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A COMPARATIVE INTERVENTIONAL STUDY ON EFFECTS OF CALCIUM CITRATE AND ISOFLAVONES ON LOW BONE MINERAL DENSITY IN PERIMENOPAUSAL WOMEN

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ABSTRACT: Perimenopause is a transitional stage in a woman's life, typically occurring in her 40s, leading up to menopause. During this time, hormonal changes, particularly a decline in estrogen levels, can have a significant impact on bone health. Calcium citrate is a commonly used calcium supplement that is known to promote bone health. Isoflavones are a type of phytoestrogen found in plants, particularlyin soybeans and soy products. The study aimed to compare the effects of calcium citrate and isoflavones on BMD in perimenopausal women with low BMD. 60 perimenopausal women with low BMD, aged 40-55 years, who were divided into two groups: Group A received Calcium citrate supplementation, while Group B received Calcium citrate+Isoflavones supplementation. BMD was measured at baseline and after 3 months using Dual-Energy X-ray Absorptiometry (DEXA). After 3 months, both groups showed improvements in BMD compared to baseline ($p < 0.05$). The increase in BMD was greater in Group B (Calcium citrate + Isoflavones) compared to Group A (Calcium citrate) ($p<0.05$) Results revealed that the combination of calcium citrate with isoflavones showed a significant improvement in bone density and calcium absorption compared to calcium citrate alone.

INTRODUCTION: Perimenopause means" around menopause" and refers to the time during which the body makes the natural transition to menopause, marking the end of the reproductive times. Perimenopause is also called the menopausal transition [1]. The loss of ovarian function during the menopausal transition has a deep impact on female skeletal system.

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Presently it has been estimated that one in every two women will witness an osteoporotic fracture [2]. Low bone mass is the major determinant of osteoporotic fractures. Bone mass in middle aged women is related to the position of peak bone mass reached during teenage and early adulthood, and to the amount of bone loss subsequently [3].

Osteoporosis is currently a major concern but underdiagnosed and undertreated, partly because it's clinically undetected until a fragility fracture occurs. Among adults, 1 out of 3 women and 1 out of 5 men will witness a fragility fracture [4]. Osteoporosis is associated with an imbalance in bone redoing, in which there's fairly lower bone

resorption than bone conformation. Still, the actual rate of bone resorption or bone conformation could be above normal (accelerated bone redoing), normal, or below normal (reduced bone redoing) [5].

In each case, the result of the bone redoing process leads to a net loss of bone material because of an imbalance in the process, independent of the rate of bone redoing. Deterioration of cadaverous microstructure and bone strength, both associated with loss of bone material, leads to increased vulnerability to fracture [6].

BMD dimension by Dual Energy X-ray Absorptiometry (DXA) [7]. It is approved by the US Food and Drug Administration (FDA) in 1988, has come as the main system by which fracture threat is assessed in the US [8]. This safe and cost- effective system of bone mass dimension predicts fracture threat as shown constantly in epidemiologic studies and randomized clinical trials [9].

Calcium citrate is a type of calcium supplement commonly used in the treatment of osteoporosis [10]. Calcium is essential for maintaining bone health, and supplementing may help prevent bone loss and fractures in individuals with osteoporosis [11].

Calcium citrate, being a water-soluble form of calcium, is absorbed well in the presence or absence of food [12]. Unlike calcium carbonate, which requires acidic environment for absorption and is better absorbed with food and calcium citrate can be absorbed effectively in various conditions [13].

Isoflavones are compounds found in plants, particularly in soybeans and soy products that have been studied for their potential effects on bone health including in the context of osteoporosis [14]. Isoflavones are phytoestrogens, meaning they have estrogen-like effects in the body [15].

Estrogen plays a crucial role in maintaining bone density, and during menopause, when estrogen levels decrease, women are at an increased risk of osteoporosis. Some studies suggest that isoflavones might help counteract bone loss by exerting estrogen-like effects [16, 17]. Isoflavones, such as genistein and daidzein found in soy, have a structure similar to estrogen [18]. They can bind to estrogen receptors in the body, exerting weak estrogenic effects [19]. This is particularly relevant in postmenopausal women when natural estrogen levels decline [20]. By binding to estrogen receptors, isoflavones may contribute to maintaining bone density [21].

Estrogen is known to have a protective effect on bones, and isoflavones may help mimic some of these effects [22]. This study aimed to compare the effects of calcium citrate and isoflavones on BMD in perimenopausal women with low BMD.

