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REVIEW ARTICLE

Effect of Isoflavones and Genistein on Glucose Metabolism in Peri- and Post-Menopausal Women: An Overview of Meta-Analysis

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The purpose of the present overview of meta-analysis is to summarize and critically assess the effect of isoflavones and genistein on glucose metabolism among the peri- and post-menopausal women. Two independent authors searched the databases of MEDLINE, Scopus and Cochrane Library for meta-analysis. Three databases were searched from inception to January 2018. Methodological quality of each meta-analysis of randomized controlled trials was evaluated using the AMSTAR (a measurement tool used to assess systematic reviews). Four meta-analyses were included to the current overview. Fasting insulin levels and homeostatic model assessment of insulin resistance (HOMA-IR) values were significantly lower in peri-menopausal and postmenopausal. Two meta-analyses showed that treatment with isoflavones could not alter fasting blood glucose. However, one meta-analysis depicted that isoflavones significantly improved blood glucose levels in non-Asian postmenopausal women. Treatment with genistein could have significant beneficial effects on fasting insulin, blood glucose and HOMA-IR in comparison to the control group. Regardless of the population, the treatment with genistein is effective in improving fasting insulin, HOMA-IR and glucose levels. Nevertheless, the high heterogeneity among studies and poor methodology of reviews made it difficult to draw a definite conclusion on the positive impacts of soy on glucose metabolism.

Key Words: Genistein, Glucose metabolism disorders, Insulins, Isoflavones, Menopause

INTRODUCTION

The post-menopausal period reportedly can be associated with some consequences such as glucose tolerance and increase insulin resistance. Approximately 20% of women in the age range of 55 to 65 years are suffering from impaired glucose tolerance and diabetes mellitus that face this group with developing cardiovascular disease (CVD) [1]. The impaired quality of life and even subsequently mortality can occur following the glucose metabolism disorders [2]. One of the most widely used therapeutic approaches in this regard is hormone replacement therapy (HRT) that has been always accompanied with determined adverse effects such as CVD, weight loss, elevated insulin-sensitivity and impaired blood lipid profiles [1,3]. Many women in treatment now decided to discontinue HRT due to a general misconception about the relationship between hormones and cancer, as well as many of the benefits of phytoestrogens advertised by trading companies relying on minimal scientific information. Hence, the increasing tendency of postmenopausal women toward com-

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pounds containing phytoestrogens as complementary and alternative medicine is clearly visible in this backward trend [4]. There are four main classes in various phytoestrogen compounds, including isoflavonoids, flavonoids, coumestans, and mammalian lignans [5]. The structure and chemical nature of the isoflavones are closely similar to estradiol (E2) as the phytoestrogens are able to match with estrogen receptors [4], but their effects physiologically are greatly less than E2 [5]. Previous systematic reviews and meta-analyses have found controversial results regarding the effect of isoflavones on the glucose metabolism [1,2,6]. Therefore, there is further need for overview of systematic reviews to draw a definite conclusion.

METHODS

Search strategy

Two authors independently searched databases of MEDLINE, Scopus, and Cochrane Library for detect meta-analysis of randomized, controlled trials on effect of isoflavones and genistein on glucose metabolism in peri- and post-menopausal women. Three databases were searched from inception to January 2018. The following keywords in English were used in search databases with no language limitations, including (insulin [Title/Abstract] OR blood glucose [Title/Abstract]) AND (isoflavone [Title/Abstract] OR genistein [Title/Abstract]). All references in systematic review were manually searched to search additional article and avoid overlooking any related information. Same authors also reviewed title and abstract to detect relevant publications. The consensus sessions were used to deal with any discrepancy. In case of disagreement, a third investigator judged the articles.

Inclusion criteria

Meta-analysis assessing the effect of isoflavones or genistein on at least one of the parameters of insulin, blood glucose and homeostatic model assessment of insulin resistance (HOMA-IR) in peri- and post-menopausal included into the overview.

Data extraction

Two authors using a pre-designed form extracted following data: year of publication, first author, study population and menopausal status (Table 1).

