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## Exploring therapeutic avenues – an experimental study investigating the effects of soy isoflavone and estradiol valerate on HbA1c, lipid profile, urogenital complaints, vaginal maturity index, and sexual function in menopausal women: a comparative analysis using MENQOL-Quality of Life Assessment

M. Ernesto Azgueva Ganis **Siregar**<sup>1,\*</sup>, M. Fidel Ganis **Siregar**<sup>1,2</sup>, Henry Salim **Siregar**<sup>1,2</sup>, Sarma N. **Lumbanraja**<sup>1,3</sup>, Rhiza Z. **Tala**<sup>1,4</sup>, Anditha **Namira**<sup>1</sup>, Irwin Lamtota **Lumbanraja**<sup>1</sup>, Jeffri **Syaputra**<sup>1</sup>, Willy Kurnia **Almon**<sup>1</sup>, Immanuel Dio **Lumbantobing**<sup>1</sup>, Selly **Azmeila**<sup>1</sup>, Putri **Wulandari**<sup>1</sup>

<sup>1</sup>Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia.

<sup>2</sup>Division of Fertility and Endocrinology Reproduction, Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia.

<sup>3</sup>Division of Fetomaternal, Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia.

<sup>4</sup>Division of Urogynecology, Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia.

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\*Corresponding author: M. Ernesto

Azgueva Ganis **Siregar**, M.D. Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Sumatera Utara, 20155 Medan, Indonesia.

Email: mhdernestorsrg@gmail.com.

ORCID: 0009-0006-4882-887X.

### ABSTRACT

**Objective.** This study aims to investigate the impact of soy isoflavone administration on HbA1c, lipid profile, urogenital complaints, vaginal maturation index, and sexual function and compare it with estradiol valerate with MENQOL in menopausal women.

**Materials and Methods.** This study is true experimental research with a pre-post-test randomized between-group design involving 30 postmenopausal women divided into three groups (n = 10 per group): soy isoflavone 50 mg/day, estradiol valerate 2 mg/day and placebo lubricant. The intervention lasted 90 days. Primary outcomes included changes in the HbA1c, Lipid Profile, Urogenital Complaints, Vaginal Maturity Index, and Sexual Function. Data were analysed using independent t-tests and Pearson Correlation test with significance set at  $p < 0.05$ .

**Results.** The initial HbA1c levels did not exhibit significant differences across the three groups; however, a significant difference in HbA1c levels was observed before and after the intervention in the soy isoflavone and estradiol valerate groups ( $p = 0.007$ ).

**Conclusions.** The study suggests that women carry a lower risk of cardiovascular disease prior to menopause than men, yet this advantage diminishes post-menopause. Both soy isoflavone and estradiol valerate significantly reduced HbA1c levels, with estradiol valerate showing a significant decrease in total cholesterol. Soy isoflavone improved urogenital symptoms based on MBS scores. Post-intervention MENQOL analysis revealed significant improvements in both treatment groups' psychosocial, physical, and total scores, with no significant differences observed in the vasomotor and sexual domains.

## INTRODUCTION

Menopause is characterized by the natural and spontaneous cessation of menstruation for a continuous period of 12 months. The annual experience of menopausal transition involves approximately 1.5 million women, often accompanied by troublesome symptoms like vasomotor issues, vaginal dryness, reduced libido, insomnia, fatigue, and joint pain. A population-based evaluation of 386 Australian women revealed that 86% sought medical consultation at least once to address menopausal symptoms. Specific symptoms exhibit a clear correlation with hormonal shifts associated with menopause, leading most women to perceive a direct link between menopause and common manifestations like hot flashes, vaginal dryness, and disrupted sleep, whether with or without night sweats [1].

Several investigations have suggested that women in developing countries, including Latin America, Indonesia, Singapore, Pakistan, Chile, and Peru, undergo natural menopause several years earlier than their counterparts in developed countries [2]. The prevalence of metabolic syndrome experiences a notable surge after menopause, ranging from 30% to 70%, in contrast to the 14-45% observed in women of reproductive age [3]. Glycated haemoglobin (HbA1c) was first recognized as an “unusual” form of haemoglobin in individuals with diabetes, serving as an indicator of the average blood glucose levels over the preceding eight to 12 weeks [4]. Okada’s study revealed a significant decrease in HbA1c levels in postmenopausal women aged 40-49 who utilized hormone replacement therapy (HRT) compared to those who did not use HRT at the same age (average + SE 4.776+0.092 vs 5.096+0.078%,  $p < 0.05$ ) [5].

The onset of menopause also triggers alterations in lipid profiles, leading to a decrease in High-Density Lipoprotein (HDL) and an increase in Total Cholesterol (TC), triglycerides (TG), LDL cholesterol, and VLDL cholesterol. This shift heightens the susceptibility to cardiovascular diseases. Clinical trials with randomization have substantiated that external estrogen intake results in a reduction of Low-Density Lipoprotein (LDL) levels and an increase in High-Density Lipoprotein (HDL) cholesterol levels, typically by around 10-15% [6].