MATERIALS AND METHODS: It was a Prospective longitudinal study conducted in Obstetrics and Gynecology department at Sree Krishna hospital Poojapura, Thiruvananthapuram, Kerala, India. The study was conducted for a period of 6 months which include data collection and follow up of the study subjects. The study subjects were enrolled by purposive sampling technique and required sample size was 60.

The participants who had been fulfilled inclusion criteria include female patients having age between 40-55 years, Cases of low Bone Mineral density detected using DEXA, FSH value proving that they are in Perimenopausal stage.

The included subjects were randomly assigned to the treatment group A (Calcium citrate) and B (Calcium citrate + Isoflavones). The base line T Scores were noted and then follow up score were observed after 6 months.

Informed consent was obtained, and confidentiality was ensured to study subjects while collecting data. All the data were entered in Microsoft excel spreadsheet and statistical analysis was done using R version 4.4.0. Corelation was assessed using Pearson corelation, p value of less than 0.05 was considered significant.The study was conducted after protocol approval by institutional Research Committee of Ezhuthachan College of Pharmaceutical Sciences and Institutional Ethics Committee of NIIMS, Neyyatinkara, Thiruvananthapuram.

RESULTS AND DISCUSSION: A comparative observational study was conducted to compare the effects of calcium citrate and isoflavones on low bone mineral density in perimenopausal women. In this study a total number of 60subjects were participated.

