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Systematic Versus Topical using of Calcium and Phosphate in Treatment of Osteoporosis in Postmenopausal Women

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Abstract : This study was conducted to determine the efficacy of systematic versus topical using of Calcium and Phosphate in treatment of osteoporosis in post-menopausal women. Thirty volunteer osteoporotic postmenopausal women participated into this study. Their ages ranged from 55 to 65 years old, their parity ranged from 1 to 3, their body mass index (BMI) < 30 kg/m2 and all of them were at least 5 years postmenopause. The patients characterized by law bone density with T score of DEXA less than -1.Patients were divided randomly into two equal groups. Group (A) (Study group): 15 patients who will receive topical Calcium and Phosphate through iontophoresis 30 min /session,3times weekly for 12 weeks, group (B) (Control group): 15 patients who will receive their routine medical treatment including systematic supplimentation of Calcium and Phosphate for 12 weeks ,Dual energy X - ray Absorptiometry (DEXA) for measurement of bone mineral density (BMD),Present pain intensity (ppi) scale , Questionnaire for assessment of quality of Life and Laboratory analysis of Calcium and Phosphate (for both groups).

The obtained results showed a highly statistically significant (P< 0.01) increase in BMD of femur and L2-L4 immediately after treatment as well as after 3 months of re-evaluation in group (A)more than group(B). Also, there was a statistically highly significant reduction in bone pain, improve the quality of life in its physical ,mental and social levels and increase Calcium and Phosphate contents in group (A)more than group(B).

Accordingly, it could be concluded that topical using of Calcium and Phosphate is very effective, noninvasive, safe, easy to perform, simple and successful for treatment of osteoporosis in postmenopausal women.

Key words: Topical treatment, Osteoporosis, Calcium, Phosphate, postmenopausal women.

Introduction

Osteoporosis is a serious disease that decreases both the quality and quantity of life[1,2]. The disease enhances morbidity and mortality, and it affects hundreds of millions of persons worldwide[3,4]. Osteoporosis is a progressive bone disease that is characterized by a reduce in bone mass and density which can cause an increased risk of fracture[5]. In osteoporosis, the bone mineral density (BMD) is decreased, bone microarchitecture deteriorates, and the quantity proteins in bone are changed. A recent meta-analysis showed reduce rates of fracture in older women with 80% or greater adherence to calcium supplementation[6]. A daily intake of calcium at least 1,200 mg is recommended for all women suffer from osteoporosis[7,8]. Recent study has shown that supplementation of 800 mg of calcium per day may helpful to prevent bone loss in postmenopausal women, and the information from clinical trials also show that such supplementation may prevent vertebral and hip fractures in the elderly.[9,10]

Postmenopausal population is at increased risk of musculoskeletal impairments[11]**.** Caused by physiological exhaustion of ovarian function[12]. Osteoporosis that is fragile bone disease, sarcopenia that is muscle wasting, and increased musculoskeletal pain, including low back pain are significant health burdens among the postmenopausal women[13].

Postmenopausal women are at risk of both osteoporosis and sarcopenia. There is evidence that these two conditions coexists and share similar risk factors. Both sarcopenia and osteoporosis are strongly linked not only to aging but also to estrogen depletion and thereby to menopausal transition. This makes the postmenopausal population significant target group for prevention of both sarcopenia and osteoporosis. While the associations between muscle strength, muscle mass, and functional capacity with clinically relevant endpoint of osteoporosis, that is, BMD and fractures, have not been shown constantly across different studies[11].

The term iontophoresis (IOP) is simply defined as ion transfer (ionto = ion; phoresis = transfer). IOP is a technique using a small electric charge to deliver a chemical drug through the skin. This process is a non-invasive method of propelling high concentrations of a charged substance transdermally by repulsive electromotive force using electrodes with small electrical charge. IOP is a well classified method for transdermal drug delivery relying on active transportation within electric field. The dominant forces of this transport are electromigration and electroosmosis, which measured in units of chemical flux (commonly in µmol/cm^2 h).[14,15] Therapeutically, electromotive drug administration (EMDA) delivers a medicine or other chemical through the skin[15]**.**

Iontophoresis is commonly used by physical therapists and occupational therapists for the application of anti-inflammatory medications. In the treatment of hyperhidrosis, tap water is often the chosen solution for mild and medium forms. In very serious cases of hyperhidrosis, a solution containing glycopyrronium bromide or glycopyrrolate, a cholinergic inhibitor, can be used[16]. Two iontophoretic patches have recently been approved for vaso-active therapeutic use by the FDA - Zecuity (2013).

