

## ORIGINAL ARTICLE

### 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

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## ABSTRACT

**Background.** Menopause is characterized by the natural cessation of menstruation for a continuous period of 12 months. This biological transition triggers alterations in lipid profiles, resulting in a decrease in High-Density Lipoprotein (HDL) and an increase in Total Cholesterol (TC), triglycerides (TG), Low-Density Lipoprotein (LDL) cholesterol, and Very Low-Density Lipoprotein (VLDL) cholesterol. These changes contribute to an elevated risk of cardiovascular diseases. Every year, 1.5 million women undergo the transition to menopause, which commonly includes bothersome symptoms like vasomotor symptoms, vaginal dryness, diminished libido, sleep disturbances, fatigue, and joint pain. 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.

**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 analyzed 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.

### **Key words**

Soy Isoflavone; HbA1c; Lipid profile; urogenital complaints; vaginal maturation index.

### **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 hemoglobin (HbA1c) was first recognized as an "unusual" form of hemoglobin 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 (MENQOL), 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 favorable 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 analyzed 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: This 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].

- Menopause: 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 woman's life, leading to the absence of both vegetative and psychological disturbances.

## **Results**

### Baseline Characteristics

Table 1 presents the demographic and baseline clinical characteristics of the study participants. Data were recorded, tabulated, and statistically analyzed 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 individuals (22%) and seven individuals (88%) experience overweight in the estradiol valerate and soy isoflavone groups, respectively.

(Table 1. Frequency distribution of characteristic data of research subjects)

#### 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 glycemic control among postmenopausal women, with the Soy Isoflavone group showing the most considerable mean reduction.

(Table 2. Comparison of HbA1c levels between groups)

#### 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 ( $p = 0.037$ ) 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.

(Table 3. Effect of Intervention on Serum Estradiol Levels in Research Subjects)

#### 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.

(Table 4. Effect of Intervention on HDL Serum Research Subjects)

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.

(Table 5. Effect of Intervention on LDL Serum Levels in Research Subjects)

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.

(Table 6. Effect of Intervention on Serum Triglyceride Levels in Research Subjects)

### 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 ( $p = 0.063$ ).

## **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 [12]. Karyati and Astuti's study also revealed that 20 (62.5%) out of 32 menopausal female respondents were aged above 60 [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 receiving 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 F 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. 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 [20]. 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 mammalian 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. 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 improvements 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 gynecologic 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-center 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**

### **Author Contribution**

M.E.A.G.S. and M.F.G.S. contributed to the conceptualization and methodology of the study and jointly supervised the project. M.E.A.G.S. led the writing of the original draft and was involved in review and editing, while M.F.G.S. contributed to data curation, formal analysis, and review and editing. H.S.S. participated in the investigation, data curation, and visualization and reviewed and edited the manuscript. S.N.L. was responsible for validation, resource acquisition, and project administration. R.Z.T. handled software management, data curation, and visualization. A.N. took part in the investigation and data curation. I.L.L. contributed to resources and project administration. J.S. was involved in formal analysis and validation. W.K.A. assisted in software management and data curation. I.D.L. contributed to the investigation and participated in the review and editing process. S.A. was responsible for project administration and resource management. P.W. contributed to the investigation and to reviewing and editing the manuscript.

### **Funding**

None

### **Study Registration**

The study is not registered in any clinical trial register.

### **Disclosure of Interest**

The authors declare no conflict of interest.

## **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). Written informed consent was obtained from all participants before their inclusion in the study.

### **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**

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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

Characteristics	Control (n=10)	Soy Isoflavone 50mg/ day (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*
Duration of Menopause (mean±SD; years)	3.40±1.90	4.10±1.97	5.00±2.75	0.293*
Parity (n, %)				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 (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%)	

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

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

**Table 3 Effect of Intervention on Serum Estradiol Levels in Research Subjects**

Group	Estradiol serum levels, mean ± SD (pg/ml)		p
	Pre-Intervention	Post-Intervention	
K1	50,74 ± 12,84	54,06 ± 19,20	0,064
K2	54,88 ± 38,86	107,96 ± 28,75	0,007
K3	88,89 ± 31,12	92,33 ± 31,95	0,037

**Table 4 Effect of Intervention on HDL Serum Research Subjects**

Group	HDL levels, mean $\pm$ SD (mg/dL)		p
	Pre-Intervention	Post-Intervention	
K1	48,30 $\pm$ 8,99	45,20 $\pm$ 110,45	0,224
K2	61,50 $\pm$ 10,64	57,00 $\pm$ 13,67	0,066
K3	56,30 $\pm$ 17,48	56,70 $\pm$ 19,57	0,001

**Table 5. Effect of Intervention on LDL Serum Levels in Research Subjects**

Group	LDL levels, mean $\pm$ SD (mg/dL)		p
	Pre-Intervention	Post-Intervensi	
K1	110,50 $\pm$ 33,66	118,40 $\pm$ 30,87	0,257
K2	129,60 $\pm$ 35,06	107,70 $\pm$ 28,38	0,003
K3	132,90 $\pm$ 36,84	56,70 $\pm$ 19,57	0,114

**Table 6. Effect of Intervention on Serum Triglyceride Levels in Research Subjects**

Group	Triglyceride levels, mean $\pm$ SD (mg/dL)		p
	Pre-Intervention	Post-Intervention	
K1	247,10 $\pm$ 156,58	246,60 $\pm$ 151,45	0,799
K2	260,50 $\pm$ 315,0	194,40 $\pm$ 152,80	0,214
K3	200,70 $\pm$ 115,01	200,30 $\pm$ 136,99	0,508

**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
Total	30	11	8	5	4	2

**Table 8. Effect of Intervention on MBS in Research Subjects**

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

**Table 9. Effect of Intervention on MBS in Research Subjects**

<b>Group</b>	<b>n</b>	<b>FSFI</b>		<b>p-value</b>
		<b>Preintervention</b>	<b>Postintervention</b>	
<b>K1</b>	10	26.1 ± 5.32	27.59 ± 2.88	0,063
<b>K2</b>	10	26.4 ± 4.64	28.8 ± 1.93	0,035
<b>K3</b>	10	26.3 ± 4.49	28.1 ± 2.23	0,031