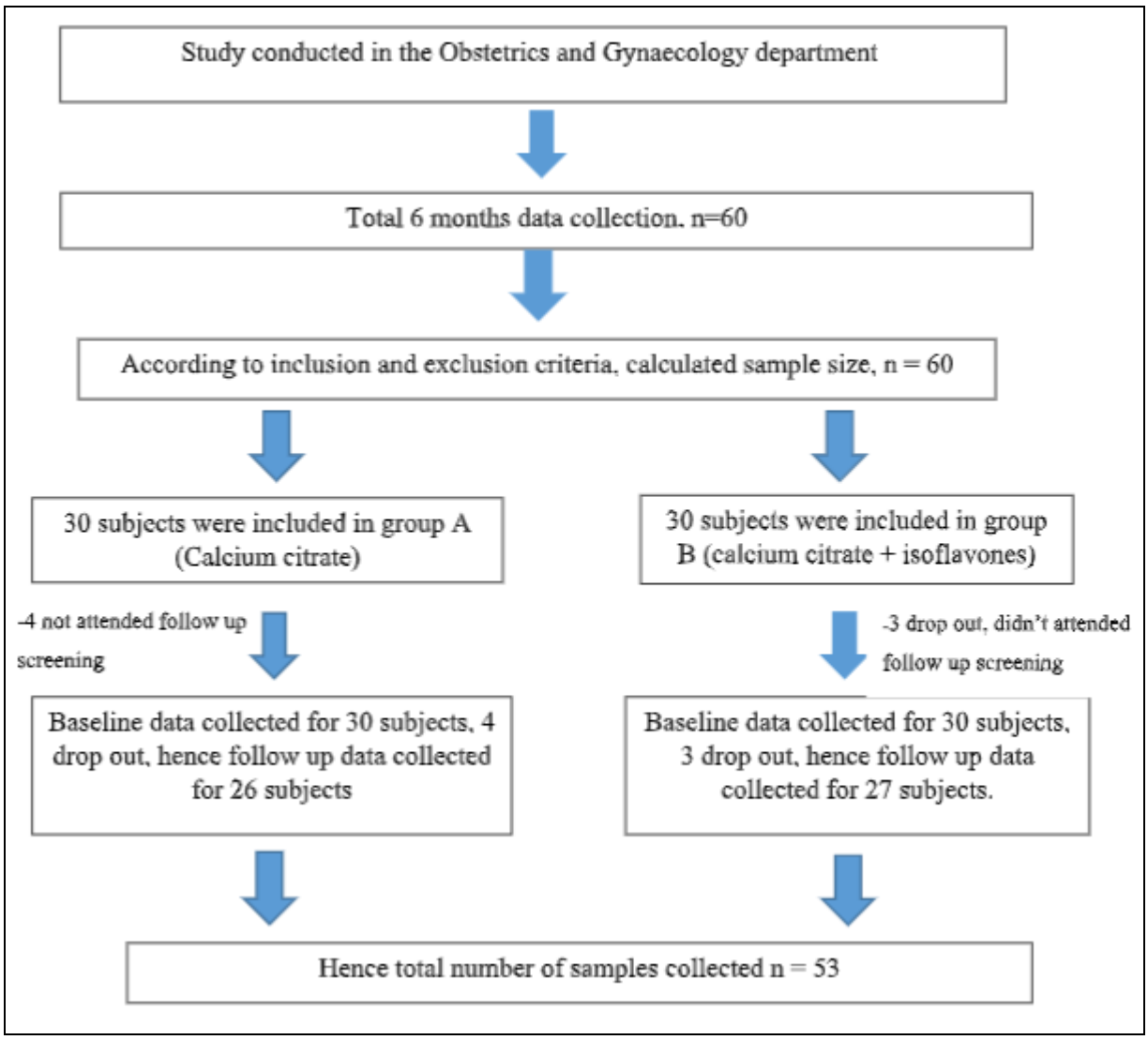

FIG. 1: ALLOCATION OF STUDY PARTICIPANTS

TABLE 1: PATIENT DEMOGRAPHIC DETAILS

Age Group (years)	Group A		MEAN ± SD	Group B		MEAN ± SD
	n	%	46.38 ± 4.352	n	%	
40-44	11	42.30		4	14.81	
45-49	8	30.76		6	22.23	46.38 ± 4.352
50-55	7	26.94		17	62.96	
Total	26	100		27	100	
BMI	**Group A**		**MEAN ± SD**	**Group B**		**MEAN ± SD**
	n	**%**		**n**	**%**	
<18.5	1	3.84	25.57±4.07	0	0	26.78 ±4.352
18.5–25	12	46.15		10	37.03	
25–30	9	34.61		10	37.03	
30–40	4	15.38		7	25.92	
>40	0	0		0	0	
Total	26	100		27	100	
FSH	**Group A**		**MEAN ± SD**	**Group B**		**MEAN ± SD**
	n	**%**		**n**	**%**	
2 to 3.9	0	0		0	0	7.46 ± 1.373
4 to 6.9	10	38.46		8	29.63	
7 to 9.9	16	61.54		19	70.37	
≥10	0	0		0	0	
Total	26	100		27	100	

TABLE 2: T SCORE DISTRIBUTION

T-Score	Baseline (Group A)			Followup (Group A)		
	n	%	MEAN ± SD	n	%	MEAN ± SD
-1to-1.49	7	26.92	-1.788 ±	10	38.46	-1.565 ±0.405
-1.5to-2.0	14	53.84	0.413	11	42.30	
-2.0to-2.5	5	19.23		5	19.24	
Above-2.5	0	0		0	0	
Total	26	100		26	100	
T-Score	**Baseline (Group B)**			**Follow Up (Group B)**		
	n	**%**	**MEAN ± SD**	**n**	**%**	**MEAN ± SD**
-1to-1.49	10	37.03	-1.677±0.427	20	74.07	-1.304 ± 0.590
-1.5to-2.0	11	40.74		4	14.82	
-2.0to-2.5	4	14.81		3	11.11	
Above-2.5	2	7.40		0	0	
Total	27	100		27	100	

TABLE 3: OSTEOPOROSIS – OSTEOPENIA DISTRIBUTION

Group	Osteoporosis- Osteopenia	n	%
Group A	Osteopenia	24	92.31
	Osteoporosis	2	7.69
Group B	Osteopenia	25	92.59
	Osteoporosis	2	7.41

Table 3 depicts the osteoporosis-osteopenia distribution in the sample population. Here 92.59% of samples were osteopenia and 7.41 % of samples were osteoporotic in both Group A (calcium citrate) and 92.31% of samples were osteopenia and 7.69% were osteoporoticin Group B (calciumcitrate+isoflavones). It showed a higher level of osteopenia in the sample population.

TABLE 4: AGE BMD CORELATION

Paramet ERS	Baselinedata (Group A)				Followup Data (Group A)			
	MEAN	SD	r VALUE	p VALUE	MEAN	SD	r VALUE	p VALUE
AGE	46.38	4.352	-0.177	0.351	46.38	4.352	-0.175	0.392
BMD	-1.788	0.413			-1.565	0.407		
Paramet ERS	**Baseline Data (Group B)**				**Follow U Pdata (Group B)**			
	MEAN	**SD**	**r Value**	**P Value**	**Mean**	**SD**	**r Value**	**p Value**
AGE	49.44	4.254	-0.391	0.033	49.44	4.254	-0.009	0.964
BMD	-1.677	0.427			-1.304	0.590		