Because menopause affects many of a woman’s metabolisms, including HbA1c, lipid profile, urogenital complaints, vaginal maturity index, and

sexual function, one of the most frequently offered treatments is hormone replacement therapy. Estrogen consists of three prototypes: estradiol, estrone, and estriol. Estradiol has the most potent estrogenic effects and occupies the most significant portion of the distribution of estrogen. It has receptors in various organs. During menopause, the primary source of estrogen is the result of aromatization by peripheral tissues, such as adipose tissue, into estrone, which is then converted into estradiol and the product of adrenal androgen [7]. Phytoestrogen (PE) is a general term used to define a group of non-steroidal compounds derived from plants or originating from the *in vivo* metabolism of precursor substances found in certain plants consumed by humans. Isoflavone is a component primarily found in soy and its derivatives. Isoflavone is classified as a phytoestrogen due to its estrogenic effects. Isoflavone administration to alleviate menopause-related complaints has been widely conducted and has shown benefits in lipid levels, cardiovascular protection, and osteoporosis protection [8]. Isoflavone is a phytoestrogen commonly found in soybeans, and several studies have indicated that isoflavone is among the most effective phytoestrogens. The use of estrogen can reduce hot flashes by up to 70%. Consuming foods high in isoflavones has been demonstrated in some prior research to reduce the occurrence of hot flashes when compared to a placebo; however, the difference is not statistically significant (45% and 30%). Therefore, the use of isoflavones to alleviate menopausal symptoms is worth considering, and further research should be conducted. The provision of soy isoflavones for 12 weeks appears to decrease menopausal symptoms in women with a normal body mass index and sufficient daily isoflavone consumption [9].

The rationale for investigating soy isoflavone lies in its potential role as a safer, non-hormonal alternative to conventional hormone replacement therapy (HRT) for managing menopausal symptoms. The evaluation of the quality of life in menopausal women can be achieved using The Menopause-Specific Quality of Life Questionnaire (MEN-QOL), which was introduced in 1996 by Hilditch from Canada as a tool for assessing health aspects related to postmenopausal quality of life [10]. Soy isoflavone, a phytoestrogen structurally similar to estradiol, binds to estrogen receptors – particularly ER- $\beta$  – with weaker potency, thereby mimicking some of the beneficial effects of estrogen while minimizing associated risks. This is particularly

relevant for postmenopausal women who decline or are contraindicated for HRT due to concerns about cardiovascular disease or hormone-sensitive cancers. Estradiol valerate, a commonly used form of estrogen in HRT, is an effective benchmark in this study to evaluate the comparative efficacy of soy isoflavone [9]. By directly comparing these two interventions, the study aims to determine whether soy isoflavone can significantly improve menopausal symptoms and quality of life with a more favourable safety profile.

## MATERIALS AND METHODS

### *Study registration, ethical and methodological standards*

This study is a true experimental study with a single-blind pre-post-test randomized between-group design using data from menopausal women. The research was conducted at various locations, including the Pratama Sari Mutiara Diski Clinic, the Pathology Anatomy Laboratory at the Faculty of Medicine, Universitas Sumatera Utara, for the processing and reading of vaginal samples, and the Gatot Subroto Medan Clinical Laboratory for the examination of the research subjects' serum estradiol. The study was conducted in 2020 after obtaining ethical clearance from the Research Ethics Commission of the Faculty of Medicine, Universitas Sumatera Utara, until the sample size was met. The case group consisted of menopausal women who had not menstruated for a minimum of 12 consecutive months. The accessible population in this study was menopausal women who came to the research location. A formal power calculation was not conducted before study initiation due to the exploratory nature of this clinical investigation and the limited available population; however, the sample size of 30 subjects (10 per group) was considered adequate for detecting within-group changes over the 90-day intervention. Participants were divided into three groups: the control group received a placebo lubricant gel, the estradiol valerate group received 2 mg orally once daily, and the soy isoflavone group received 50 mg orally once daily. All treatments were administered for a continuous period of 90 days. Compliance was monitored through patient-reported intake logs and weekly follow-up contacts, ensuring adherence to the prescribed regimen.

### *Statistical analysis*

The evaluation of the effects of Soy isoflavones on HbA1c, lipid profile, urogenital complaints, vaginal maturity index, and sexual function in menopausal women involved a comprehensive data analysis incorporating both univariate and bivariate tests. Univariate analysis presented data through frequency distribution, mean, median, and standard deviation. The initial step in bivariate analysis included assessing data normality and variance using the Shapiro-Wilk test and a homogeneity test utilizing the Levene test.

