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Comparative analysis of effect of life style modification with and without isoflavones for menopausal symptoms

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Abstract
Background: Natural or spontaneous menopause is a transition period in a woman's life from the reproductive to the non-reproductive phase. It happens with the final menstrual period, which is known to happen after 12 months of amenorrhea with no obvious pathological or physiological causes.[1,2] It promotes aging and hastens the progression of non-communicable diseases. Menopause occurs between the ages of 45 and 55 worldwide.[2] Menopause symptoms manifest not only in the female genital tract, but also in the skeletal, cardiovascular, and psychological systems. With rising life expectancy, women are more likely to experience long periods of menopause, accounting for roughly one-third of their age. As a result, the morbidity burden has increased.
Aim and Objectives: To compare the effects of lifestyle modification with & without isoflavones supplementation for menopausal symptoms.
Methods: The study was conducted in Department of Obstetrics and Gynaecology, Upper India Sugar Exchange Maternity Hospital, GSVM Medical College in Kanpur of Uttar Pradesh state. This hospital is a tertiary care teaching hospital. The study was conducted in obstetrics department of the hospital. Postmenopausal women who had at least 1 year history of cessation of menses were included. Availability of subjects for the entire study period and willingness to adhere to protocol requirements as evidence by written informed consent. Perimenopausal females of age >40 years. Perimenopausal is the period immediately prior to and up to 1 year after the final menstrual period.
Conclusion: The present study was a triple arm randomized clinical trials study conducted to determine the comparative analysis of effect of lifestyle modification with and without Isoflavanis for menopausal symptoms was performed at the department of Obstetrics and gynaecology, Upper India Sugar Exchange Maternity Hospital, GSVM Medical College, Kanpur. The following are the important conclusion drawn from the study. In our study majority of the women were 50 - 69 years age group from urbon population and housewives in occupation in all three groups respectively. In our study majority of the patients had normal BMI and blood pressure in all groups Isoflavanis life style modification and lifestyle Isoflavanis respectively. In our study Vasomotor symptoms psychological and urogenital symptoms reduce after the lifestyle dietary and yoga with Isoflavane and intervention which is shown by reduction in MRS score after the intervention. The results of the present study strongly recommend lifestyle modification dietary supplementation yoga and Isoflavane supplementation resulted in reduction of menopausal symptoms. Thus importance of life-style management yoga and Isoflavane to be incorporated in daily routine under the supervision and motivation / adherence can be mandatory. The mean, Vasomotor symptoms were significantly lower in lifestyle mod which Isoflavane group III group at 2nd visit and 3rd visit. In our study regarding the safety profile of phyto-estrogen Isoflavane no majoride effect, were found and only minor side effect like headache, nausea, vomiting were present. No breakthrough bleeding (every women with hormone therapy).

Keywords: Isoflavone, daidzein, genistein, equol, menopause

Introduction
Natural or spontaneous menopause is a transition period in a woman's life from the reproductive to the nonreproductive phase. It happens with the final menstrual period, which is known to happen after 12 months of amenorrhea with no obvious pathological or physiological causes [1, 2].

Menopause occurs between the ages of 45 and 55 worldwide [2]. As a result, the morbidity burden has increased. An understanding of the risk factors, their clinical manifestations, and their management.[3] Menopause is a biological process that can cause various troublesome symptoms such as hot flashes and emotional changes, but can also increase mortality risk due to subsequent osteoporosis and reduced metabolism. Hormone replacement therapy (HRT) would be the most intuitive way to combat these changes; however, the 2002 Women's Health Initiative (WHI) study showed that hormone replacement therapy increased the risk of breast cancer, stroke, and coronary heart disease in healthy postmenopausal women [4]. Since then, healthcare professionals and women have been seeking alternative therapies. Vasomotor symptoms (VMS) such as hot flushes and sweating, are very common in menopausal populations and can cause physical and mental discomfort [5]. Estrogen remains the most effective therapy for hot flashes and is approved by the U.S. Food and Drug Administration (FDA) [6].

Although some women may prefer lifestyle modification, there is no evidence that lowering the room temperature, exercising. Currently, HRT is indicated for the prevention of osteoporosis and relief of the VMS and vulvovaginal atrophy associated with menopause. Moreover, HRT increases bone mineral density (BMD) and reduces the incidence of osteoporotic fractures [7]. Due to the serious side effects mentioned above, HRT should be given in the lowest effective doses for the shortest duration to meet the treatment goals. In fact, the FDA recommends that approved non-estrogen treatments can first be carefully considered before relying solely on HRT for osteoporosis prevention [8].

Aim and Objectives

To compare the effects of lifestyle modification with & without isoflavones supplementation for menopausal symptoms. To estimate the magnitude of post-menopausal symptoms in post-menopausal and perimenopausal women using MRS II score in hospital setup. To evaluate the effect of lifestyle modification & diet supplementation & yoga on menopausal symptoms. To evaluate the effect of isoflavones supplementation on menopausal symptoms.

Materials and Methods

The study was conducted in Department of Obstetrics and Gynaecology, Upper India Sugar Exchange Maternity Hospital, GSVM Medical College in Kanpur of Uttar Pradesh state. This hospital is a tertiary care teaching hospital. The study was conducted in obstetrics department of the hospital.