Table 4 shows the Age - BMD correlation of Group A, Calcium Citrate. In the baseline data the mean age was found to be 46.38 + 4.352 and BMD was -1.788 + 0.413 with a p value of 0.351 which showed that there was no significant correlation between age and BMD. The follow up data showed a mean age of 46.38 + 4.352 with mean BMD of -1.565 + 0.407 with a p value of 0.392, which showed no significant relation between age and BMD. The Age - BMD correlation of Group B, Calcium Citrate + Isoflavones. In the baseline data the mean age was found to be 49.44 + 4.254 and mean BMD was -1.677 + 0.427 with a p value of 0.033 which showed that there was significant correlation between age and BMD. The follow up data showed a mean age of 49.44 + 4.254 with mean BMD of -1.304 + 0.590 with a p value of 0.964, which also showed no significant relation between age and BMD.

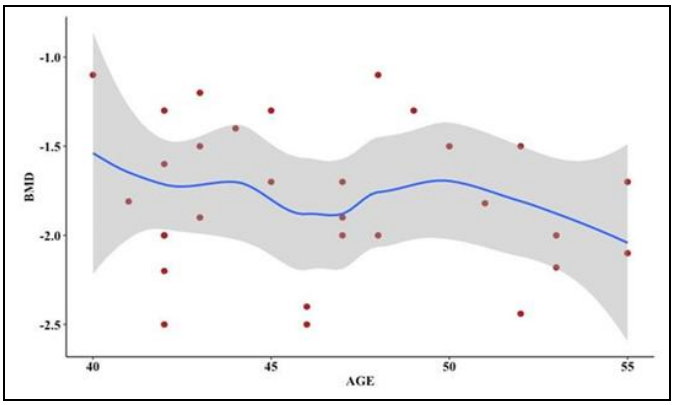

FIG. 2A: AGE–BMD CORRELATION GROUP A (BASELINE)

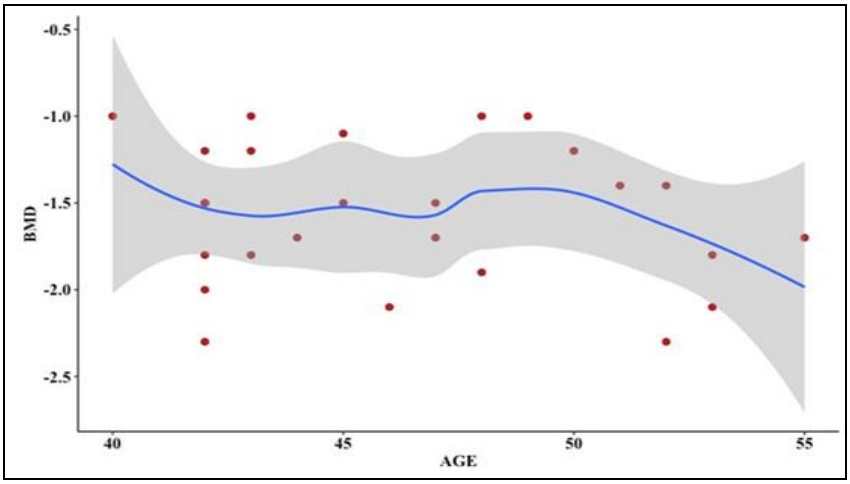

FIG. 2B: AGE–BMD CORRELATION - GROUP A (FOLLOW UP)

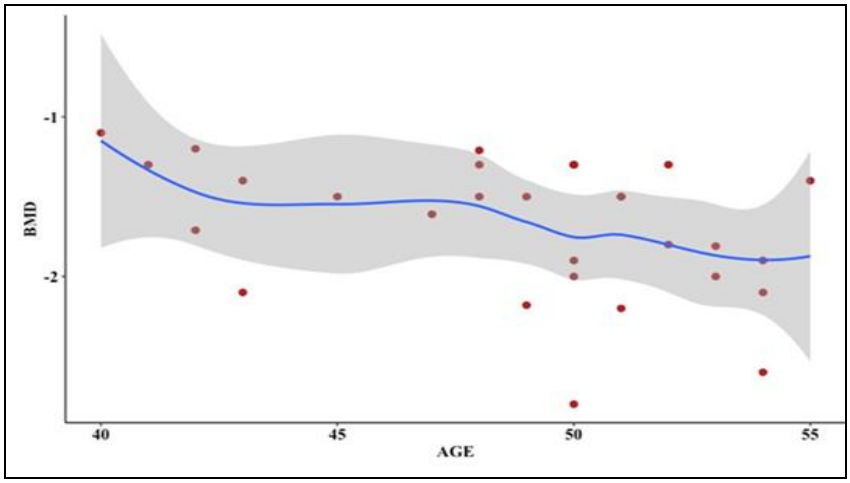

FIG. 3A: AGE–BMD CORRELATION GROUP B (BASELINE)