During the process negatively charged ions (chloride ions) of the skin transit to the anode, therefore under the positive electrode acid accumulation is probable. Alkaline would accumulate under the negative electrode, because of the transit of positively charged sodium ions of the skin[15,17].

Transdermal delivery of Ca^{2+} through different membrane models was investigated by spontaneous and IOP diffusion, using Ca^{2+}containing compounds with different dissociation constants. These experiments were carried out on bentonite (a natural mineral clay with a large ion exchange capacity), previously enriched in calcium ions in its lattice. Calcium ion transport through the pig skin has been investigated in vitro in diffusion cells applying IOP. The best Ca^{2+} transmission efficiency was achieved using court period (CP) current: the amount of the calcium ions penetrating through the pig skin by IOP was 5 to 10 times higher than that of the passive transport. The results of these in vitro studies opened a new field of the application pattern of IOP[18].

The delivery of calcium ions into these tissues was assisted by the electrophoretic method. As a result of bentonite IOP, calcium concentrations of the treated bones significantly increased in an average nearly 1.8-fold[19].

This study was conducted to investigate the difference between systematic versus topical using of calcium and phosphate in the the treatment of osteoporosis in postmenopausal women.

Subjects, Materials and Methods

I. Subjects:

Thirty volunteer osteoporotic post menopausal women were participated into this study. They were selected from the outpatient clinic of of obstetric and gynecology and outpatient clinic of Physical Therapy, (Kasr Elainy hospital)Faculty of Medicine, Cairo University. Their age will ranged from 55-65 years and all of them at least 3 years post menopause before engagement to the study. Their parity ranged from 1to 3, and their Body Mass Index (BMI) $\leq$ 30 kg/m^2. The patients characterized by low bone density with T score of DEXA

less than -1. They had no history of bone diseases, renal, liver or endocrinal disorders, cardiac affection, using a pace maker, any drugs which may affect bone metabolism, history of smoking or epileptic fits. Patients with hearing aids were asked to remove them before the treatment session Informed consent form was signed by each subject before starting the study .After initial assessment of osteoporosis by radio diagnosis Faculty of Medicine, Cairo University, and then the women were referred to the gynecologist to confirm the diagnosis.

These patients were divided randomly into 2 equal groups (A and B).**Group A (study group):** 15 patients who received topical Calcium and Phosphate through iontophoresis 30 min /session,3times /week for 12 weeks (36 sessions).**Group B (control group):** 15 patients who received placebo topical Calcium and Phosphate through iontophoresis 30 min /session, 3times /week for 12 weeks (36 sessions), in addition to their routine medical treatment including systematic supplimentation of Calcium and Phosphate for 12 weeks.

II – Materials :

1- For Evaluation:

1. Weight-height scale: Was used to measure body weight and height, and then body mass index was calculated for each subject in the 2 groups (A and B).

2- Dual energy X - ray Absorptiometry (DEXA): used to measure BMD at the lumbar spine (L2-L4) and the neck of femur for patients in both groups (A and B).

3- Laboratory analysis :(calcium and phosphate): Plasma concentrations of Calcium and phosphate were measured for all participants of both groups (A&B).

4-Present Pain Intensity (ppi) scale: It is a graphic rating scale with numerical values (0-4) help the subject to place her estimate of pain on the line **.**

5-Quality of Life questionnaire (Modified MENCAV scale):This questionnaire consists of questions to assess: physical state and social support which includes 10 questions for each, mental/emotional state by 9 questions.

2- For treatment :

1-Direct Current Generator: Sonopuls 692(EnrafNonius): We had selected program of Galvanic (Iontophoresis) current, set the treatment time (in our study,30 min.) and begun treatment. Active(drug) electrode was attached to positive lead and the dispersive electrode was attached to negative lead. **2.** The elastic straps were used to stabilize the dispersive electrode.**3.**Cotton was wetted with alcohol to clean the lumbar area before electrode placement .**4.**The syring was used for drug injection.