Study population

The study population constituted patients attained menopause. The study participants who fulfilled inclusion criteria were included in the study.

Inclusion criteria

1. Postmenopausal women who had at least 1 year history of cessation of menses were included.
2. Availability of subjects for the entire study period and willingness to adhere to protocol requirements as evidence by written informed consent.
3. Perimenopausal females of age >40 years. Perimenopausal is the period immediately prior to and up to 1 year after the final menstrual period.

Exclusion criteria

1. Women on hormone replacement therapy.
2. Women taking drugs such as antidiabetes, antihypertensive, antilipidemic.
3. Surgical menopause.
4. Premature ovarian insufficiency.
5. Patient with severe hepatic impairment
6. Patient with severe renal impairment
7. Patient with severe asthma
8. Coexistence of any other chronic illness.
9. Regular cycles during the past three months before enrollment in the trial.
10. Mandatory indication for hormone therapy (e.g.,postsurgical menopause or active osteoporosis)
11. Treatment of climacteric complaints with drugs containing estrogen/progestogen during the past 65 months before enrollment in to the trial, and/or any other treatment for climacteric complaints during the past 3 months before enrollment into the trial
12. Pap smear of class iii/iv and/or endometrial hyperplasia
13. Known or suspected hypersensitivity to the investigational medication
14. Concomitant medication that might impair the trial result (e.g., hormones, corticosteroids, centrally acting antihypertensives, psychoactive drugs including sedatives, laxatives).

Method of randomization

Randomization used was a simple randomization and there was a equal chance of being included in either of groups. Randomization of each patients was done into three groups one of who received isoflavone, second group received lifestyle modification, dietary supplementation and yoga and third group was lifestyle modification, dietary supplementation, yoga and isoflavane. Randomization was done using codes obtained from computer generated random tables and allocation ratio of 1:1:1, codes were kept sealed in numbered envelopes.

Groups

Group 1

Those allocated to the intervention group received isoflavone (isoflave CR capsule 65gm)

Group 2

Those allocated to the control group was given lifestyle modification, dietary supplementation and yoga. Three interventions given were

Lifestyle modification

a) Dietary - A balanced diet plan shall be prescribed for average weight Indian perimenopausal,
b) Yoga, Breathing exercise (11-13 poses (Asanas: restrorative, inverted, twists) suggested for VMS relief, Yoga nidra.

Group 3

Those allocated to the control group was given lifestyle modification with isoflavone

Lifestyle modification

a) Dietary: A balanced diet plan shall be prescribed for average weight Indian perimenopausal women

b) Yoga:

1. Breathing exercise
2. 11-13 poses (Asanas: restrorative, inverted, twists) suggested for VMS relief
3. Yoga nidra

Isoflavone (isoflave CR capsule 65 gm)

Study duration

This study was carried out from January 2021 to June 2023.

Results & Observation

Table 1: Comparison of the three groups in terms of change in total protein (G/DL) over time

Total Protein (g/dL)	Group			P value for comparison of the three groups at each of the time points (Kruskal Wallis Test)
	1	2	3	
	Mean (SD)	Mean (SD)	Mean (SD)	
1st Visit	5.76 (0.67)	5.87 (0.67)	5.78 (0.66)	0.557
2nd Visit	5.77 (0.67)	6.06 (0.54)	6.04 (0.53)	<0.001
3rd Visit	5.76 (0.67)	6.12 (0.51)	7.15 (9.39)	<0.001
P Value for change in Total Protein (g/dL) over time within each group (Friedman Test)	0.368	<0.001	<0.001	
Overall P Value for comparison of change in Total Protein (g/dL) over time between the three groups (Generalized Estimating Equations)	<0.001			

The three groups differed significantly in terms of Total Protein (g/dL) at the following time points: 2nd Visit, 3rd Visit.

