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EFFECT OF SOY ISOFLAVONE ADMINISTRATION ON HBA1C LEVELS IN MENOPAUSE WOMEN

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Abstract
Background: Metabolic syndrome prevalence increases significantly after menopause, this is mainly due to hormone replacement therapy and is associated with diabetes incidence as reflected by HbA1c levels. Currently, especially in Asia, isoflavones are proving to be promising alternative therapies replace hormone therapy for symptoms in menopausal women.
Objective: This research aims to determine effect of soy isoflavone administration on HbA1c levels in postmenopausal women
Methods: This research is a true experimental study with pre-post test randomized between-group design at Sari Mutiara Diski Pratama Clinic in July 2020–December 2020. Menopausal women aged 45-65 years who have met inclusion criteria were classified into 3 groups according to intervention given, namely placebo, estradiol valerate and isoflavone. Analysis of pre-posttest data in each group was analyzed by using T-paired test if data was normally distributed and Wilcoxon test if data were not normally distributed.
Results: The mean sample age in estradiol valerate group was the oldest, followed by soy isoflavone and control group (54.7 ± 2.75 years; 52.5 ± 1.51 years; 52.4 ± 2.01 years). The highest level of HbA1c before intervention was found in Soy Isoflavone group (6,30). However, after intervention, the highest HbA1c levels were found in estradiol group (5,11) and lowest in soy isoflavone group (4,85).
Conclusion: The difference in HbA1c levels before and after the intervention was found to be significant in after administration of either 50 mg soy isoflavone and estradiol valerate.

Keywords: menopause, estrogen replacement therapy, isoflavone, estradiol valerate

I.INTRODUCTION

Menopausal women are women who experience perimenopause and postmenopause. Perimenopause is period in which a woman has irregular ovulation and menstrual cycles leading to menopause and continuing for up to 12 months after her last period. Perimenopause is also known as menopausal or climacteric transition. Postmenopause: The time after menopause has occurred, starting when a woman didn't had menstrual period for 12 consecutive months.[1]

Indonesia's population is estimated to reach 273.6 million in 2025. In the same year, life expectancy is estimated at 73.7 years, a large increase compared to current 69.0 years. With increasing life expectancy, a large number of women will live more than 20 years after menopause and spend a third or more of their lives with estrogen deficiency.[2]

The Women's Health Across the Nation (SWAN) study suggested that lower E2 concentrations increase risk of type 2 diabetes mellitus (T2DM) 47% higher during menopausal transition. European Prospective Investigation into Cancer (EPIC) - InterAct, after evaluation on women for 11 years, showed that menopause before < 40 was associated with 32% higher risk of developing type 2 diabetes mellitus (T2DM). A recent analysis of data from Women's Health Initiative (WHI) study, which examined 124,379 postmenopausal

women, concluded that women with a reproductive period (difference between age at menarche and age at last period) <30 years had 37% higher risk of developing T2DM than women with reproductive period 36-40 years.[3]

In post-menopausal women, endogenous testosterone and estradiol (E2) are associated with development of type 2 diabetes mellitus through adiposity and insulin resistance. One study showed that low FSH levels were associated with an increased incidence of pre-diabetes and diabetes in post-menopausal women. Research by Wang et al. (2016) found that FSH is closely related to fasting blood sugar levels and HbA1c levels, where a decrease in FSH will be followed by increase in fasting blood sugar and HbA1c levels.[4] Research by Okada showed HbA1c levels were significantly lower in postmenopausal women aged 40-49 years taking HRT than in women of same age without HRT (mean ± SE 4.776±0.092 vs 5.096±0.078%, P<0 ,05).[5]