In the comparative study between soy isoflavone and estradiol valerate, descriptive analysis was utilized to scrutinize the frequency distribution of the variables under consideration. The difference in means between variables was examined through an independent t-test. The relationship between characteristic variables and menopause was assessed using the Shapiro-Wilk Normality test. The correlation between estradiol valerate and soy isoflavone with menopause was analysed using the Pearson Correlation test, with a significance level set at  $p < 0.05$ . The confidence interval for this study was established at 95%.

### *Patient and public involvement*

The current study notes an average age of menopause at 49.9 years, ranging from a minimum of 41.5 years to a maximum of 58.3 years. Menopause is the transitional period between the reproductive and senescent phases [11].

Premenopause is the period 4-5 years before menopause, around the age of 40, marked by irregular, prolonged, light, or heavy menstrual cycles, sometimes accompanied by pain [17].

Upon entering menopause, consistently elevated FSH levels ( $> 35$  mIU/ml) are observed. In early menopause, estrogen levels may be low, although in overweight women, estrogen levels are typically high. If a woman has not menstruated for 12 months and has FSH levels  $> 35$  mIU/ml and estradiol levels.

Postmenopause refers to the 3-5 year period after menopause. It is the time after menopause until senescence, beginning after 12 months of amenorrhea. High FSH and LH (Luteinizing Hormone) levels ( $>35$  mIU/ml) and low estradiol levels result in endometrial atrophy, making menstruation unlikely to occur again.

Senescence is the period after postmenopause when a new balance has been achieved in a wo-

**Table 1.** Frequency distribution of characteristic data of research subjects.

| Characteristics                              | Control (n = 10) | Soy Isoflavone 50 mg/day (n = 10) | Estradiol Valerate (n = 10) | P-value |
|--|------------------|-----------------------------------|-----------------------------|---------|
| Age (mean $\pm$ SD; years)                   | 52.40 $\pm$ 2.01 | 52.50 $\pm$ 1.51                  | 54.70 $\pm$ 2.75            | 0.040*  |
| Duration of Menopause (mean $\pm$ SD; years) | 3.40 $\pm$ 1.90  | 4.10 $\pm$ 1.97                   | 5.00 $\pm$ 2.75             | 0.293*  |
| Parity (%)                                   |                  |                                   |                             | 0.136** |
| Nulliparous                                  | 2 (20%)          | 2 (20%)                           | 0 (0%)                      |         |
| Primiparous                                  | 0 (0%)           | 2 (20%)                           | 0 (0%)                      |         |
| Multiparous                                  | 8 (80%)          | 6 (60%)                           | 10 (100%)                   |         |
| Grand multiparous                            | 0 (0%)           | 0 (0%)                            | 0 (0%)                      |         |
| BMI (%)                                      |                  |                                   |                             | 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%)                      |         |

man's life, leading to the absence of both vegetative and psychological disturbances.

## RESULTS

### Baseline characteristic

**Table 1** presents the demographic and baseline clinical characteristics of the study participants. Data were recorded, tabulated, and statistically analysed following an experimental study using a non-randomized pre-post-test design at Klinik Mutiara Diski Medan for three months, from September 2020 to December 2020. The study involved 32 research samples, 16 of which were for the soy isoflavone and estradiol valerate groups that met the inclusion and exclusion criteria. **Table 1** shows that the mean age for the estradiol valerate group is  $56.06 \pm 2.35$  years, and for the soy isoflavone group is  $53.81 \pm 2.34$  years. For systolic blood pressure, the mean is  $120.31 \pm 7.18/79.06 \pm 5.23$  mmHg for the estradiol valerate group and  $117.19 \pm 7.52/77.19 \pm 6.05$  mmHg for the soy isoflavone group, respectively. Then, for the parity, the majority of patients are multiparous, with 16 individuals (55%) and 13 individuals (45%) for the estradiol valerate and soy isoflavone groups, respectively, while there are only three individuals (100%) primiparous in the soy isoflavone group. Based on the duration, both groups are balanced, with one person for 1-2 years, five people for 3-4 years, and 10 people for > 5 years. Based on Body Mass Index (BMI), the majority of samples have normal weight, with 14 individuals (61%) and nine individuals (39%) for the estradiol valerate and soy isoflavone groups, respectively. Then, only two in-

**Table 2.** Comparison of HbA1c levels between groups.

| HbA1c Levels (%)          | Pre-Intervention | Post-Intervention | P-value |
|---------------------------|------------------|-------------------|---------|
| Control                   | 5.61 $\pm$ 0.63  | 5.04 $\pm$ 0.643  | 0.088   |
| Soy Isoflavone 50 mg/ day | 6.30 $\pm$ 2.64  | 4.85 $\pm$ 0.78   | 0.007*  |
| Estradiol Valerate        | 6.10 $\pm$ 1.14  | 5.11 $\pm$ 1.58   | 0.007*  |

**Table 3.** Effect of intervention on serum estradiol levels in research subjects.

| Group | Estradiol serum levels |                    | P-value |
|-------|------------------------|--------------------|---------|
|       | Pre-Intervention       | Post-Intervention  |         |
| K1    | 50.74 $\pm$ 12.84      | 54.06 $\pm$ 19.20  | 0.064   |
| K2    | 54.88 $\pm$ 38.86      | 107.96 $\pm$ 28.75 | 0.007   |
| K3    | 88.89 $\pm$ 31.12      | 92.33 $\pm$ 31.95  | 0.037   |

dividuals (22%) and seven individuals (88%) experience overweight in the estradiol valerate and soy isoflavone groups, respectively.