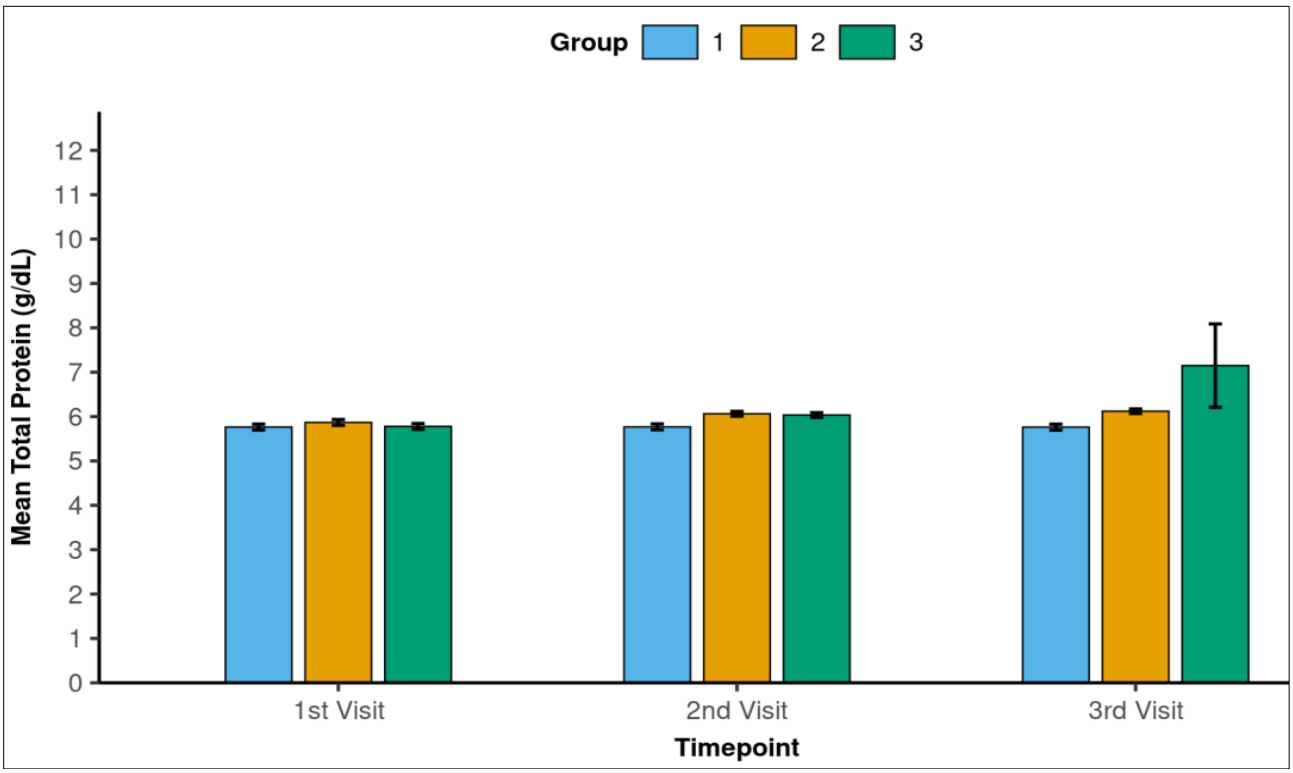


Fig 1: Change in Total Protein (g/dL) Over Time

Table 2: Comparison of the three groups in terms of change in total cholesterol (MG/DL) over time

Total Cholesterol (mg/dL)	Group			P value for comparison of the three groups at each of the time points (Kruskal Wallis Test)
	1	2	3	
	Mean (SD)	Mean (SD)	Mean (SD)	
1st Visit	164.89 (61.65)	160.41 (67.23)	164.27 (60.65)	0.667
2nd Visit	164.86 (61.63)	147.13 (50.95)	146.85 (39.21)	0.049
3rd Visit	164.66 (61.55)	139.45 (40.60)	132.82 (22.24)	<0.001
P Value for change in Total Cholesterol (mg/dL) over time within each group (Friedman Test)	0.368	<0.001	<0.001	
Overall P Value for comparison of change in Total Cholesterol (mg/dL) over time between the three groups (Generalized Estimating Equations)	<0.001			

The three groups differed significantly in terms of Total Cholesterol (mg/dL) at the following timepoints: 2nd Visit, 3rd Visit.

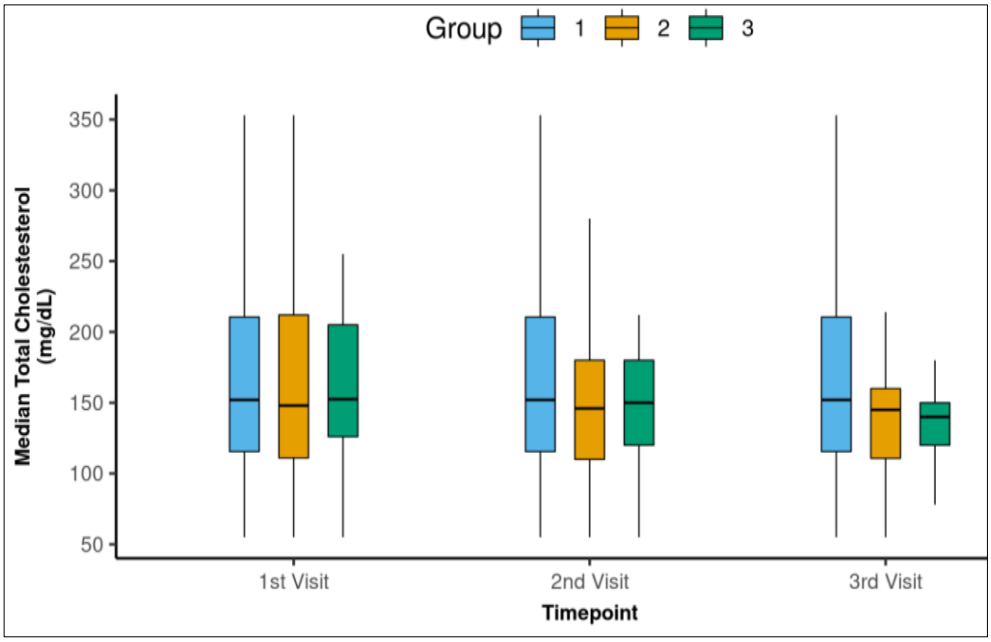


Fig 2: Change in Total Cholesterol (mg/dL) Over Time

Table 3: Comparison of the three groups in terms of change in mrs: physical score over time