In Canada, it has been found that 60% to 90% of women would consider using complementary and/or alternative medicine for menopausal symptoms, but are concerned about efficacy and cost.[6] Some of most popular today are treatments based on foods or supplements fortified with phytoestrogens, plant-based chemicals that have an estrogenic action.[7] In several previous studies, consumption of foods that contain lots of isoflavones reduced hot flashes incidence compared to placebo although the difference was not too large (45% and 30%). Supplementation of soy isoflavone for 12 weeks tends to reduce menopausal symptoms prevalence in women with normal body mass index and adequate daily dietary isoflavone intake.[8]

Compared with rosiglitazone, an anti-diabetic drug, maximal PPAR activity by Isoflavone ranges from 23% to 32%. Isoflavones have potential to be used as treatment for metabolic syndrome through glycemic control without side effects of weight gain. PPARs play an important role in glucose metabolism and insulin sensitization, which are usually molecular targets for certain antidiabetic drugs.[6]

For now, women tend to prefer alternative medicine over medical drugs, and several previous studies have also shown that soy isoflavone can be an alternative treatment option for women's health complaints and problems during menopause. Therefore, researchers are interested in discussing this topic "The effect of giving soy isoflavone on HbA1c levels in postmenopausal women".

II.RESEARCH METHODOLOGY

This research is a true experimental study with pre-post test randomized between-group design. There were 3 (three) treatment groups for 30 menopausal women, namely group I control with 10 menopausal women without intervention; group II estradiol valerate as many as 10 postmenopausal women who received intervention of estradiol valerate 1-2 mg/day and group III Supplementation of soy isoflavone as many as 10 menopausal women who received intervention of soy isoflavone supplement 50 mg/day.

The study began in July 2020–December 2020 and was conducted at Sari Mutiara Diski Pratama Clinic which was selected as a clinic for menopause counseling and elderly exercise programs by USU Medical Faculty, after obtaining ethical clearance from USU Medical Faculty Ethics Committee. The study samples were postmenopausal women who had met inclusion criteria, namely women aged >40 years, spontaneous cessation of menstruation for 12 months accompanied by signs and symptoms of menopause and had never received hormone replacement therapy; and not included in exclusion criteria, namely loss of follow-up or withdrawal from the study, non-natural menopause, with a history of metabolic, cardiovascular disease, and currently using hormonal therapy.

Statistic analysis

Data analysis includes univariate and bivariate tests. Univariate analysis is presented in form of frequency distribution, mean, median, and standard deviation. The bivariate started with data normality test and data variance using Saphiro-Wilk test and also homogeneity test using Levene test. If data was normally distributed with same data variance of more than two unpaired groups, then analysis proceed with One-Way Anova parametric test continued with Tukey Post Hoc test. If data was not normally distribured, Kruskall-Wallis non-parametric test is carried out then followed by Mann-Whitney test. Analysis of pre-posttest data for each group was analyzed by using paired T-test if data was normally distributed and using Wilcoxon as alternative test if data was not normally distributed..

III.RESULT

Research subjects in estradiol valerate group had oldest mean age, followed by soy isoflavone group and control group (54.7 ± 2.75 years; 52.5 ± 1.51 years; 52.4 ± 2.01 years). In addition, based on menopause duration, study subjects in control group had shortest duration of menopause compared to other two groups (3.4 ± 1.9 years; 4.1 ± 1.97 years; 5 ± 2.75).

Table 1. Distribution of Research Subject Characteristics

Characteristics	Control (n=10)	Soy Isoflavone 50mg/ days (n=10)	Estradiol Valerate (n=10)	P
Age (mean±SD; years)	52.40±2.01	52.50±1.51	54.70±2.75	0.040*
Menopausal duration (mean±SD; years)	3.40±1.90	4.10±1.97	5.00±2.75	0.293*
Parity (n, %)				0.136**
Nuliparous	2 (20%)	2 (20%)	0 (0%)	
Primiparous	0 (0%)	2 (20%)	0 (0%)	
Multiparous	8 (80%)	6 (60%)	10 (100%)	
Grande multiparous	0 (0%)	0 (0%)	0 (0%)	
BMI (n, %)				0.355**
Underweight	0 (0%)	0 (0%)	0 (0%)	
Normal	9 (90%)	10 (100%)	10 (100%)	
Overweight	1 (10%)	0 (0%)	0 (0%)	
Obesity	0 (0%)	0 (0%)	0 (0%)	