### Comparison of HbA1c levels

**Table 2** shows that both Soy isoflavone and estradiol valerate interventions significantly reduced HbA1c levels ( $p = 0.007$  for both), while the control group did not exhibit a statistically significant change ( $p = 0.088$ ). These findings indicate that both treatments effectively improved glycaemic control among postmenopausal women, with the Soy Isoflavone group showing the most considerable mean reduction.

### Comparison of serum estradiol levels

**Table 3** shows a significant increase in serum estradiol levels was observed in the soy isoflavone ( $p = 0.007$ ) and estradiol valerate groups ( $p = 0.037$ )

**Table 4.** Effect of intervention on HDL serum research subjects

| Group | HDL levels. mean ± SD (mg/dL) |                   | P-value |
|-------|-------------------------------|-------------------|---------|
|       | Pre-Intervention              | Post-Intervention |         |
| K1    | 48.30 ± 8.99                  | 45.20 ± 110.45    | 0.224   |
| K2    | 61.50 ± 10.64                 | 57.00 ± 13.67     | 0.066   |
| K3    | 56.30 ± 17.48                 | 56.70 ± 19.57     | 0.001   |

**Table 5.** Effect of intervention on LDL serum levels in research subjects.

| Group | LDL levels. mean ± SD (mg/dL) |                   | P-value |
|-------|-------------------------------|-------------------|---------|
|       | Pre-Intervention              | Post-Intervention |         |
| K1    | 110.50 ± 33.66                | 118.40 ± 30.87    | 0.257   |
| K2    | 129.60 ± 35.06                | 107.70 ± 28.38    | 0.003   |
| K3    | 132.90 ± 36.84                | 56.70 ± 19.57     | 0.114   |

**Table 6.** Effect of intervention on serum triglyceride levels in research subjects.

| Group | Triglyceride levels. mean ± SD (mg/dL) |                   | P-value |
|-------|--|-------------------|---------|
|       | Pre-Intervention                       | Post-Intervention |         |
| K1    | 247.10 ± 156.58                        | 246.60 ± 151.45   | 0.799   |
| K2    | 260.50 ± 315.0                         | 194.40 ± 152.80   | 0.214   |
| K3    | 200.70 ± 115.01                        | 200.30 ± 136.99   | 0.508   |

post-intervention. The control group did not exhibit a statistically significant change ( $p = 0.064$ ). These results confirm the estrogenic activity of both interventions, with Soy Isoflavone demonstrating a robust enhancement in circulating estradiol.

**Comparison of lipid profile**

**Table 4** highlights changes in HDL cholesterol levels. A significant improvement was only observed in the estradiol valerate group ( $p = 0.001$ ), suggesting its potential efficacy in enhancing HDL levels. The soy isoflavone and control groups showed non-significant reductions in HDL ( $p = 0.066$  and  $p = 0.224$ , respectively), indicating limited or no impact on HDL from these treatments.

In **Table 5**, the soy isoflavone group recorded a significant decrease in LDL levels ( $p = 0.003$ ), indicating its lipid-lowering potential. In contrast,

the control and estradiol valerate groups did not demonstrate statistically significant changes ( $p = 0.257$  and  $p = 0.114$ , respectively), highlighting soy isoflavone’s more pronounced lipid-modifying effect compared to estradiol valerate in this context. As illustrated in **Table 6**, none of the groups exhibited significant changes in triglyceride levels post-intervention, with P-values exceeding 0.2 in all groups. Although numerical reductions were observed, particularly in the soy isoflavone group, the high variability likely reduced the statistical power to detect significant differences.

**The effect of soy isoflavone on the urogenital system**

**Table 7** documents the frequency of menopausal bladder symptoms such as dryness, dyspareunia, itch, discharge, and micturition. Across all intervention groups, symptoms were variably distributed with no striking differences between treatments. Notably, dyspareunia and dryness were the most commonly reported symptoms, underscoring their prevalence in menopausal women regardless of intervention.

**Vaginal maturation index in research subjects**

The values of the Vaginal Maturation Index (VMI) in menopausal women in this study are presented in **Table 8**. The mean VMI value in this study is  $40.45 \pm 8.02$ . Thus, menopausal women who were sampled in the research exhibit vaginal atrophy conditions with VMI values  $< 52$ .