MRS: Physical Score	Group			P value for comparison of the three groups at each of the time points (Kruskal Wallis Test)
	1	2	3	
	Mean (SD)	Mean (SD)	Mean (SD)	
1st Visit	7.87 (3.15)	9.27 (3.15)	7.12 (2.49)	<0.001
2nd Visit	4.33 (2.06)	5.35 (2.13)	2.49 (1.32)	<0.001
3rd Visit	2.39 (1.75)	3.52 (1.98)	0.89 (0.75)	<0.001
P Value for change in MRS: Physical Score over time within each group (Friedman Test)	<0.001	<0.001	<0.001	
Overall P Value for comparison of change in MRS: Physical Score over time between the three groups (Generalized Estimating Equations)	0.040			

The three groups differed significantly in terms of MRS: Physical Score at the following time points: 1st Visit, 2nd Visit, 3rd Visit.

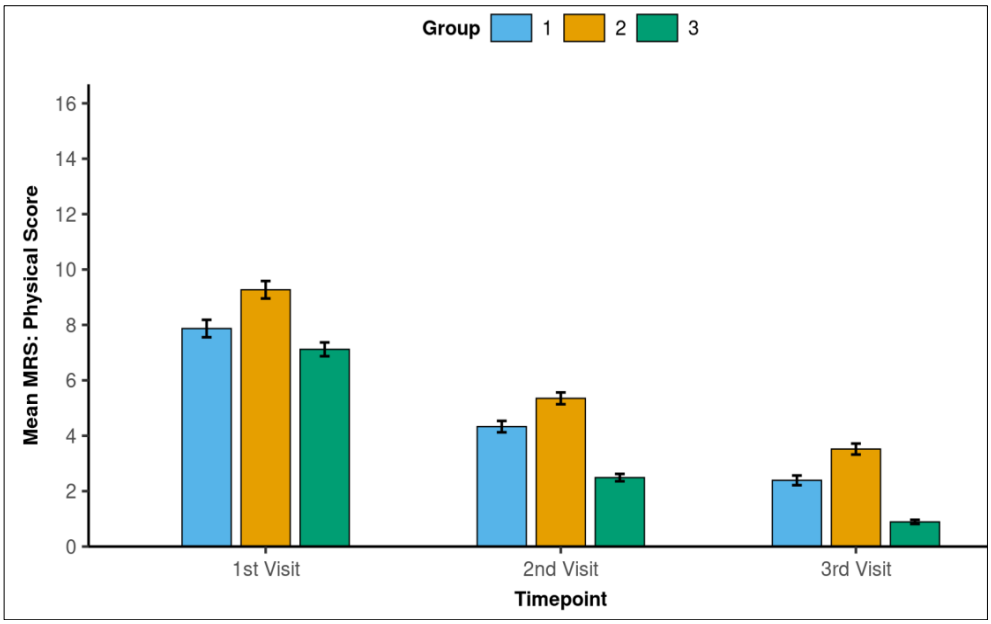


Fig 3: Change in MRS: Physical Score Over Time

Table 4: Comparison of the three groups in terms of change in mrs: psychological score over time

MRS: Psychological Score	Group			P value for comparison of the three groups at each of the time points (Kruskal Wallis Test)
	1	2	3	
	Mean (SD)	Mean (SD)	Mean (SD)	
1st Visit	4.76 (1.99)	4.87 (2.37)	4.43 (2.24)	0.041
2nd Visit	3.47 (1.31)	3.45 (1.65)	2.02 (0.84)	<0.001
3rd Visit	2.85 (1.19)	2.63 (1.20)	1.45 (0.56)	<0.001
P Value for change in MRS: Psychological Score over time within each group (Friedman Test)	<0.001	<0.001	<0.001	
Overall P Value for comparison of change in MRS: Psychological Score over time between the three groups (Generalized Estimating Equations)	<0.001			

