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A Comparative Study of the Effect of Sodium Alendronate plus Thyme and Sodium Alendronate alone in Treatment of Postmenopausal Women with Osteoporosis

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Abstract
Osteoporosis is a chronic, progressive disease of multifactorial etiology characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility. The disease often does not become clinically apparent until a fracture occurs . It occurs in the elderly of both sexes but is most pronounced in postmenopausal women .The aim of this study was to assess the efficacy of sodium alendronate plus Thyme in treatment of postmenopausal women with osteoporosis and compare it's effect with Sodium alendronate alone . Forty postmenopausal women with osteoporosis were randomly divided into two groups(each group include twenty women) .The duration of treatment was 6 months . First group was given Sodium alendronate 70mg weekly and Thyme capsule 500mg twice daily, second group was given Sodium alendronate 70mg once weekly .The following parameters were measured for two groups at baseline and at 6 months intervals bone mineral density(BMD) and t score except ESR and serum ionized calcium were measured at baseline and at 2 months interval . There were a significant increase in BMD and significant increase in t score in group treated with Sodium alendronate plus Thyme after 6 months as compared with baseline and with group treated with Sodium alendronate . Also there were a significant reduction in mean serum ionized calcium and mean ESR in group treated with Sodium alendronate plus Thyme and group treated with Sodium alendronate alone after 2,4,6 months as compared with baseline($P<0.05$) .
Keywords: Thyme, BMD, Sodium alendronate, Osteoporosis, t score

Introduction

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 (1). In osteoporosis, the bone mineral density (BMD) is reduced, and the quantity of proteins in bone are changed **.** The disease increases morbidity and mortality, and it influences hundreds of millions of persons worldwide (2,3) .A recent meta-analysis showed reduce rates of fracture in older women with 80% or greater adherence to calcium supplementation (4) . Oral bisphosphonates suppress osteoclastic activity and are potent antiresorptive agents. Randomized clinical trials confirmed a reduction of hip and vertebral fractures with alendronate (5,6) . Alendronate also show effectiveness in men(7,8) and in glucocorticoid-induced osteoporosis(9,10). Nitrogen-containing bisphosphonates suppress the mevalonate metabolic pathway, while bisphosphonates without nitrogen are metabolized inside the cell to give cytotoxic analogues of adenosine triphosphate . Bisphosphonates with very short plasma half-life , but the half-life of bisphosphonates deposited in bone with half-life probably up to 10 years and could be longer (11) . In large, randomized, controlled trials, alendronate decrease vertebral and non-vertebral fractures (5,12,13) . Rates of symptomatic vertebral fractures were decrease by 28–36% over 3–4 years of treatment, while rates of asymptomatic and radiographically diagnosed vertebral deformities were decrease by 44–47% and of hip fracture by 51%. (14,15) . Bisphosphonates are poorly absorbed from the GIT .Oral administration of alendronate requires fasting before and directly after the drug is taken. It has been postulated that these drugs change both osteoclast function and activation (16,17) . Therefore, bisphosphonate compound inhibits the activity of osteoclast , enhances the mineral content of bone in both hip and spine when taken in a cyclic fashion (with or without a calcium supplement), and reduces the risk of fractures(18) . One review recorded that sage , thyme extract, rosemary, , and other plants, appear to inhibit osteoclast activity, increasing bone density in animals, but more study is needed in humans(19) . The essential oil of thyme (Thymus vulgaris), contains 20–54% thymol (20) . Essential oil of Thyme also contains a range of additional compounds, like linalool, myrcene, p-Cymene, and borneol (Chemical Composition of Thyme Essential Oil) . Thymol, an antiseptic, is the major active component in several commercially produced mouth washes like Listerine (21) . Before the discovery of modern antibiotics, thyme oil was used to medicate bandages(22) . Thymol has also been noted to be effective against different fungi that commonly infect toenails(23). Thymol can also be present as the active component in some natural, alcohol free hand sanitizers. In One study introduced by Leeds Metropolitan University recorded that thyme may be helpful in treating acne **(**24, 25) .