**The effect of intervention on FSFI scores**

The effect of intervention on each group’s mean FSFI scores before and after intervention is presented in **Table 9**. Statistically, there is a significant difference in the mean FSFI scores before and after intervention in the estradiol valerate group ( $p = 0.035$ ) and the soy isoflavone group ( $p = 0.031$ ). In contrast, no significant difference was observed in the mean FSFI scores before and after intervention in the placebo group ( $p = 0.063$ ).

**Table 7.** Effect of intervention on MBS in research subjects.

| Group        | n         | MBS       |             |          |           |             |
|--------------|-----------|-----------|-------------|----------|-----------|-------------|
|              |           | Dryness   | Dyspareunia | Itch     | Discharge | Micturition |
| K1           | 10        | 4         | 2           | 2        | 1         | 1           |
| K2           | 10        | 3         | 3           | 1        | 2         | 1           |
| K3           | 10        | 4         | 3           | 2        | 1         | 0           |
| <b>Total</b> | <b>30</b> | <b>11</b> | <b>8</b>    | <b>5</b> | <b>4</b>  | <b>2</b>    |

**Table 8.** Effect of intervention on MBS in research subjects.

| Group        | n         | IMV                 |
|--------------|-----------|---------------------|
| K1           | 10        | 43.2 ± 7.48         |
| K2           | 10        | 40.3 ± 6.94         |
| K3           | 10        | 37.87 ± 9.34        |
| <b>Total</b> | <b>30</b> | <b>40.45 ± 8.02</b> |

## DISCUSSION

### Main findings

This study involved 30 menopausal women divided into control, soy isoflavone 50 mg/day, and estradiol valerate groups. The research results indicate that the subjects in the estradiol valerate group had the oldest mean age ( $54.7 \pm 2.75$  years) and a longer duration of menopause ( $5 \pm 2.75$ ) compared to the other groups.

### Interpretation and comparison with other literature

Okada *et al.*'s study also showed similar results, with the mean age of menopausal women being  $56.5 \pm 6.9$  years and a duration of menopause of  $8.1 \pm 5.8$  years [5]. Karyati and Astuti's study also revealed that 20 (62.5%) out of 32 menopausal female respondents were aged above 60 [12].

Furthermore, a study by Igweh *et al.* indicates that menopause acts as an independent risk factor for cardiovascular disease, evidenced by a significant reduction in cardioprotective HDL and VLDL alongside an elevation in LDL levels among postmenopausal women [13]. In addition, estrogen loss during menopause is the major cause of progressive urogenital atrophy, presenting with prevalent symptoms like vaginal dryness and dyspareunia that severely impact women's quality of life [14]. Moreover, the menopausal transition is accompanied by metabolic changes that predispose women to type 2 diabetes mellitus, highlighting a complex interplay where menopause accelerates both metabolic and cardiovascular risks [15].

Significant differences in estradiol levels were exclusively observed in the estradiol valerate and soy isoflavone groups, with corresponding P-values of 0.020 and 0.037, signifying an elevation in both estradiol and soy isoflavone levels post-intervention. These outcomes align with the findings of Waaseth *et al.*, where a comparison of estradiol levels pre- and post-estradiol valerate administration indicated an increase in plasma estradiol levels proportional to the estradiol valerate dosage. The study also highlighted that 88% of participants re-

**Table 9.** Effect of intervention on MBS in research subjects.

| Group | n  | FSFI             |                   | P-value |
|-------|----|------------------|-------------------|---------|
|       |    | Pre-intervention | Post-intervention |         |
| K1    | 10 | 26.1 ± 5.32      | 27.59 ± 2.88      | 0.063   |
| K2    | 10 | 26.4 ± 4.64      | 28.8 ± 1.93       | 0.035   |
| K3    | 10 | 26.3 ± 4.49      | 28.1 ± 2.23       | 0.031   |

ceiving estradiol valerate exhibited estradiol levels surpassing those of counterparts who did not undergo the intervention [16].

Studies indicate that before menopause, women exhibit a lower susceptibility to cardiovascular disease compared to men; however, this advantage diminishes post-menopause. Findings from the Framingham Study suggest that the incidence of coronary heart disease (CHD) in women rises more rapidly than in men beyond the age of 45 [17].

Current research is investigating differences in lipid levels between premenopausal and postmenopausal women. Key discoveries from this analysis reveal that triglyceride levels, total cholesterol, low-density lipoprotein (LDL), and the ratio of total cholesterol to HDL are notably elevated in postmenopausal women compared to their premenopausal counterparts. HDL levels, however, show no disparity between premenopausal and postmenopausal women. Additional findings propose that the decline in estrogen levels during menopause adversely impacts the comprehensive lipid profile of postmenopausal women [18].