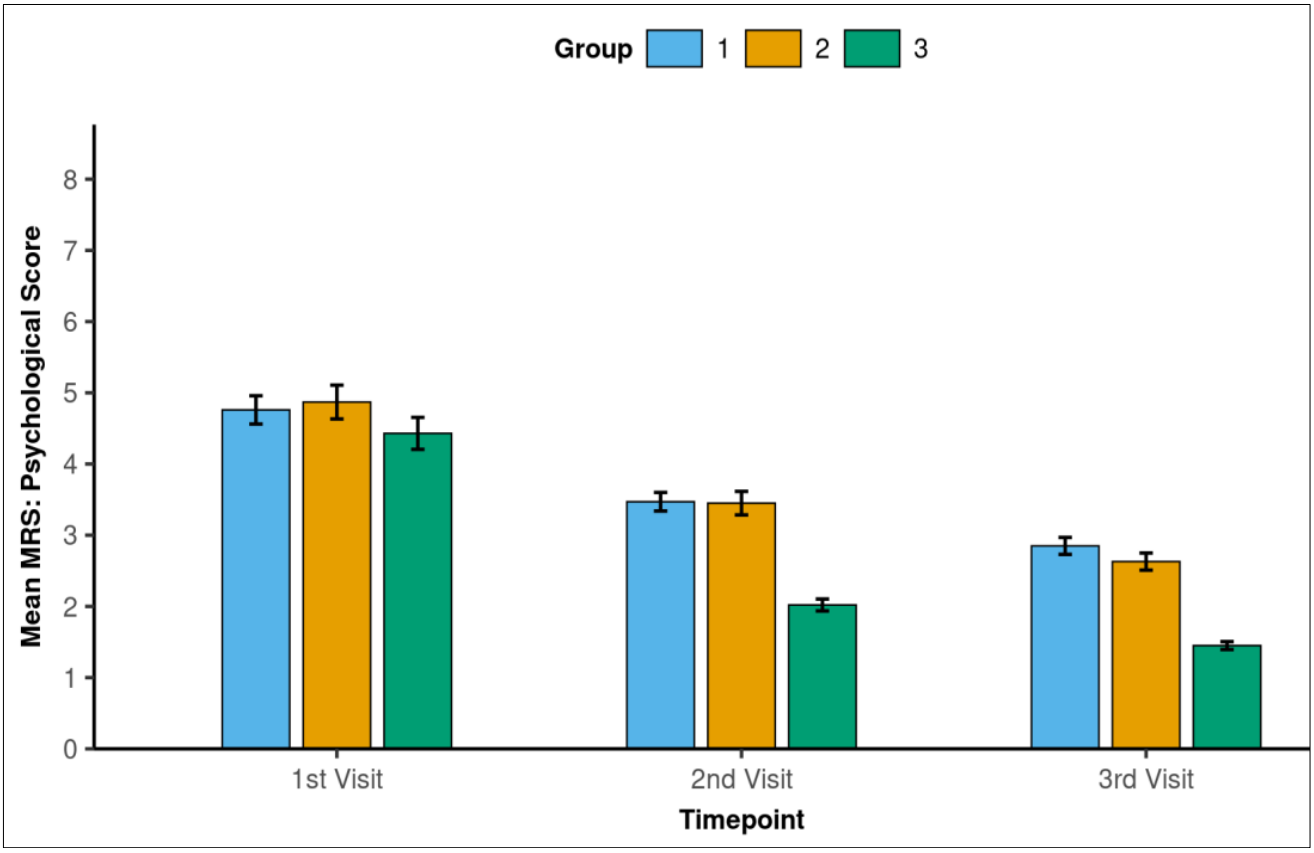


Fig 4: Change in MRS: Psychological Score Over Time

Table 5: Comparison of the three groups in terms of change in mrs: urogenital score over time

MRS: Urogenital Score	Group			P value for comparison of the three groups at each of the time points (Kruskal Wallis Test)
	1	2	3	
	Mean (SD)	Mean (SD)	Mean (SD)	
1st Visit	4.19 (2.01)	4.17 (2.42)	3.82 (2.07)	0.220
2nd Visit	3.16 (1.40)	2.77 (2.01)	1.84 (0.99)	<0.001
3rd Visit	2.66 (1.27)	2.01 (1.20)	1.26 (0.63)	<0.001
P Value for change in MRS: Urogenital Score over time within each group (Friedman Test)	<0.001	<0.001	<0.001	
Overall P Value for comparison of change in MRS: Urogenital Score over time between the three groups (Generalized Estimating Equations)	0.002			