Patients, Materials, and methods

Patients

This is a randomized prospective clinical trial study. It was conducted in Merjan Teaching Hospital in DEXA unit which present in Rheumatology department. The study was conducted between March 2014 and March 2015.The study was approved by ethical committee at Al- Nahrain University/Faculty of Medicine.

Sample size

The sample of the study include (40 postmenopausal women suffering from Osteoporosis) .They divide into two groups, each group include 20 patient . The duration of treatment is 6 months .

Study Groups

Group I:- received Sodium alendronate 70mg weekly plus Thyme capsule 500mg twice daily .
Group I I:-received Sodium alendronate 70mg once tablet weekly.
All the following parameters were measured for all groups at baseline and at 2 months interval for 6 months duration except BMD ,t score was measured before treatment and 6 months of treatment, parameters include ESR, Serum ionized calcium.

Data collection

The method of collecting information depend on direct(personal) interview in a specific room attached to unit DEXA measurement. The data were collected through the used of developed questionnaire and the structured interview technique patients. Data were collected from the patients in organized fashion and individually with all the patients. The interview lasted for about (30) minutes, knowing that the data collection was only every Monday and Wednesday from every week, begin at 8: 00 am. and continue until 2:00 pm.

Statistical analysis

Statistical analyses were performed using SPSS 16.0 for windows.Inc. An expert statistical advice was consulted for tests used. Data of quantitative variables were expressed as mean ± SEM . Differences in each variable through treatment intervals in the same group were compared using paired-sample Student's t-test. Analysis of Variance (ANOVA) followed by post-hoc tests using LSD method were used for the multiple comparisons among all groups. In all tests, $P<0.05$ was considered to be statistically significant unless another levels were stated .

Results

Anthropometry

Between the two groups included in this study, there were no significant difference in anthropometric data as shown in table (1).

Table 1: Anthropometric data for all included patients in this study

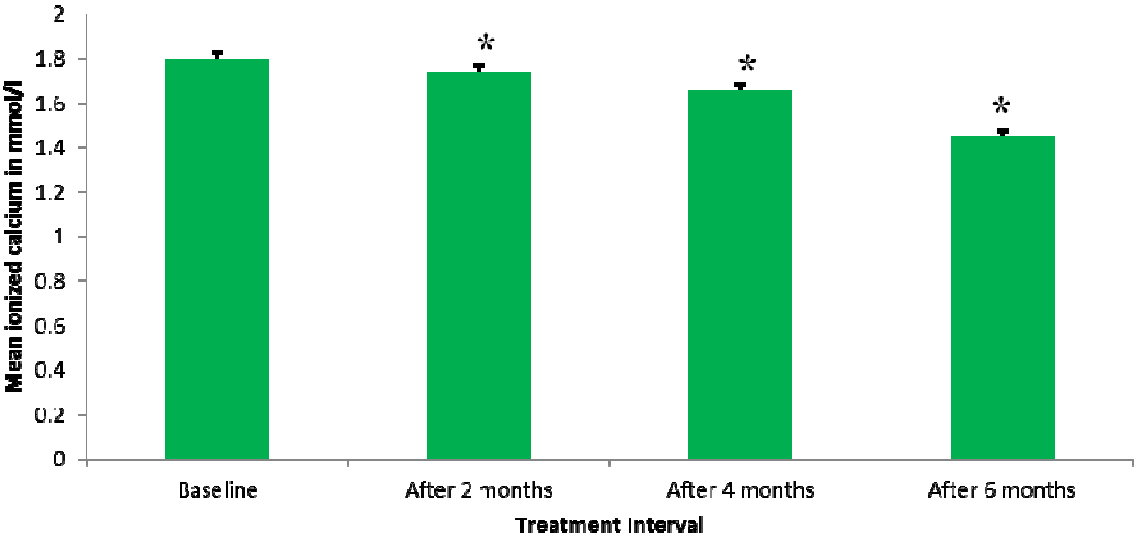
Mean± SEM (Group I I)	**Mean± SEM (Group** I)	**Anthropometric data**
57.95±1.6	**60.55±1.7**	**Age(year)**
79.85±3.81	**81.65±3.11**	**Weight(kg)**
155.15±1.61	**154.4±1.42**	**Height(cm)**