Procedures :

I. Evaluative Procedures:

Every subject in both groups was subjected to history taking and measure BMD at the lumbar spine and the neck of femur before the treatment sessions to determine patients with T-score of less than -1 to participate in this study[20,21]. Then **Weight-height scale** was used to measure body weight and height, and then body mass index was calculated by divided Weight in (Kg) on [Height (m)] ^{2}.Also,Plasma concentrations of Calcium and phosphate were measured .In addition to **Present Pain Intensity (ppi) scale:** It is a graphic rating scale with numerical values placed equidistantly along a line. The descriptors and numbers help the subject to place her estimate of pain on the line[22]. **Also ,Quality of Life questionnaire (Modified MENCAV scale)** to assess: physical state and social support which includes 10 questions for each, in addition to assessment of mental/emotional state by 9 questions. This was used for all participants of both groups (A&B) before and after the treatment programe.

II. Treatment procedure:

Group A: Each patient in this group was treated with topical Calcium and Phosphate through iontophoresis (2gm. Mono Calcium Phosphate solved in 100 ml. water) 30 min /session,3times /week for 12 weeks (36 sessions).

The patients were asked to evacuate her bladder before starting the treatment sessions then placed in comfortable prone lying position. The area (lumbar spine L2-L4) were cleaned with alcohol. The patient were informing that they may felt an itchy or prickly sensation during the treatment under the active electrode. Dispersive electrode pad were wetted with tap water were secured at least 3 inches away from the drug (active) electrode site and any burning sensation was indicating potential risk for skin burning secondary to the effect of direct current and the current should be decreased. Continuous current was increased slowly in order to accommodate for dc sensation, which is applied. The electric current was raised slowly to a maximum of 4.0 mA, and was continued until a total dose of 40.0 mA mins was delivered (30 mins).Any burning sensation was indicating potential risk for skin burning secondary to the effect of direct current and the current should be decreased.

Group B : Each patient in this group under the same procedure as in group (A) but the device o f iontophoresis was switched off, in addition tomedicaltreatment that consists of (Bone one) tablets: one tablet after lunch, Osteoval tablets: one tablet after breakfast and one after dinner, Fosamax tablets (Bisphosphonates): one tablet every week, all medications for 12 weeks. An optimal diet for treatment of osteoporosis includes an adequate intake of calories (to avoid malnutrition).

Statistical analysis:

Results are expressed as mean ± standard deviation (SD). Comparison between different variables in the two groups was performed using either unpaired t test or Mann Whitney test whenever it was appropriate. In normally distributed variables, pair-wise comparison (pre- versus both post-assessment and reevaluation) within the same group for different variables was performed using repeated measure ANOVA. In Scale variables, pair-wise comparison (pre- versus both post-assessment and reevaluation) within the same group for different variables was performed using Friedman ANOVA followed by Wilcoxon Sign Ranks test.

Results

Physical characteristics of the Subjects :

There was no statistical significant differences (P>0.05) were observed between both groups (A) and (B) in their general characteristics (age, weight, height and BMI) between subjects of the two groups where their t and p-values were (0.056, 0.956),(-0.764, 0.451),(0.388, 0.701)and(-1.232, 0.228) respectively as shown in table (1).

Table (1):Physical (General) characteristics of the two studied groups.

	Group A (n= 15)	Group B (n= 15)	t value	P value
Age (yrs.)	58.53 ± 3.11	58.47 ± 3.38	0.056	0.956 (NS)
Weight (kg)	69.13 ± 5.88	70.60 ± 4.55	-0.764	0.451 (NS)
Height (cm)	160.80 ± 6.76	159.87 ± 6.41	0.388	0.701 (NS)
BMI (Kg/m^2)	26.79 ± 2.29	27.65 ± 1.44	-1.232	0.228 (NS)

Data are expressed as mean ± SD. NS= p> 0.05= not significant.
***SD: standard deviation, P: probability, S: significance, NS: non-significant.**

Effect of two treatment regimen on DEXA, Present pain intensity scale, Quality of Life questionnaire, Calcium and Phosphate content.