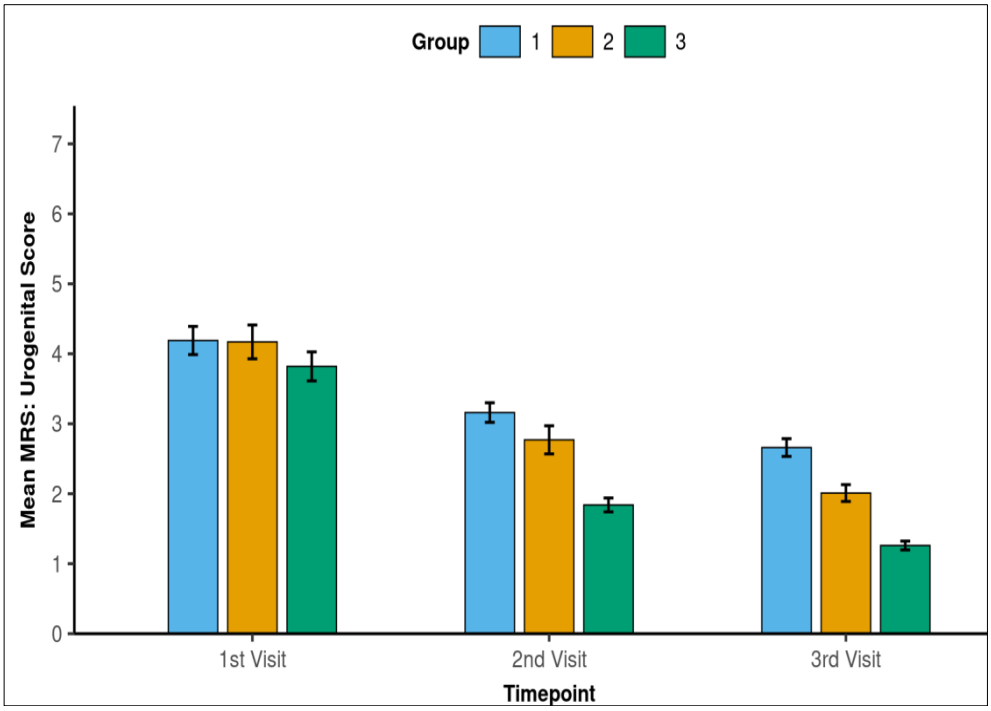
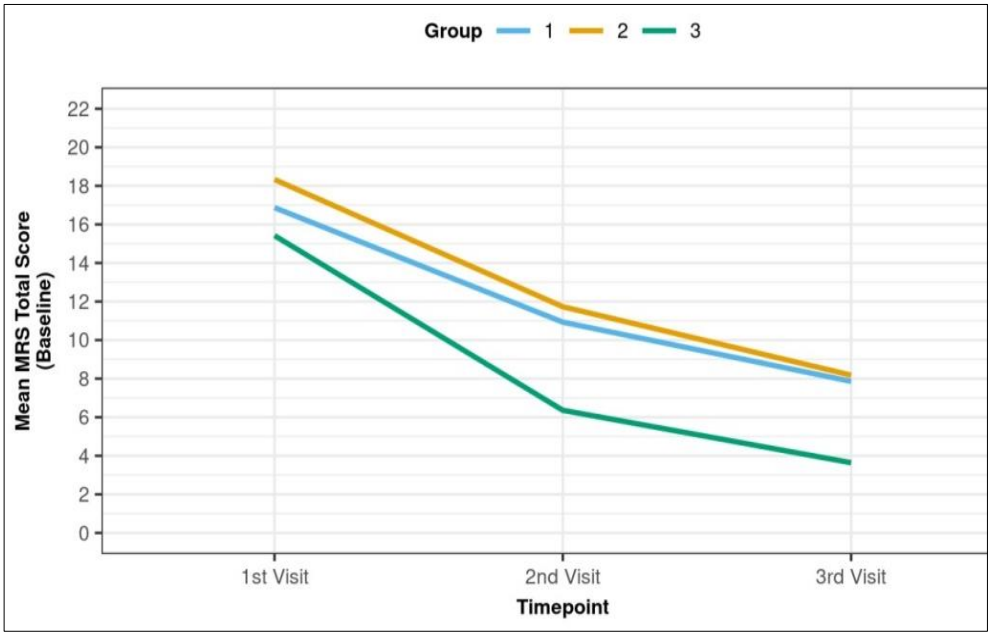


Fig 5: Change in MRS: Urogenital Score Over Time

Table 6: Comparison of the three groups in terms of change in mrs total score (baseline) over time

MRS Total Score (Baseline)	Group			P value for comparison of the three groups at each of the time points (Kruskal Wallis Test)
	1	2	3	
	Mean (SD)	Mean (SD)	Mean (SD)	
1st Visit	16.87 (5.54)	18.33 (5.48)	15.42 (5.17)	<0.001
2nd Visit	10.93 (3.36)	11.73 (3.09)	6.36 (2.09)	<0.001
3rd Visit	7.86 (3.03)	8.18 (0.85)	3.64 (0.85)	<0.001
P Value for change in MRS Total Score (Baseline) over time within each group (Friedman Test)	<0.001	<0.001	<0.001	
Overall P Value for comparison of change in MRS Total Score (Baseline) over time between the three groups (Generalized Estimating Equations)	<0.001			