*One-way Anova test **Chi-Square test

Comparison of FSH Levels between Control, Soy Isoflavone and Estradiol Valerate Group

FSH levels before intervention were found in control group (53.48 ± 35.47) followed by estradiol valarate (72.40 ± 45.21) and soy isoflavone (88.95 ± 29.71). FSH levels after intervention decreased in soy isoflavone and estradiol valerate groups, but increased in control group. The difference in FSH levels in all groups was not statistically significant ($p > 0.05$).

Table 2. Comparison of FSH levels between groups

FSH Levels (mlU/ml)	Before Intervention	After Intervention	P*
Control	53.48±35.47	72.33±35.33	0.279
Soy Isoflavone 50mg/ days	88.95±29.71	80.04±33.75	0.439
Estradiol Valerate	72.40±45.21	65.14±35.64	0.520

* T dependent test

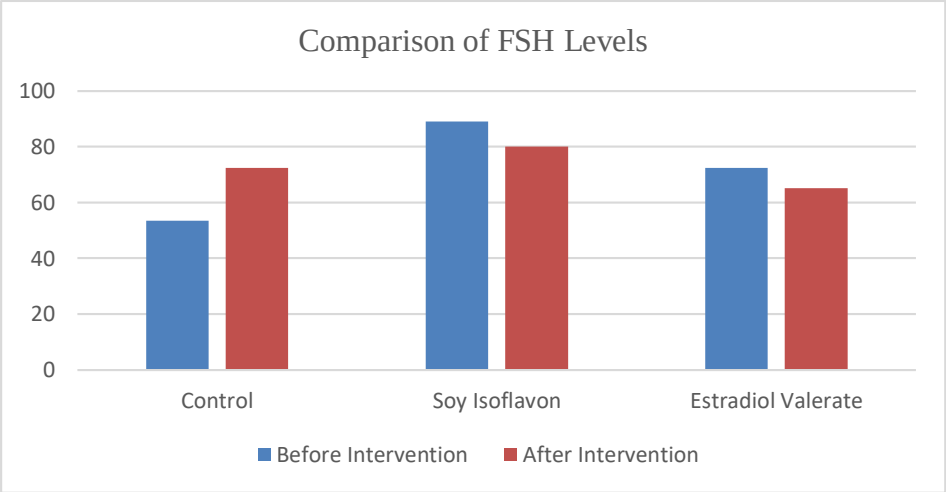

Figure 1. Comparison graph of FSH levels before and after intervention

FSH levels decreased in soy isoflavone and estradiol valerate groups after intervention with highest post-intervention FSH levels found in Soy Isoflavone group.

Comparison of Estradiol Levels between Control, Soy Isoflavone and Estradiol Valerate Group

The estradiol valarate group had lowest estradiol levels before intervention compared to other two groups (43.79 ± 20.01), however, estradiol levels increased after intervention was found in all groups with highest levels found in Soy Isoflavone group (68.33 ± 14.93). The results of statistical analysis showed a significant estradiol levels difference in estradiol valerate and Soy Isoflavone groups ($p<0.05$).

Table 3. Comparison of estradiol levels between groups

Estradiol Levels (pg/ml)	Before Intervention	After Intervention	P*
Control	50.75±12.91	53.35±15.66	0.403
Soy Isoflavone 50mg/ days	49.49±24.60	68.33±14.93	0.037
Estradiol Valerate	43.79±20.01	56.66±26.50	0.020