There were a statistical significant increase in the mean value of DEXA (Neck of femur) at post-treatment, in group A (-1.92 ± 0.23) when compared with its corresponding value in group B (-2.17 ± 0.25) (t

test = 2.777 and p value = 0.010). Also at reevaluation, in group A (-1.99 ± 0.26) when compared with its corresponding value in group B (-2.35 ± 0.20) (t test = 4.171 and p value = 0.00) (Table 2 ; Fig. 1).

Table (2) : Comparison between mean values of DEXA (Neck of femur) of the two studied groups measured at different time of measurements.

	Group A (n= 15)	Group B (n= 15)	t value	P value
Pre treatment	-2.51 ± 0.29	-2.46 ± 0.18	-0.605	0.550 (NS)
Post treatment	-1.92 ± 0.23	-2.17 ± 0.25	2.777	0.010**
Reevaluation	-1.99 ± 0.26	-2.35 ± 0.20	4.171	0.001**

Data are expressed as mean ± SD. NS= p> 0.05= not significant; **p< 0.01= highly significant.

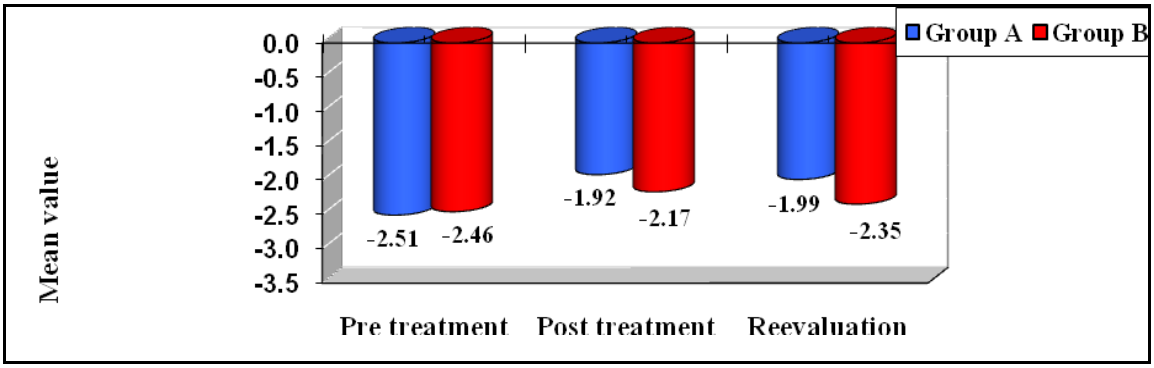

Fig.(1) : Comparison between mean values of DEXA (Neck of femur) of the two studied groups measured at different time of measurements.

There were a statistical significant increase in the mean value of DEXA (L2-L4) in group A -1.34 ± 0.11) when compared with its corresponding value in group B (-1.79 ± 0.26) (t test = 6.138 and p value = 0.010). Also at reevaluation, in group A (-1.47 ± 0.19) when compared with its corresponding value in group B(-1.87 ± 0.27) (t test = 4.643 and p value = 0.001) (Table 3; Fig.2)

Table.(3) : Comparison between mean values of DEXA (L2-L4) of the two studied groups measured at different time of measurements.

	Group A (n= 15)	Group B (n= 15)	t value	P value
Pre treatment	-1.92 ± 0.18	-1.97 ± 0.30	0.516	0.611 (NS)
Post treatment	-1.34 ± 0.11	-1.79 ± 0.26	6.138	0.001**
Reevaluation	-1.47 ± 0.19	-1.87 ± 0.27	4.643	0.001**

Data are expressed as mean ± SD. NS= p> 0.05= not significant; **p< 0.01= highly significant.