Urogenital complaints differ from vasomotor complaints in menopausal women in terms of onset and progression. Vasomotor complaints occur at the end of the menopausal transition or early postmenopause and tend to improve with increasing age at menopause. On the other hand, urogenital complaints are more frequently experienced by women in the late postmenopausal phase and worsen over time. This is directly related to the decrease in the levels of estradiol and progesterone hormones, leading to physiological changes in the urogenital tract of menopausal women [19]. Palma *et al.* reported that, out of 900 postmenopausal women undergoing routine examinations, 84% complained of urogenital symptoms related to menopause. Recent survey results state that at least half of menopausal women have urogenital complaints. Dry vagina is the most commonly reported urogenital complaint in menopausal women, occurring in about 3% during the premenopausal period and increasing to 47% three years after menopause. Furthermore, the

North American Menopause Society emphasizes that this genitourinary syndrome of menopause (GSM) affects up to 84% of postmenopausal women and can significantly impair health, sexual function, and overall quality of life, yet it often remains underdiagnosed and undertreated [20]. Epidemiological findings depend heavily on several risk factors, including age, duration of menopause, frequency of sexual activity, general health status, partner availability, and social background [17]. In this study, a control or placebo group was used, given non-hormonal vaginal lubricant gel as a comparison with oral estrogen and oral soy isoflavone therapy. The administration of hormonal vaginal lubricant gel in the placebo group aimed to meet ethical requirements. The placebo gel used was hydroxyethylcellulose gel, which has minimal effects on vaginal microbiota and inflammation [21].

In this study, an examination of serum estradiol levels before and after the administration of estradiol valerate showed significant results ( $p < 0.05$ ). This is because estradiol valerate, or E2V, is an ester prodrug [DB00783], a natural hormone circulating endogenously in the human body. Estradiol is the most potent form of all mammals steroid estrogens and is the primary female sex hormone.

Similarly, serum estradiol levels before and after soy isoflavone administration were examined in this study. The results showed no significant changes ( $p > 0.05$ ). Soy isoflavones are compounds with biological activity. The available data is currently insufficient, and it is premature to definitively conclude the suitability of isoflavones as an estrogen alternative for hormone replacement in postmenopausal women. Jenks *et al.* [19] suggested that S-equol, a metabolite originating from soy isoflavone daidzein, might have a potential role in alleviating menopausal symptoms. They conducted a comparative study between the natural S-equol supplement, SE5-OH, and isoflavones to relieve hot flashes and other menopausal symptoms. A study involving 102 postmenopausal women concluded that a daily dose of 10 mg of S-equol appears to be as effective as soy isoflavones in reducing the frequency of hot flashes. Furthermore, at a daily dosage of 20 mg, S-equol exhibited a more substantial reduction in facial flushing compared to soy isoflavones in women experiencing more than eight hot flashes per day.

The findings of this study demonstrate that both soy isoflavone and estradiol valerate significantly improved urogenital symptoms and sexual function in menopausal women, as reflected by im-

provements in FSFI scores and vaginal maturation index. These results align with growing interest in therapeutic strategies that address genitourinary syndrome of menopause (GSM) and sexual dysfunction, particularly in populations with hormone sensitivity concerns, such as breast cancer survivors. In this context, the systematic review by D’Oria *et al.* highlighted the clinical utility of fractional CO<sub>2</sub> laser therapy as a non-hormonal option for managing vulvovaginal atrophy in gynaecologic cancer patients. Their findings support the efficacy and safety of CO<sub>2</sub> laser in improving vaginal symptoms, elasticity, and sexual function, offering an alternative for individuals in whom estrogen therapy is contraindicated [22]. The large prospective observational study by Di Donato *et al.* also supports this trend, demonstrating the efficacy of fractional CO<sub>2</sub> laser therapy in significantly improving symptoms of GSM, including vaginal dryness, irritation, and dyspareunia, with good tolerability and patient satisfaction. When compared to our findings, both hormonal (estradiol valerate) and non-hormonal (soy isoflavone) systemic approaches, as well as local interventions like laser therapy, appear to contribute meaningfully to symptom relief [23]. When juxtaposed with the current study’s results, it becomes evident that individualized therapeutic approaches – whether phytoestrogen-based, hormonal, or device-assisted – are vital to enhancing the quality of life among postmenopausal women [22].

Further supporting the need for individualized therapies, the review by Vizza *et al.* (2023) emphasized that sexual dysfunction remains highly prevalent among breast cancer survivors, with up to 75% experiencing symptoms such as vaginal dryness, dyspareunia, and reduced libido. The study underscores that addressing these symptoms is crucial for quality of life, psychological well-being, and treatment adherence. While hormonal treatments remain effective, non-hormonal strategies – including lubricants, moisturizers, laser therapy, and pelvic floor rehabilitation – are increasingly explored for their safety profiles in hormonally sensitive populations. In line with this, the current study demonstrates the beneficial effects of soy isoflavone – a phytoestrogen with weaker estrogenic activity – and estradiol valerate in improving sexual function and urogenital health. Although soy isoflavone did not significantly raise serum estradiol levels, it yielded meaningful clinical improvements, suggesting a potential role in symptomatic relief among

women seeking alternatives to systemic hormone therapy. These findings reinforce the importance of tailoring menopausal care to individual patient contexts, including oncologic history, symptom burden, and therapeutic preferences [24].