* T dependent test

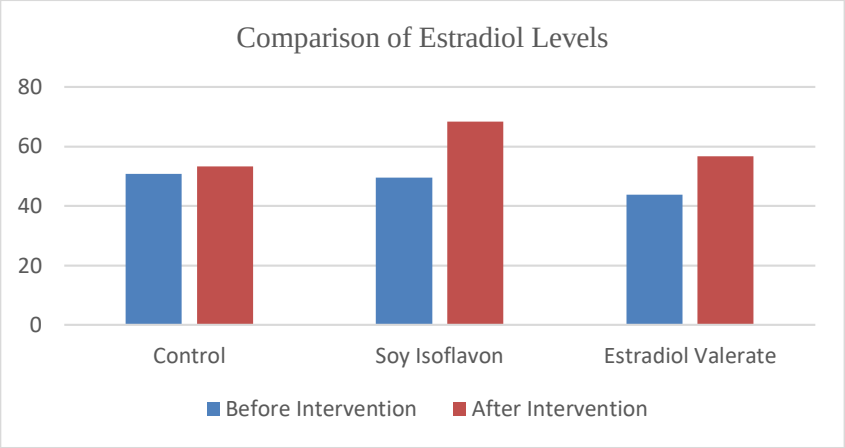

Figure 2. Comparison graph of estradiol levels before and after intervention

Changes in estradiol levels before and after intervention, where estradiol levels increased after intervention in all groups with highest post-intervention estradiol levels found in Soy Isoflavone group.

Comparison of HbA1c Levels between Control, Soy Isoflavone and Estradiol Valerate Group

The highest HbA1c level before intervention was found in Soy Isoflavone group (6,30). The findings were found after intervention, highest HbA1c levels were found in estradiol group (5,11) and lowest in soy isoflavone group (4,85). Significant differences in HbA1c levels before and after intervention could be found in soy isoflavone and estradiol valerate groups ($p < 0.05$).

Table 4. Comparison of HbA1c levels between groups

HbA1c Levels (%)	Before Intervention	After Intervention	P*
Control	5.61±0.63	5.04±0.643	0.088
Soy Isoflavone 50mg/ days	6.30±2.64	4.85±0.78	0.007*
Estradiol Valerate	6.10±1.14	5.11±1.58	0.007*

*T dependent test , *Wilcoxon test

HbA1c levels showed a significantly decrease in soy isoflavone and estradiol valerate groups than control group.

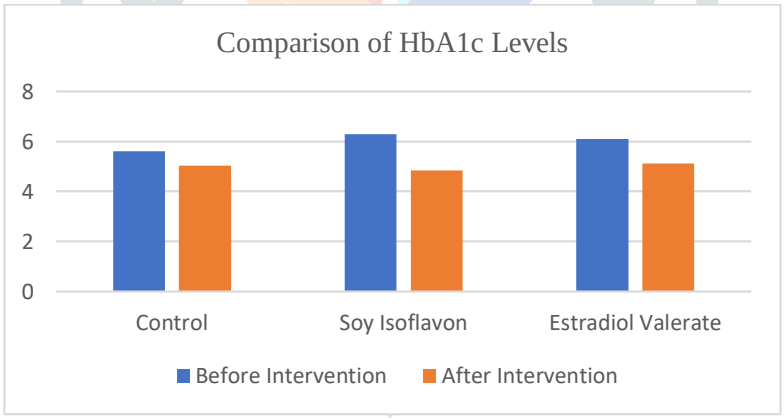

Figure 3. Comparison graph of HbA1c levels before and after intervention

IV. DISCUSSIONS

Menopause is condition of absence menstrual periods for 12 consecutive months associated with hypergonadotropic conditions. Menopause onset is related to genetic, behavioral and environmental factors. Menopause onset usually occurs at age of 45-55 years old, generally due to limited number of ovarian follicles.[9] Menopause is characterized by hot flashes, decreased libido and changes in body composition. These changes occur due to estradiol decrease, increasing age and lifestyle changes accompanied by lack of exercise and decrease of body fitness. These factors affect fat and carbohydrate metabolism and can cause insulin resistance and diabetes in menopausal women. Hormone replacement therapy with estrogen has been used for a long time to treat clinical symptoms that arise due to decreased estradiol levels. However, several recent studies have shown that isoflavones as phytoestrogens that have estrogenic and nonestrogenic activity can improve glycemic control, insulin resistance and HbA1c.[10]

