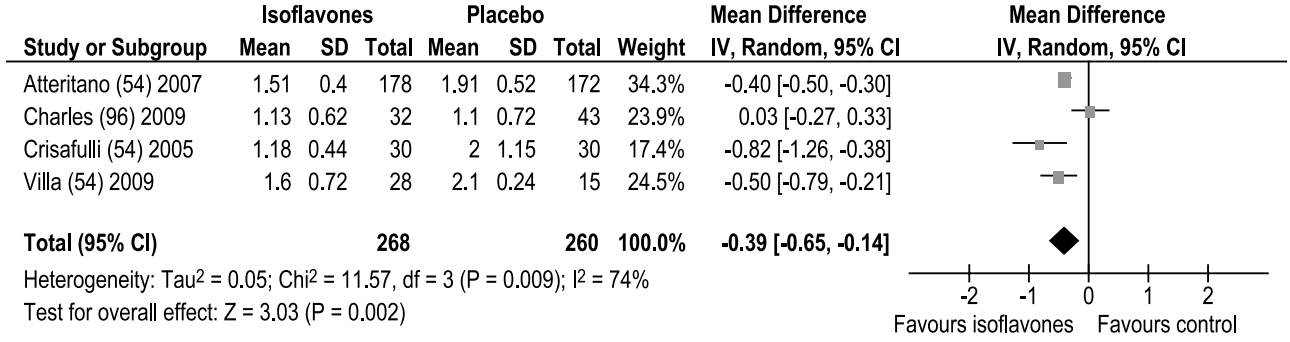

FIG. 3. Effects of soy isoflavones compared with placebo on homeostasis model assessment of insulin resistance. IV, inverse variance.

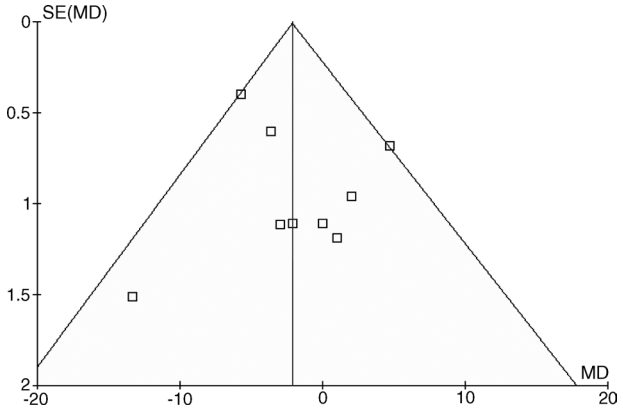

FIG. 4. Funnel plot of selected studies comparing soy isoflavones to placebo effects on fasting blood glucose.

that may complicate the identification of a clinically significant effect of the isoflavones included in the different formulations.

The major limitation of this meta-analysis was the large between-study heterogeneity in the effects of soy isoflavones on glycemia. Large heterogeneity might and, in our case, did cause pooled results differing from the results of some individual studies. We conducted subanalyses to identify the potential sources of heterogeneity, but no clear explanation emerged. The underlying causes of the conflicting results are probably related to the variability of experimental designs and exposition protocols (administration route, composition, dose, and duration), the capacity of individuals to produce equol, and genetic susceptibility.

Our study had several strengths. The relatively large number of pooled participants provided adequate statistical power to detect a clinically important treatment effect. The result was improbable owing to publication bias: the funnel plot did not show any important asymmetry (Fig. 4). Moreover, the analysis was performed selecting only non-Asian women, that is, a sample that does not have a lifelong soy product consumption habit in its usual diet. As we are considering isoflavones as an alternative therapy rather than a healthy habit, we chose to select studies where women did not consume isoflavones habitually. Finally, all studies were high-quality trials according to the considered evaluation criteria.[27]

Even though we did not find any effect of isoflavone mixtures on fasting blood glucose, a significant and homogeneous effect on insulin and HOMA-IR was seen, although few studies reported these outcomes. Particularly, only one study[30] on isoflavone mixtures reported this outcome, but it did not find any difference between the treated and placebo groups. These studies suggested that soy isoflavones and genistein alone had a beneficial effect on glucose metabolism. However, the heterogeneity among studies makes it difficult to draw firm conclusions regarding the beneficial effect of soy on glucose metabolism.

In vitro studies suggested several mechanisms for a direct pharmacological action of soy on glycemic control, including a tyrosine kinase inhibitory action, changes in insulin receptor numbers and affinity, intracellular phosphorylation, and alterations in glucose transport.[37] Recently, it has been suggested that dietary soy improves insulin sensitivity by increasing glucose uptake, preferentially in skeletal muscles.[38] A recent animal study[21] attributed the beneficial effects of isoflavones to increased insulin secretion by the β-islet cells of the pancreas and to increased levels of reduced glutathione, providing antioxidant protection.

However, a differential effect of isoflavones, in particular of genistein, on glycoinsulinemic metabolism in normoinsulinemic and hyperinsulinemic women has also been suggested. In particular, isoflavone-treated hyperinsulinemic women showed an improvement in glycemic indexes,[28] with mean HOMA-IR decreasing to the normal mean value. In the placebo group, no statistical difference was observed after treatment.

Consistently, in a recent study[39] including only postmenopausal women with insulin resistance and comparing soy isoflavones (40 mg daily) and placebo (both arms received a dietary and physical exercise intervention), the authors concluded that isoflavone use added to lifestyle changes reduced insulin resistance significantly better than did lifestyle changes alone during a 2-year intervention.

CONCLUSIONS

In this meta-analysis, we observed that ingesting a daily dose of isoflavone mixtures ranging from 40 to 120 mg did not affect the serum levels of glucose, whereas genistein-treated women consistently showed a fasting blood glucose decrease compared with those treated with placebo. A positive effect on glucose metabolism emerged, but more standardized studies are needed to evaluate putative beneficial effects further.

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