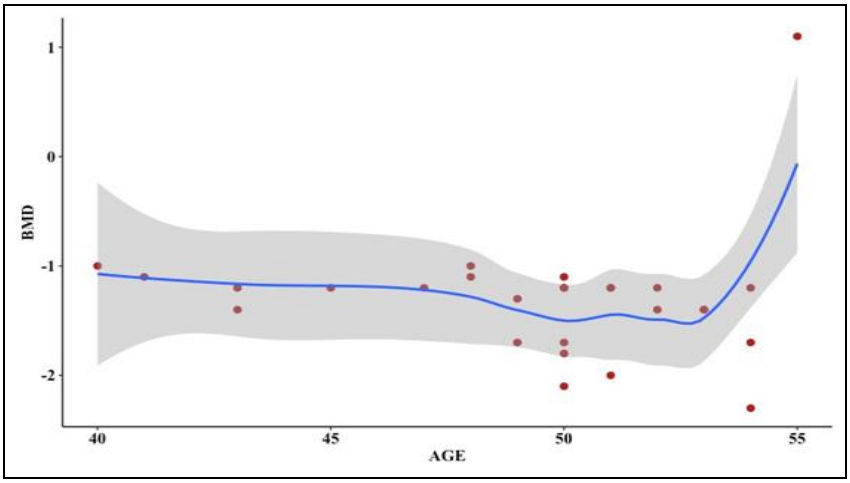

FIG. 3B: AGE–BMD CORRELATION - GROUP B (FOLLOW UP)

TABLE 5: COMPARISON OF EFFECT OF GROUP A AND GROUP B

Term	DF	Sum of Squares	Mean Sum of Squares	F Ratio	P Value
BMD	1	7.493	7.493	62.842	0.000
Var	1	0.641	0.641	5.372	0.025
Residuals	50	5.962	0.119	-	-

For comparing the effect of two treatment groups, here the improvement in the BMD values from baseline and follow up were assessed. While considering the mean value of both groups, they

showed a significant improvement in BMD values in the follow up data. It showed the effect of the drug in the sample population. Also Group B (Calcium citrate + Isoflavones) showed more improvement compared to Group A (Calcium citrate). Group B showed an improvement in the BMD values after follow up. In the current study the prevalence of low bone mineral density in perimenopausal women were found to be 54.86 %. Here total of 144 samples in perimenopausal age groups were analyzed, out of this n = 79 was found to have low bone mineral density and n = 90 was found to be normal. In this it provides an insight of prevalence of osteoporosis and osteopenia in perimenopausal women.

CONCLUSION: The study included 60 samples of perimenopausal women aged 40-55 years. They are grouped into two, Group A (Calcium citrate) and Group B (Calcium citrate + Isoflavones). Samples were selected on the basis of FSH values. The study found that 41.66 % of women is suffering from low bone mineral density.Then adherence was checked weekly. Then follow up was done after 3 months and follow up BMD score were taken. Our analysis shown that there was a slight improvement in the BMD scores of Group B. In conclusion, our comparative interventional study suggests that both calcium citrate and isoflavones have positive effects on low bone mineral density (BMD) in perimenopausal women. However, Calcium citrate together with Isoflavones appeared to be more effective in improving BMD compared to Calcium citrate alone. These findings highlight the potential benefits of calcium citrate supplementation together with Isoflavones in managing low BMD in perimenopausal women. Further research is needed to explore the mechanisms underlying these effects and to determine the long-term impact of these interventions on bone health.

Author Contribution: All authors are collectively contributed to the successful execution of the project. Their roles included conceptualizing the study, designing the methodology, collecting and analyzing data, performing statistical evaluations, and drafting the manuscript. Each author played a vital role in ensuring the accuracy, quality, and completion of the work, reflecting their collaborative efforts and expertise.

Ethical Approval: The study was conducted after protocol approval by institutional Research Committee of Ezhuthachan College of Pharmaceutical Sciences and Institutional Ethics Committee of NIIMS, Neyyatinkara, Thiruvananthapuram.

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