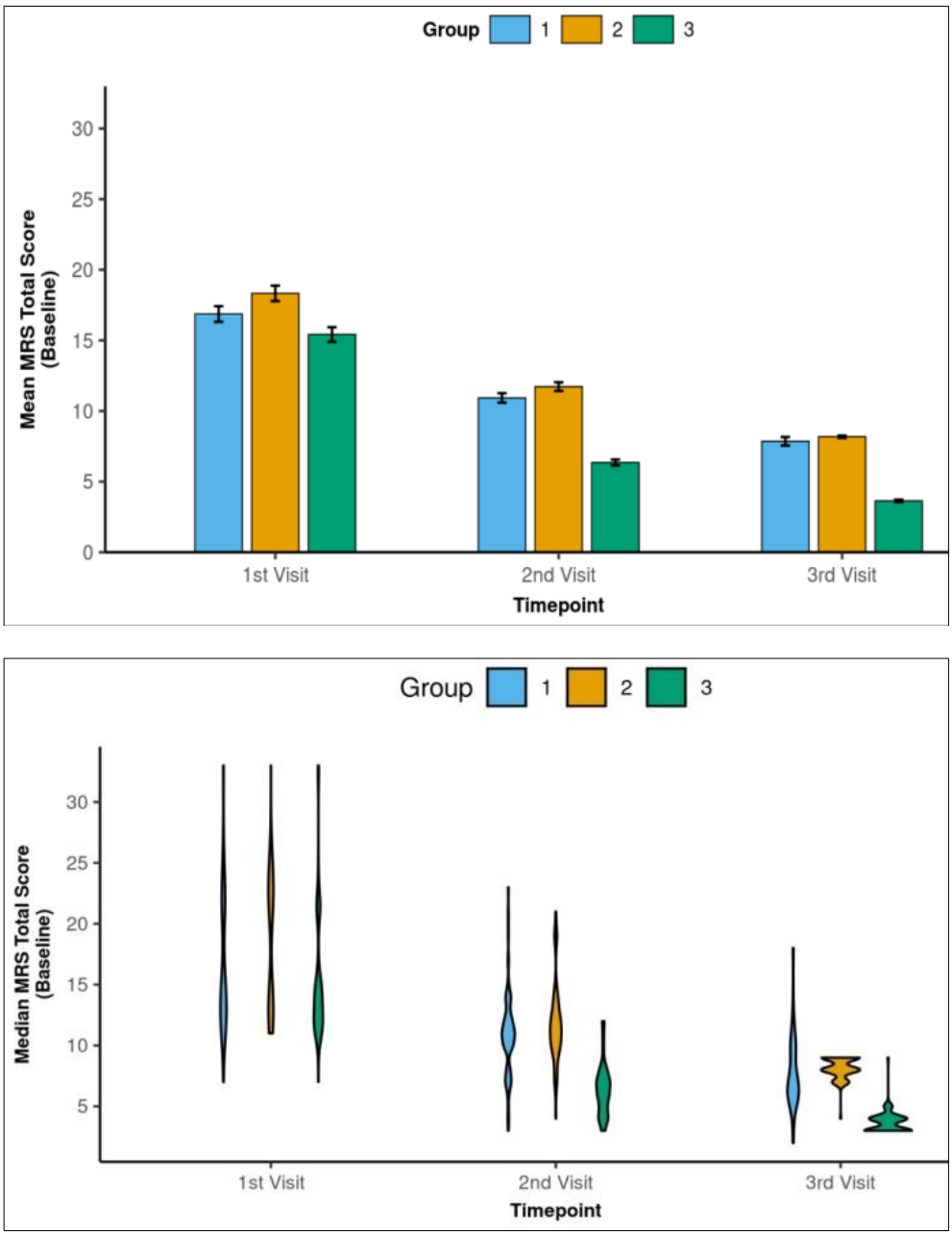


Fig 6: Change in MRS Total Score (Baseline) Over Time

Table 7: Analysis of absolute change in mrs total score (Baseline) over time

Time point Comparison	Change in MRS Total Score (Baseline) from 1st Visit to Follow-up Timepoints						P-Value for Comparison of the three Groups in Terms of Difference of MRS Total Score (Baseline) from 1st Visit to Follow-up Timepoints
	Group: 1		Group: 2		Group: 3		
	Mean (SD) of Absolute Change	P Value of Change Within Group	Mean (SD) of Absolute Change	P Value of Chang e Within Group	Mean (SD) of Absolute Change	P Value of Change Within Group	
2nd Visit - 1st Visit	-5.94 (4.91)	<0.001	-6.60 (5.54)	<0.001	-9.06 (5.55)	<0.001	<0.001
3rd Visit - 1st Visit	-9.01 (5.50)	<0.001	-10.15 (5.64)	<0.001	-11.78 (5.21)	<0.001	0.002

The following table summarizes the mean change in MRS Total Score (Baseline) from the 1st Visit time point to the various follow-up time points. It also summarizes the statistical comparison of the three groups in terms of this difference.

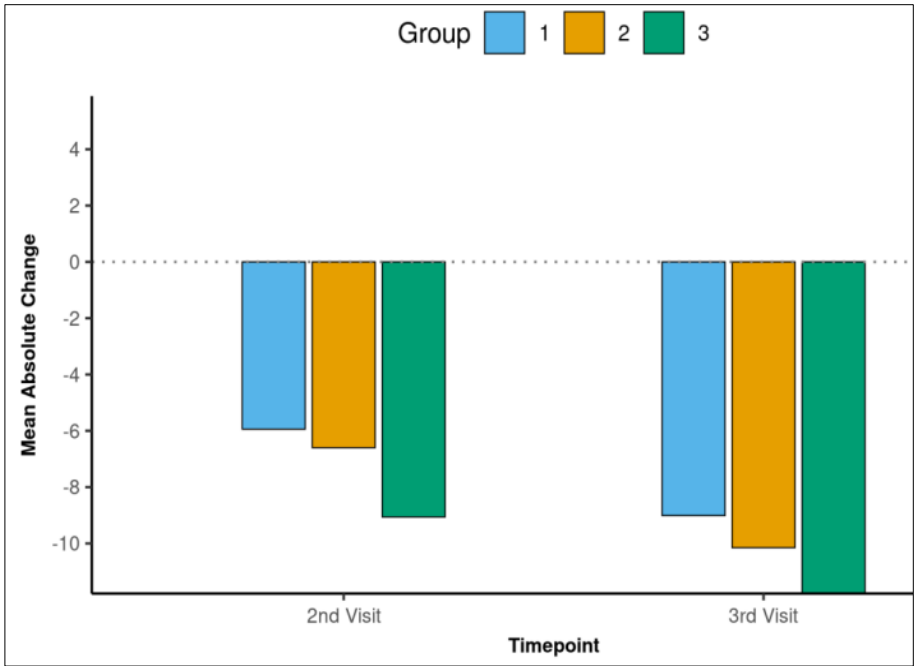


Fig 7: Comparison of difference of MRS Total Score (Baseline) between the 1st Visit time point and the follow-up time points