Assessment of methodological quality

The same assessors appraised the methodological quality of each meta-analysis of randomized controlled trials using the AMSTAR (a measurement tool to assess reviewer), which contains 11 items developed by Oxman et al. [7] to assess the methodological quality. Individual items were categorized as three responses of "Yes", "No", "Can't Answer" (Table 1).

RESULTS

Process of selecting review is showed in Figure 1. Table 1 showed characteristic of 4 meta-analysis include in over view. Table 2 also showed methodological quality assessment of systematic reviews using the AM-

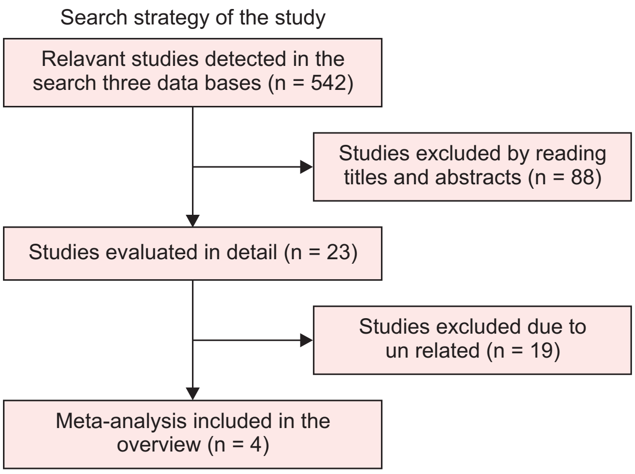

Fig. 1. Process of selecting review is showed.

Table 1. Characteristic of 4 meta-analysis included in this overview

Study (year)	Age (y)	Population	Type intervention/control
Zhang et al. [1] (2013)	52–63	Non-Asian postmenopausal women	Soy isoflavones supplementation/placebo
Liu et al. [8] (2017)	54–60	Post menopause	Genistein/placebo group
Ricci et al. [6] (2010)	Not mentioned	Perimenopausal and postmenopausal non-Asian women	Isoflavone/placebo
Fang et al. [2] (2016)	48–63	Menopausal women	Isoflavone/placebo

Table 2. Methodological quality assessment of met-analysis using the AMSTAR rating

Study (year)	AMSTAR items[a]										
	1	2	3	4	5	6	7	8	9	10	11
Zhang et al. [1] (2013)	Yes	Yes	Yes	Yes	Can not answer	Yes	Yes	Yes	Yes	Can not answer	No
Liu et al. [8] (2017)	Yes	Yes	Yes	Can not answer	Can not answer	Yes	Yes	Yes	Yes	Can not answer	Yes
Ricci et al. [6] (2010)	Yes	Not	Can not answer	Not	Not	Can not answer	Not	Not	Yes	Can not answer	Yes
Fang et al. [2] (2016)	Yes	Not	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

AMSTAR: a meaurement tool to assess reviewer.
[a]1: "Was an 'a priori' design provided?", 2: "Was there duplicate study selection and data extraction?", 3: "Was a comprehensive literature search performed?", 4: "Was the status of publication (i.e., grey literature) used as an inclusion criterion?", 5: "Was a list of studies (included and excluded) provided?", 6: "Were the characteristics of the included studies provided?", 7: "Was the scientific quality of the included studies assessed and documented?", 8: "Was the scientific quality of the included studies used appropriately in formulating conclusions?", 9: "Were the methods used to combine the findings of the studies appropriate?", 10: "Was the likelihood of publication bias assessed?", 11: "Was the conflict of interest stated?".

STAR rating.