Based on this study results, comparison of FSH levels was not significant in all three groups, where FSH levels decrease only occurred in soy isoflavone and estradiol valerate groups after intervention ($p < 0.05$). The Hooper et al meta-analysis results stated that administration of soy isoflavone did not significantly reduce FSH levels in postmenopausal women, but it was proven to reduce FSH and free LH in premenopausal women.[11] The

results of another study also reported that there was no difference in FSH levels after administration of soy isoflavone 50 mg/day for 6 weeks. Soy isoflavone contains low doses of phytoestrogens that can suppress LH and FSH, but have no effect on gonadotropins at high doses because soy isoflavone has minimal estrogen-like effects at pituitary level.[12]

A significant comparison of estradiol levels was only found in estradiol valerate and soy Isoflavone groups with p = 0.020 and p = 0037, where levels of estradiol and soy isoflavone increased after intervention. These results are in line with Waaseth et al results who reported that there was a comparison of estradiol levels before and after estradiol valerate administration and plasma estradiol levels increased with increasing doses of estradiol valerate. The study results also reported that 88% of research subjects who received estradiol valerate had estradiol levels above research subjects who did not receive intervention.[13] Bartsch's study showed that giving estradiol valerate for 12 weeks has been shown to increase estradiol levels results in relieving hot flushes symptoms compared to placebo group, which had an average of 5 hot flushes per day. In addition, estradiol valerate has also been shown to reduce 50% insomnia incidence.[14] After estradiol valerate administration, there will be an increase in maximum serum estrogen concentration for about 40 pg/ml on first day and reaches 80-100 pg/ml on daily administration with a minimum mean serum estradiol (days 1-26) as 33.6-64.7 pg/ml.[15] Serum estrone levels will also increase up to 4-6 times after estradiol valerate administration.[16]

The HbA1c levels before intervention were not significantly different between all three groups, but there was a significant HbA1c levels difference before and after intervention in soy isoflavone and estradiol valerate groups (p = 0.007). The Baranska et al meta-analysis showed that soy isoflavone supplementation significantly reduced HbA1c levels (p < 0.001). Research by Jayagopal et al has also shown that isoflavone administration can improve insulin resistance and HbA1c in postmenopausal women with type 2 diabetes. The mechanisms underlying anti-diabetic effect of soy isoflavones are (1) stimulation of insulin secretion by inhibiting tyrosine kinase; (b) activates adenosine-5'-monophosphate (AMP)-activated protein kinase (AMPK) which causes a decrease in hepatic glucose levels and stimulates glucose uptake independently in skeletal muscle and modulates glucose transport to peripheral tissues; (c) activates peroxisome proliferator-active receptor gamma (PPARγ), thereby increasing expression and translocation of GLUT-1 and GLUT-4 which causes an increase glucose uptake in adiposity and muscle cells with decreases plasma glucose levels; (d) inhibits alpha-glucosidase which causes a slowdown intestinal glucose absorption, directly modulates pancreatic beta cell function and provides protection from apoptosis through mechanisms involving cyclic AMP/protein kinase A (cAMP/PKA) signaling.[17,18] Two randomized clinical trials comparing control and estradiol valerate groups in postmenopausal women with type 2 diabetes mellitus, showed that estradiol valerate administration reduced fasting blood sugar, HbA1c and insulin resistance without affecting postprandial blood sugar levels. Administration of estradiol valerate has been shown to reduce HbA1c and significantly increase insulin suppression of hepatic glucose production.[19]

V. CONCLUSION

The administration of soy isoflavone 50 mg and estradiol valerate 1-2 mg result in significant HbA1c levels changes before and after the intervention..