Effect of the two treatment regimen on BMD, t score, serum ionized calcium, ESR

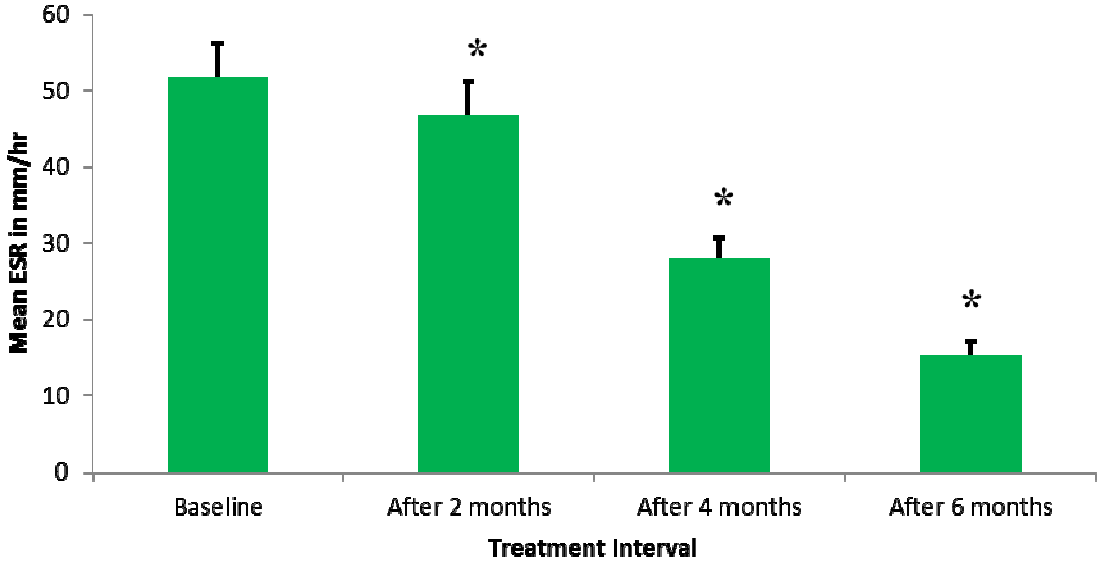
There were a significant reduction in mean serum ionized calcium, ESR in group treated with sodium alendronate plus thyme after 2,4,6 months($P<0.05$) as compared with baseline as shown in figure(1,2), also there were a significant increase in mean t score, BMD after 6 months($P<0.05$) as compared with baseline as shown in figure(3,4) . There were a significant reduction in mean serum ionized calcium, ESR in group treated sodium alendronate after 2,4,6 months($P<0.05$) as compared with baseline as shown in figure(5,6), also there were a significant increase in mean t score, BMD after 6 months($P<0.05$) as compared with baseline as shown in figure(7,8) . In multiple comparison sodium alendronate plus thyme more efficacious than sodium alendronate alone in treatment of postmenopausal osteoporosis as shown in table(2) .

Table(2) percentage of patients remain osteoporosis, become osteopenia or normal after end of treatment