The effect of isoflavones on insulin

Three meta-analyses assessed the effect of isoflavones on insulin. Ricci et al. [6] in 2010 reported that the fasting blood insulin level was significantly lower in the isoflavone compounds group (mean difference [MD] = –1.39, P = 0.03, 95% confidence interval [CI] = –2.65 to –0.13, heterogeneity [I^2 = 61%], P = 0.05; 4 trials; 66 subjects for isoflavones compound and 73 subjects for placebo). Fang et al. [2] in 2016 reported that mean of insulin in soy isoflavone compounds group was significantly lower than placebo group (MD = –0.43, P = 0.003, 95% CI = –0.71 to –0.14, I^2 = 76%, P < 0.0001; random-effect model; 12 trials; 497 women for soy isoflavone and 489 subjects for control group). Zhang et al. [1] in 2013 found that the fasting insulin levels were significantly lower in women treated with soy isoflavone supplementation compared to control group (weighted mean difference [WMD] = –0.918, 95% CI = –1.7 to –0.137, heterogeneity [I^2 = 65%], P = 0.021; 12 trials; 581 subjects for soy isoflavone supplementation and 561 subjects for control group).

The effect of genistein on fasting blood insulin

Three meta-analyses assessed the effect of genistein on insulin. According to Fang et al. [2] insulin-lowering effect was more in women treated with genistein than those with placebo (MD = –0.62, P < 0.00001, 95% CI = –0.82 to –0.41, I^2 = 31%, P = 0.201; random-effect model; 6 trials; 341 women for treatment and 322 for control group). Ricci et al. [6] reported that the mean of fasting blood insulin was significantly lower in the genistein (MD = –1.32, P < 0.00001, 95% CI = –1.78 to –0.86, heterogeneity [I^2 = 0%], P = 0.48; 3 trials; 236 for isoflavones and 217 for placebo) in comparison to placebo. Liu et al. [8] found that treatment with genistein can significantly reduce fasting insulin in comparison to placebo (WMD = –1.92, 95% CI = –3.04 to –0.79, P = 0.0008, heterogeneity [I^2 = 55%], P = 0.021; 6 trials; 306 subjects for genistein and 285 subjects for control group).

Fasting blood glucose

The effect of isoflavone on fasting blood glucose

Three meta-analyses assessed the effect of isoflavone on fasting blood glucose. In Ricci et al.'s meta-analysis in 2010 [6], the mean of fasting blood glucose was not different between soy isoflavone group and placebo group (MD = –2.16, 95% CI = –5.21 to 3.35, P = 0.17; random-effect model; 9 trials; 405 women in intervention and 389 in placebo group).

In Fang et al.'s meta-analysis in 2016 [2], the mean of fasting blood glucose showed a significantly higher decrease in isoflavone group than placebo group (MD = –0.22, 95% CI = –0.38 to –0.07, P = 0.004, I^2 = 79%, P < 0.00001; random-effect model; 15 trials; 764 in intervention group and 646 in control group).

In Zhang et al.'s meta-analysis in 2013 [1], a significant borderline decrease was observed in blood glucose in isoflavone supplementation group in comparison with control group (WMD = –0.143, 95% CI = –0.294 to 0.009, P = 0.065, heterogeneity [I^2 = 70%]; 12 trials; 581

subjects for soy isoflavone supplementation and 601 subjects for control group). However, after exclusion of one study, significant level increased to below 0.05 (WMD = –0.189, 95% CI = 0.344 to –0.033) [1].

The effect of genistein on the fasting blood glucose

Three meta-analyses assessed the effect of genistein on the fasting blood glucose. In Fang et al.'s meta-analysis in 2016 [2], the genistein was more effective than the placebo in attenuating fasting blood glucose (MD = –0.42 mmol/L, $P < 0.00001$, 95% CI = –0.54 to –0.29 mmol/L; I^2 = 22%, $P < 0.00001$; random-effect model; 6 trials; 341 for intervention group and 332 for control group). In Liu et al.'s meta-analysis in 2017 [8], fasting blood glucose in genistein group were significantly lower compared to placebo (MD = –6.35 mg/dL, $P = 0.005$, 95% CI = –10.78 to –1.93 mg/dL, heterogeneity [I^2 = 93%], $P < 0.00001$; 6 trials; 564 women) [8]. In Ricci et al.'s meta-analysis [6], fasting blood glucose significantly decreased in the genistein group than the placebo group (MD = –7.15 mg/dL, $P = 0.001$, 95% CI = –11.74 to – 2.82 mg/dL, I^2 = 94%, $P < 0.00001$; 3 trials; 453 women).