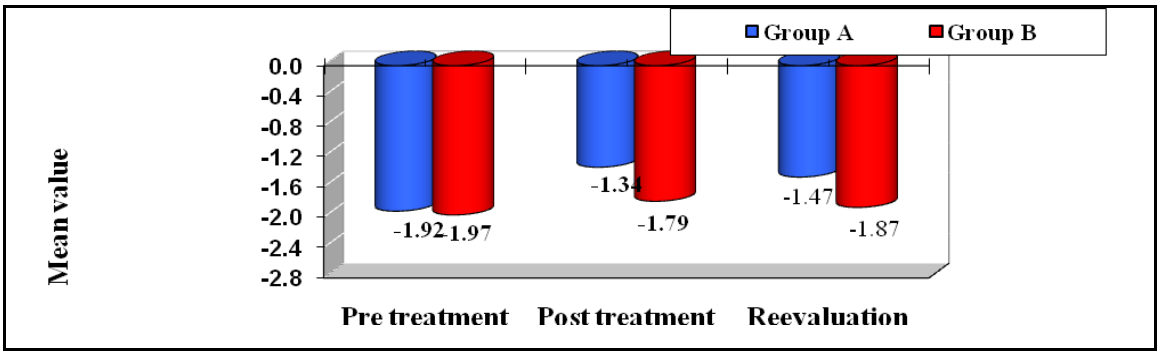

Fig. (2) : Comparison between mean values of DEXA (L2-L4) of the two studied groups measured at different time of measurements.

There were a statistical significant decrease in the mean value of (PPI**)** in group A (0.60 ± 0.74) when compared with its corresponding value in group B (1.27 ± 0.80) (t test = -2.201and p value = 0.037) .Also at reevaluation, in group A (1.00 ± 0.85) when compared with its corresponding value in group B (2.07 ± 0.88) (t test = -2.804 and p value = 0.006) (Table4 ; Fig.3).

Table.(4): Comparison between mean values of present pain intensity scale (PPI) of the two studied groups measured at different time of measurements.

	Group A (n= 15)	Group B (n= 15)	Z value	P value
Pre treatment	2.73 ± 0.96	2.80 ± 0.86	-0.111	0.935 (NS)
Post treatment	0.60 ± 0.74	1.27 ± 0.80	-2.201	0.037*
Reevaluation	1.00 ± 0.85	2.07 ± 0.88	-2.804	0.006**

Data are expressed as mean ± SD.NS= p> 0.05= not significant; *p< 0.05= significant; **p< 0.01= highly significant.

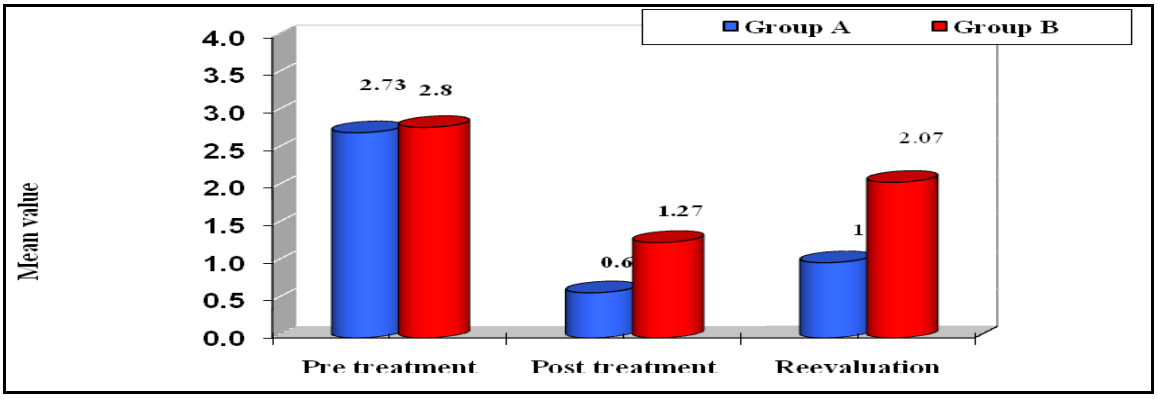

Fig. (3): Comparison between mean values of present pain intensity scale (PPI) of the two studied groups measured at different time of measurements.

At the other hand at post-treatment, there were a statistical significant increase in the mean value of quality of life questionnaire (total score) in group A (74.13 ± 6.22) when compared with its corresponding value in group B (78.00 ± 3.53) (Z value = -2.244 and p value = 0.023). Also at reevaluation, in group A (75.20 ± 5.03) when compared with its corresponding value in group B (81.00 ± 2.70) (Z value = -3.374 and p value = 0.001 (Table 5 ; Fig. 4).

Table.(5) : Comparison between mean values of quality of life questionnaire (total score) of the two studied groups measured at different time of measurements .