### **Limitations**

This study has several limitations. First, the relatively small sample size may limit the generalizability of the findings, as the number of participants in each intervention group was modest. A larger cohort would be necessary to confirm these results and better account for potential variability among subjects. Second, the duration of the intervention – although sufficient to observe short-term effects – may not fully capture the long-term impact of soy isoflavone or estradiol valerate on metabolic parameters, urogenital symptoms, and sexual function. Additionally, the study did not include long-term follow-up to assess the sustainability of symptom improvement after discontinuation of therapy. Finally, while the survey employed validated tools such as the FSFI and MENQOL, the absence of blinding in subjective assessments could introduce potential bias. Future research with larger, multi-centre samples and extended follow-up periods is warranted to substantiate and expand upon these preliminary findings.

### **CONCLUSIONS**

HbA1c levels in the soy isoflavone 50 mg and estradiol valerate groups differ significantly before and after the intervention. The group that received both soy isoflavone and estradiol valerate showed a reduction in total cholesterol; however, only the estradiol valerate group showed a statistically significant decrease. Improvement in urogenital complaints, as assessed through the MBS with a substantial difference in values before and after intervention, was observed in the soy isoflavone group. When the mean menopausal complaints based on the MENQOL scale were compared between the groups after the intervention, significant differences were found between the administration of soy isoflavone and estradiol valerate in the psychosocial, physical, and total MENQOL categories. However, after the intervention, there were no significant differences between the administration of soy isoflavone and estradiol valerate in the vasomotor or sexual domains.

### **COMPLIANCE WITH ETHICAL STANDARDS**

#### **Authors' contribution**

M.E.A.G.S., M.F.G.S.: Conceptualization, methodology, supervision. M.E.A.G.S.: Writing – original draft, writing – review & editing. M.F.G.S.: Data curation, formal analysis, writing – review & editing. H.S.S.: Investigation, data curation, visualization, writing – review & editing. S.N.L.: Validation, resource, project administration. R.Z.T.: Software, data curation, visualization. A.N.: Investigation, data curation. I.L.L.: Resources, project administration. J.S.: Formal analysis, validation. W.K.A.: Software, data curation. I.D.L., P.W.: Investigation, writing – review & editing. S.A.: Project administration, resource.

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None.

#### **Study registration**

None.

#### **Disclosure of interests**

The authors declare that they have no conflict of interests.

#### **Ethical approval**

This study was conducted by the Declaration of Helsinki and was approved by the Ethics Committee, University of North Sumatra (Approval Number: NO.403/KEP/USU/2020).

#### **Informed consent**

This study was conducted in accordance with ethical guidelines and principles outlined in the Declaration of Helsinki. Informed consent was obtained from all participants (or their legal representatives) prior to their inclusion in the study.

#### **Data sharing**

Data are available under reasonable request to the corresponding author.

### **REFERENCES**

1. Takahashi TA, Johnson KM. Menopause. *Med Clin North Am.* 2015;99(3):521-34. doi: 10.1016/j.mcna.2015.01.006.
2. Gold EB. The timing of the age at which natural menopause occurs. *Obstet Gynecol Clin*