REFERENCES

1. NICE. Menopause: diagnosis dan management. NICE Guidelines. 2020
2. Wulandari P; Soeroso Y; Maharani DA; Rahardjo A. Validity and Reliability of a modified Utian Quality of Life Scale for Indonesian Postmenopausal Women. Journal of International Dental and Medical Research. 2018; 11(1): 232-237
3. Slopien R; Ozegowska EW; Frontczak AR; Mecxekalski B; Ziolkieqicz; Jaremek JD; et al. Menopause and diabetes: EMAS clinical guide. Maturitas. 117 (2018) 6–10
4. Wang X, Zhang H, Chen Y, Du Y, Jin X, Zhang Z. Follicle stimulating hormone, its association with glucose and lipid metabolism during the menopausal transition. Journal of Obstetrics and Gynaecology Research. 2020;46(8):1419-1424
5. Okada M; Nomura S; Ikoma Y; Yamamoto E; Ito T; Mitsui T; et al. Effects of Postmenopausal Hormone Replacement Therapy on HbA1c Levels. Diabetes Care. 2003; 26(4): 1-5
6. Chen LR; Ko NY; Chen KH. Isoflavonee Supplements for Menopausal Women: A Systematic Review. Nutrients 2019, 11, 2649; doi:10.3390/nu11112649
7. Lethaby A, Marjribanks J, Kronenberg F. Phytoestrogens for vasomotor menopausalsymptoms (Cochrane Review). Chichester, UnitedKingdom: John Willey & Sons; 2007.
8. Wratsangka R & Mayasari AC. Suplementasi kedelai-Isoflavone cenderung berkurang gejala menopause pada wanita pascamenopause. Universa Medicina. 2013; 32(2):1- 10

9. Perlman B, Kulak D, Goldsmith LT, et al. The etiology of menopause: not just ovarian dysfunction but also a role for the central nervous system. Global Reproductive Health. 2018; 3: 1-6.
10. Charles C, Yuskavage J, Carlson O, et al. Effects of high-dose Isoflavonees on metabolic and inflammatory markers in healthy postmenopausal women. Menopause. 2009; 16(2): 395-400
11. Hooper L, Ryder JJ, Kurzer MS, et al. Effects of soy protein and Isoflavonees on circulation hormone concentrations in pre-and post- menopausal women: a systematic review and meta-analysis. Human Reproduction Update. 2009; 15(4): 432-440
12. Foth D, Nawroth F. Effect of soy supplementation endogenous hormones in postmenopausal women. Gynecol Obstet Invest.2003; 55: 135-138
13. Waaseth M, Bakken K, Dumeaux V, et al. Hormone replacement therapy use and plasma levels of sex hormones in the Norwegian Women and Cancer Postgenome Cohort-a cross-sectional analysis. BMC Women's Health. 2008; 8(1): 1-11.
14. Bartsch V. Gynaecological uses of dienogest alone and in combination with oestrogens. Journal of Medical Drug Reviews. 2015; 5:1-31.
15. Fruzzetti F, Tremollieres F, Bitzer J. An overview of the development of combined oral contraceptives containing estradiol: focus on estradiol valerate/dienogest. Gynecological Endocrinology. 2012; 28(5): 400-408.
16. Kuhl H. Pharmacology of estrogens and gestagens. Menopause Andropause.2005: 33-48.
17. Baranska A, Blaszczuk A, Dacewicz MP, et al. Effects of soy Isoflavonees on glycemic control and lipid profile in patients with type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. Nutrients. 2021; 13: 1886.
18. Jayagopal V, Jennings P, Albertazzi P, et al. Beneficial effects of soy phytoestrogen intake in postmenopausal women with type 2 diabetes. Diabetes Care 2002; 25: 1709–1714.
19. Jarvis FM; Manson JE; Stevenson JC; Fonseca VA. Menopausal Hormone Therapy and Type 2 Diabetes Prevention: Evidence, Mechanisms, and Clinical Implications. Endocrine Reviews, June 2017, 38(3):173–188