	Group A (n= 15)	Group B (n= 15)	Z value	P value
Pre treatment	85.53 ± 3.44	85.00 ± 3.40	-0.418	0.683 (NS)
Post treatment	74.13 ± 6.22	78.00 ± 3.53	-2.244	0.023*
Reevaluation	75.20 ± 5.03	81.00 ± 2.70	-3.374	0.001**

Data are expressed as mean ± SD. NS= p> 0.05= not significant; *p< 0.05= significant; **p< 0.01= highly significant.

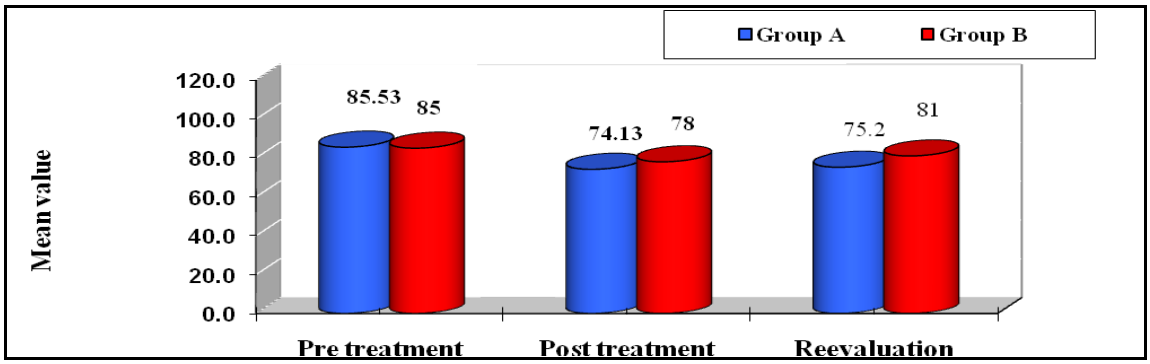

Fig.(4). : Comparison between mean values of quality of life questionnaire (total score) of the two studied groups measured at different time of measurements.

Also at post-treatment, there were a statistical significant increase in the mean value of calcium content in group A (9.36 ± 0.26) when compared with its corresponding value in group B (8.91 ± 0.20) (t test = 5.262 and p value = 0.001). Also at reevaluation, in group A (9.31 ± 0.29) when compared with its corresponding value in group B (8.67 ± 0.21) (t test = 6.908 and p value = 0.001) (Table 6 ; Fig.5).

Table.(6) : Comparison between mean values of calcium content (mg/dl) of the two studied groups measured at different time of measurements.

	Group A (n= 15)	Group B (n= 15)	t value	P value
Pre treatment	8.4 ± 0.21	8.41 ± 0.21	-0.171	0.865 (NS)
Post treatment	9.36 ± 0.26	8.91 ± 0.20	5.262	0.001**
Reevaluation	9.31 ± 0.29	8.67 ± 0.21	6.908	0.001**

Data are expressed as mean ± SD.NS= p> 0.05= not significant; **p< 0.01= highly significant.

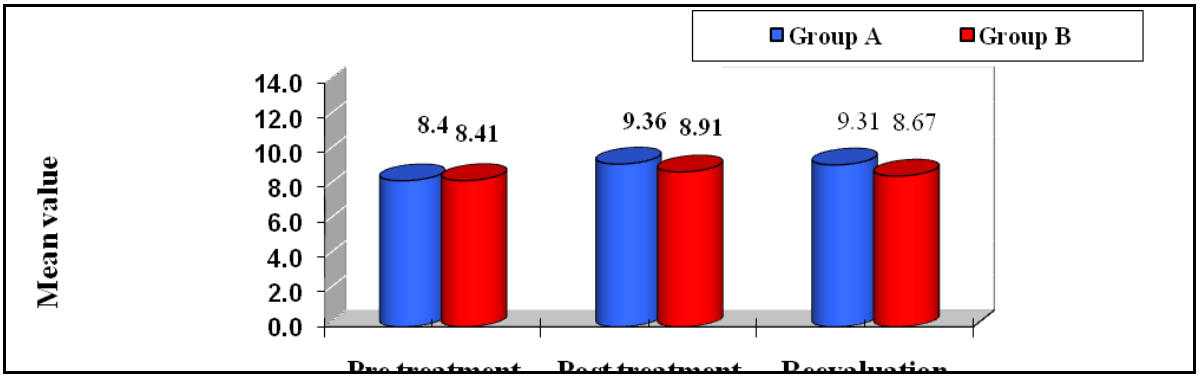

Fig.(5). : Comparison between mean values of calcium content (mg/dl) of the two studied groups measured at different time of measurements.