- North Am. 2011;38(3):425-40. doi: 10.1016/j.ogc.2011.05.002.
3. Slopian R, Wender-Ozegowska E, Rogowicz-Frontczak A, Meczekalski B, Zozulinska-Ziolkiewicz D, Jaremek JD, et al. Menopause and diabetes: EMAS clinical guide. *Maturitas*. 2018;117:6-10. doi: 10.1016/j.maturitas.2018.08.009.
  4. Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus: Abbreviated Report of a WHO Consultation. Geneva: World Health Organization; 2011.
  5. Okada M, Nomura S, Ikoma Y, Yamamoto E, Ito T, Mitsui T, Tamakoshi K, Mizutani S. Effects of postmenopausal hormone replacement therapy on HbA(1c) levels. *Diabetes Care*. 2003;26(4):1088-92. doi: 10.2337/diacare.26.4.1088.
  6. Reddy Kilim S, Chandala SR. A comparative study of lipid profile and oestradiol in pre- and postmenopausal women. *J Clin Diagn Res*. 2013;7(8):1596-8. doi: 10.7860/JCDR/2013/6162.3234.
  7. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015;136(5):E359-86. doi: 10.1002/ijc.29210.
  8. Chen LR, Ko NY, Chen KH. Isoflavone Supplements for Menopausal Women: A Systematic Review. *Nutrients*. 2019;11(11):2649. doi: 10.3390/nu11112649.
  9. Khapre S, Deshmukh U, Jain S. The Impact of Soy Isoflavone Supplementation on the Menopausal Symptoms in Perimenopausal and Postmenopausal Women. *J Midlife Health*. 2022;13(2):175-84. doi: 10.4103/jmh.jmh\_190\_21.
  10. Van Dole KB, DeVellis RF, Brown RD, Funk ML, Gaynes BN, Williams RE. Evaluation of the Menopause-Specific Quality of Life Questionnaire: a factor-analytic approach. *Menopause*. 2012;19(2):211-5. doi: 10.1097/gme.0b013e31822817f9.
  11. Burger HG. The endocrinology of the menopause. *J Steroid Biochem Mol Biol*. 1999;69(1-6):31-5. doi: 10.1016/s0960-0760(98)00145-9.
  12. Fajrani AM. The relationship between physical activity, nutritional status, and blood glucose levels in menopausal women in the Kini Jaya Housing Complex, Semarang City. Naskah Publikasi. Semarang: Universitas Muhammadiyah Semarang; 2018.
  13. Igweh JC, Nwagha IU, Okaro JM. The effects of menopause on the serum lipid profile of normal females of South East Nigeria. *Niger J Physiol Sci*. 2005;20(1-2):48-53.
  14. Calleja-Agius J, Brincat MP. The urogenital system and the menopause. *Climacteric*. 2015;18 Suppl 1:18-22. doi: 10.3109/13697137.2015.1078206.
  15. Lambrinoudaki I, Paschou SA, Armeni E, Goulis DG. The interplay between diabetes mellitus and menopause: clinical implications. *Nat Rev Endocrinol*. 2022;18(10):608-22. doi: 10.1038/s41574-022-00708-0.
  16. Waaseth M, Bakken K, Dumeaux V, Olsen KS, Rylander C, Figenschau Y, Lund E. Hormone replacement therapy use and plasma levels of sex hormones in the Norwegian Women and Cancer postgenome cohort - a cross-sectional analysis. *BMC Womens Health*. 2008;8:1. doi: 10.1186/1472-6874-8-1.
  17. Palma F, Volpe A, Villa P, Cagnacci A; Writing group of AGATA study. Vaginal atrophy of women in postmenopause. Results from a multicentric observational study: The AGATA study. *Maturitas*. 2016;83:40-44. doi:10.1016/j.maturitas.2015.09.001.
  18. Ambikairajah A, Walsh E, Tabatabaei-Jafari H, Cherbuin N. Fat mass changes during menopause: a metaanalysis. *Am J Obstet Gynecol*. 2019;221(5):393-409.e50. doi: 10.1016/j.ajog.2019.04.023.
  19. Jenks BH, Iwashita S, Nakagawa Y, Ragland K, Lee J, Carson WH, et al. A pilot study on the effects of S-equol compared to soy isoflavones on menopausal hot flash frequency. *J Womens Health (Larchmt)*. 2012;21(6):674-682. doi:10.1089/jwh.2011.3153.
  20. The NAMS 2020 GSM Position Statement Editorial Panel. The 2020 genitourinary syndrome of menopause position statement of The North American Menopause Society. *Menopause*. 2020;27(9):976-92. doi: 10.1097/GME.0000000000001609.
  21. Richardson BA, Kelly C, Ramjee G, Fleming T, Makanani B, Roberts S, et al. Appropriateness of hydroxyethylcellulose gel as a placebo control in vaginal microbicide trials: a comparison of the two control arms of HPTN 035. *J Acquir Immune Defic Syndr*. 2013;63(1):120-5. doi: 10.1097/QAI.0b013e31828607c5.
  22. D'Oria O, Giannini A, Buzzaccarini G, Tinelli A, Corrado G, Frega A, et al. Fractional CO<sub>2</sub> laser for vulvo-vaginal atrophy in gynecologic cancer patients: A valid therapeutic choice? A systematic review. *Eur J Obstet Gynecol Reprod Biol*. 2022;277:84-9. doi: 10.1016/j.ejogrb.2022.08.012.

23. Di Donato V, D'Oria O, Giannini A, Scudo M, Sher C, Fischetti M, et al. The efficacy of fractional CO<sub>2</sub> laser in the treatment of genitourinary syndrome of menopause: a large prospective observational study. *Clin Exp Obstet Gynecol.* 2022;49(9):212. doi: 10.31083/j.ceog4909212.
24. Vizza R, Capomolla EM, Tosetto L, Corrado G, Bruno V, Chiofalo B, et al. Sexual dysfunctions in breast cancer patients: evidence in context. *Sex Med Rev.* 2023;11(3):179-95. doi: 10.1093/sxmrev/qead006.