HOMA–IR value

The effect of isoflavones on HOMA–IR value

In Fang et al.'s meta-analysis in 2016 [2], the mean HOMA-IR value showed a statistically significant difference in the isoflavones group than placebo group (MD = –0.52, 95% CI = –0.76 to 0.28, I^2 = 81%; 12 trials; random-effect model; 528 women for intervention and 519 for control). In Ricci et al.'s meta-analysis in 2010 [6], HOMA-IR level showed a larger decrease in isoflavone group compared to placebo (MD = –0.39, $P = 0.002$, 95% CI = –0.65 to –0.14, heterogeneity [I^2 = 74%], $P = 0.16$; 4 trials; 268 for soy isoflavones and 260 for placebo).

The effect of genistein on HOMA–IR

Two meta-analyses assessed the effect of genistein on HOMA-IR. Based on the findings of Fang et al.'s meta-analysis in 2016 [2], the genistein was more effective in comparison to control group in reducing HOMA-IR (MD = –0.66, $P < 0.00001$, 95% CI = –0.92 to –0.41, I^2 = 66%; 6 trials; random-effect model; 6 trials; 341 women for intervention group and 332 placebo group). In Liu et al.'s meta-analysis in 2017 [8], soy isoflavones were found to be more efficacy than placebo (MD = –0.74, $P = 0.002$, 95% CI = –1.21 to –0.28, heterogeneity [I^2 = 74%], $P = 0.004$; 5 trials; 306 for soy gen and 285 for placebo).

DISCUSSION

The purpose of the current overview was to summarize and critically assess the effect of isoflavones and genistein on glucose metabolism among peri- and post-menopausal women. HOMA-IR value and fasting insulin levels were significantly lower in studies used either isoflavones or genistein compared to placebo. Two meta-analyses showed that treatment with isoflavones could not alter fasting blood glucose [2,6]. However, one of meta-analyses suggested that isoflavones significantly improved blood glucose levels in non-Asian post-menopausal women [8]. We found a discrepancy between mrta anlysis and meta-analyses included to current study. One of the reasons can be attributed to the differences in various methodological and statistical aspects to report findings among the selected trials conducted on non-Asian versus mixed populations reviewed in our meta-analysis.

Several studies have been performed to detect potential mechanisms of the effect of isoflavones on glucose metabolism. For example, the soy in diet can improve the insulin sensitivity due to incremental glucose uptake by skeletal muscles [9]. In-vitro studies showed that several mechanisms of action may involve in the effect of soy on the glucose metabolism, such as an inhibitory action of tyrosine kinase, changes in the number of insulin receptor, impaired glucose transport and intracellular phosphorylation [6]. Villa et al. [10] divided 54 postmenopausal women into two groups of receiving 54 mg/day of genistein and placebo. Genistein affected significantly the glycoinsulinemic metabolism. They also performed a subgroup analysis in the patients of genistein group based on hyperinsulinemic and normoinsulinemic subjects. Their results revealed that glycemic indexes were improved in hyperinsulinemic group [10].

The current overview has several limitations that should be discussed. There were moderate to high heterogeneities in all reviews included to our overview. Based on AMSTAR criteria, at least two databases must be searched, and graphical plot should be drown in combination with statistical test when reporting publication bias. One of the studied reviews only searched one database and some of meta-analyses evaluated neither Begg's nor Egger's tests in combination with graphical plot. Hence, the publication bias might affect their studies. List of included and excluded studies were not reported in two out of four reviews. Moreover, none of authors of systematic reviews stated whether they include grey literature. Future systematic review and meta-analyses should be well designed to meet AMSTAR criteria.

CONCLUSION

Regardless of population, the treatment with genistein is effective on improving fasting insulin, HOMA-IR and glucose levels. Nevertheless, the high heterogeneity among studies and poor methodology of reviews make it difficult to draw a definite conclusion on the positive impacts of soy on glucose metabolism.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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