There were a statistical significant increase in the mean value of phosphate content in group A (-3.80 ± 0.17) when compared with its corresponding value in group B (3.04 ± 0.05) (t test = 16.310 and p value = 0.010). Also at reevaluation, in group A (3.77 ± 0.18) when compared with its corresponding value in group B (3.09 ± 0.10) (t test = 12.954 and p value = 0.001) (Table7 ; Fig.6).

Table.(7) : Comparison between mean values of phosphate content (mg/dl) of the two studied groups measured at different time of measurements.

	Group A (n= 15)	Group B (n= 15)	t value	P value
Pre treatment	3.30 ± 0.18	3.33 ± 0.21	-0.475	0.638 (NS)
Post treatment	3.80 ± 0.17	3.04 ± 0.05	16.310	0.001**
Reevaluation	3.77 ± 0.18	3.09 ± 0.10	12.954	0.001**

Data are expressed as mean ± SD.NS= p> 0.05= not significant; **p< 0.01= highly significant.

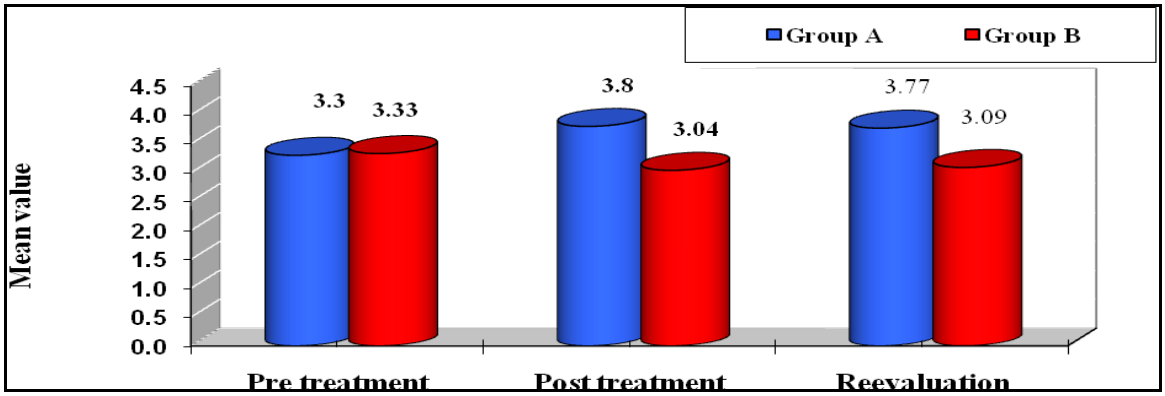

Fig.(6) : Comparison between mean values of phosphate content (mg/dl) of the two studied groups measured at different time of measurements.

Discussion

Osteoporosis is a bone disease in which the quantity of bone is reduced and the structural integrity of trabecular bone is disturbed. Cortical bone becomes more porous and thinner. This renders the bone very weak and more likely to fracture. Osteoporosis is characterized by reduce bone mineral density (BMD) and enhanced likelihood of bone fracture[23]. Bone is a living tissue. It supports muscles, protects internal organs, on the other hand it serves as a mineral reservoir containing 99 percent of total calcium and 85 percent of total phosphorus of the body[24]**.** Menopause is characterized by the progressive reduction of estrogens resulting to cessation of menses. It is associated with an increase of cardiovascular risk factors such as hyperglycemia, hypertension, dyslipidemia and of abdominal and/or selective visceral fat mass deposition leading to obesity which is promoted by an obesogenic environment that interacts with the genetic background[25]. Bone density decreases at a rapid rate after menopause and some women develop osteoporosis[26]**.** BMD decreased faster in the early postmenopausal years. During the first 6 years postmenopause, the decrease in BMD of the femoral neck and trochanter was 3-10 times higher than the change in the decade prior to menopause. About 20% of the lifetime femoral neck loss and 30% of the trochanteric loss occurred in the early postmenopausal period. So that menopause is the major determinant of BMD in women[27].