Discussion

In our study, when life style modification implement with yoga and exercise and diet supplement improve menopausal symptoms and compared in between 3 group 2 and group 3 had shown better improvement as compared to group 1 with p value <0.001 in group 2 and p value <0.001 in group 3 which statistical significant.

Susan D Reed *et al.* 2014 studied menopausal quality of life

RCT of yoga exercise and omega- 3 supplements and this shown that yoga improvement were seen for MENQOL total – 0.3 (p=0.02) Vasomotor symptom domain (p=0.02) and sexuality domain (p=0.02) score in theory thus study match our results.

In the present study, mean (SD) menopause rating scale after the intervention of participant in group 1 was 7.86±(3.03) where patient was in group 2, 8.18± 0.85 and in group 3, 3.64±(0.85). MRS score after intervention was compared between three groups It was found from the analysis that the MRS score found to be better in group 3 compared to group 1 and 2 after intervention. This was found to statistically significant.

A study was done by Cormer H *et al*. on 27th Feb. 2017 to conduct a systemic review and meta-analysis of the efficacy of yoga for menopausal symptoms. Yoga and shown that yoga reduced total menopausal symptoms (SMD = -1.05, 95% CI -1.57 to -0.53) psychological (SMD -0.75, 95% CI -1.17 to -0.34) somatic, (SMD -0.65; 95% CI -1.05 to -0.25), vasomotor (SMD = -0.76; 95% CI.-1.27 to -0.25) and urogenital symptoms (SMD -0.53; 95% CI -0.81 to -0.25 this study match our results.

M. Shophrd *et al*., 2017 studied Improving vasomotor system psychological symptoms; and health related quality of life in peri-postmenopausal women through Yoga, An umberella systemic review and metanalysis is shown that Yoga reduced VMS (SMD -0.27, 95% CI -0.49 to -0.05) and psychological symptoms (SDM -0.32; 95% CI -0.47 to -0.17). This study match on results.

In our study when the menopause rating scale scoring in menopause women was compared in between 3 group, groupd 3 had shown better improvement in MRI scaling with p value <0.001 which is statistical significant.

Marya Ahsan *et al*., In 2017 studied The effect of Soy Isoflavone on the menopause rating scale scoring in perimenopausal and post-menopausal women and this study shows soy Isoflavone improves the MRS score among both the perimenopaual and postmenopausal women As the most effective for somatic and psychological symptoms. This study matched our study.

In our study when total cholesterol was compared in preterm 3 grous. Group 3 had shown much decrease in total cholesterol as compared to group 1 and 2 with p value <0.001 which statistical significant.

Jian Wu *et al*. in 2006 studied cooperative effect of Isoflavone and excessive on bone and lipid metabolism in postmenopausal Japanes women, RCT and this shown serum HDL cholesterol concentration significantly increased (p = 0.03). This study matched our result.

Suzonne *et al.* in 2007 studied soy Isoflavone supplementation and fasting serum glucose and lipid profile among postmenopausal Chinese women double blind randomized placebo controlled trial and this shown little effect of soy Isoflavone on women lipid among the treatment group. This study matched with our study.

Conclusion

The present study was a triple arm randomized clinical trials study conducted to determine the comparative analysis of effect of lifestyle modification with and without Isoflavanis for menopausal symptoms was performed at the department of Obstetrics and gynaecology, Upper India Sugar Exchange Maternity Hospital, GSVM Medical College, Kanpur. The following are the important conclusion drawn from the study.

1. In our study majority of the women were 50 - 69 years age group from urbon population and housewives in occupation in all three groups respectively.

2. In our study majority of the patients had normal BMI and blood pressure in all groups Isoflavanis life style modification and lifestyle Isoflavanis respectively.
3. In our study Vasomotor symptoms psychological and urogenital symptoms reduce after the lifestyle dietary and yoga with Isoflavane and intervention which is shown by reduction in MRS score after the intervention
4. The results of the present study strongly recommend lifestyle modification dietary supplementation yoga and Isoflavane supplementation resulted in reduction of menopausal symptoms. Thus importance of life-style management yoga and Isoflavane to be incorporated in daily routine under the supervision and motivation / adherence can be manditary.
5. The mean, Vasomotor symptoms were significantly lower in lifestyle mod which Isoflavane group III group at 2nd visit and 3rd visit.
6. In our study regarding the safety profile of phyto-estrogen Isoflavane no major ide effect, were found and only minor side effect like headache, nausea, vomiting were present.
7. No breakthrough bleeding (every women with hormone therapy).

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