This study was done to investigate the efficacy of topical using of calcium and phosphate in the the treatment of osteoporosis in postmenopausal women. After treatment ,when comparing the results of both groups, there was a statistically highly significant decrease (P< 0.01) at the end of treatment programe in group (A) than group(B). Also, the comparative analysis between both groups (A&B) indicated that there was a highly statistically significant (P>0.01) improvement of the subjective assessment in group (A) at the end of the treatment programme. Regarding the effect of topical using of calcium and phosphate in the the treatment of osteoporosis in postmenopausal women, the results of the current study were supported by the results of of **Watts et al.,** [28]**,** who suggested that iontophoresis of certain compounds may have beneficial effects on fracture healing or osteoporosis .Results of this study agreed with those reported by **Pap et al.,** [29]**,** who found that the local treatment of osteoporosis, and delivery of calcium and phosphate ions into the underlying bone. Also, **Nowicki and Zhou,**[30,31]**,** found that IOP has also been used to deliver various chemicals and drugs into humans for the treatment of osteoporosis .**Anderson et al.,**[32]**,** confirmed that iontophoresis application delivered greater amount of ketoprofen down to fascia compared with passive drug delivery.

These findings were in line with findings of study by **Sims et al.,** And **Canpolat, et al.,**[33,34]**,** who determine the effects of topical calcium and phosphate iontophoresis versus systemic estrogen therapy .At the end of the study, calcium concentrations remained significantly elevated even 10 weeks after the last IOP treatment. Calcium and Phosphate concentrations IOP resulted in considerable elevations. **Bialocerkowski et al., and Watts et al.,**[35,38], who stated that Topical IOP and calcium ionostasis have been used in bone fractures, delayed union and algoneurodystrophy for decades. **Szanto et al.,**[18] **,** confirmed a new method for the local administration of calcium ions by IOP had been invented and developed by our research group **.**

These findings were in consistency with the results of study by **Szanto et al.,**[18,36]**,** who concluded that the transdermal delivery of Ca^{2+} through different membrane models was investigated by spontaneous and IOP diffusion, using Ca^{2+}-containing compounds with different dissociation constants, Calcium ion transport through the pig skin has been investigated in vitro in diffusion cells applying IOP. The best Ca^{2+} transmission efficiency was achieved using court period (CP) current: the amount of the calcium ions penetrating through the pig skin by IOP was 5 to 10 times higher than that of the passive transport. The results of these in vitro studies opened a new field of the application pattern of IOP . **Gomez et al.,** [19]**,** found that the using of calcium IOP , calcium concentrations of the treated bones significantly increased in an average nearly 1.8-fold. calcium IOP was performed on porcine tissues *in vitro.* The porcine tissue system containing skin, fat, muscle and bone was found the most appropriate for these experiments. The delivery of calcium ions into these tissues was assisted by the electrophoretic method described above. As a result of bentonite IOP, calcium concentrations of the treated bones significantly increased in an average nearly 1.8-fold. These findings were in line with findings of study by **Emri et al.,**[29], who concluded that the favorable results of calcium iontophoresis, specially modified forms of calcium and phosphate donating microparticles appropriate for transdermal IOP delivery for topical treatment of osteoporosis. Accordingly, it was found that the topical using of calcium and phosphate are effective method in the treatment of osteoporosis in postmenopausal women.

Conclusion

This study was designed to detect the efficacy of topical using of calcium and phosphate in the treatment of osteoporosis in postmenopausal women. So, it could be concluded that topical using of calcium and phosphate iontophoresis significantly increase bone mineral density and they have a long term effect as it decrease the rate of bone deterioration after stopping the treatment, significantly reduce bone pain and aches more than systemic treatment as well as quality of life in its physical ,mental and social levels in better way than systemic treatment of osteoporotic postmenopausal women. Thus ,topical using of calcium and phosphate iontophoresis was found to be an effective ,noninvasive method in improving BMD and pain as well as quality of life in osteoporotic postmenopausal women. As it was an effective, simple, realistic, safe, inexpensive and successful treatment method for treating osteoporotic postmenopausal women.

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