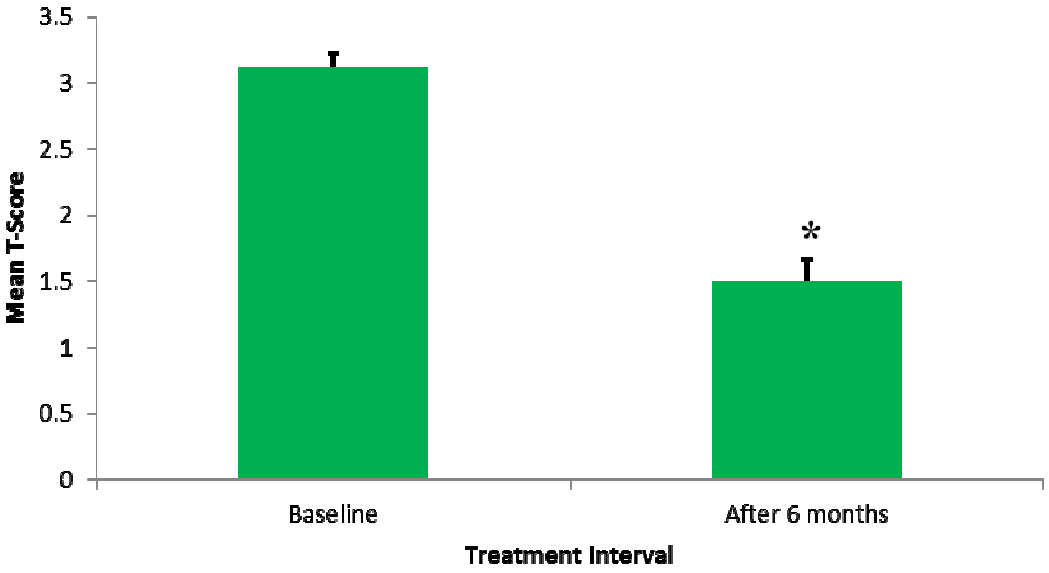
Group	Normal (No. ,%)	Osteopenia (No. ,%)	Osteoporosis (No. ,%)
Sodium alendronate plus Thyme	13, 65%	4, 20%	3, 15%
Sodium alendronate	10, 50%	6, 30%	4, 20%



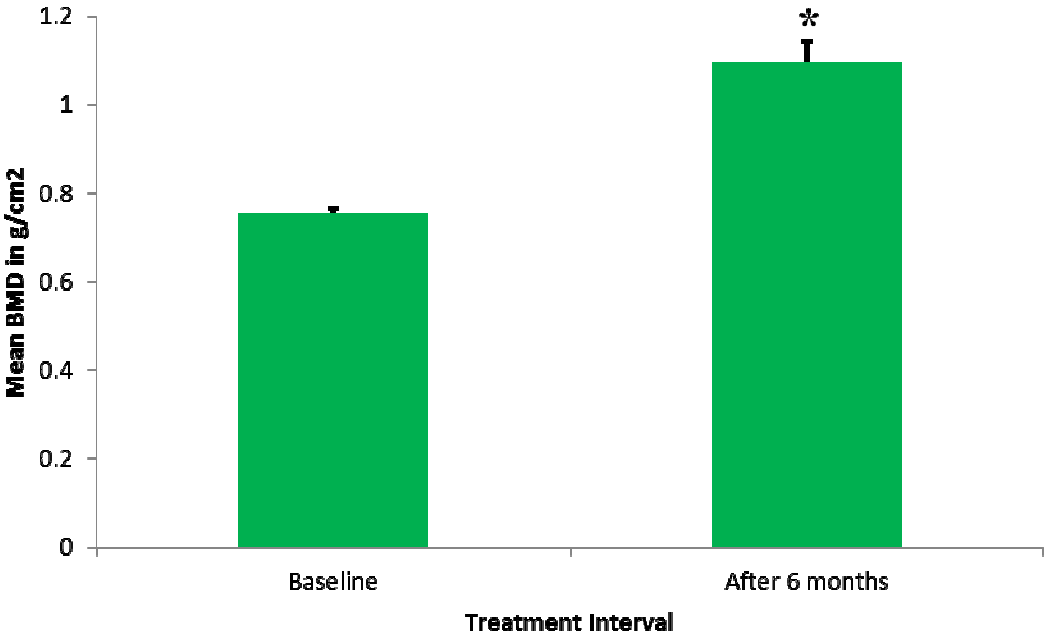
Figure(1):-A comparative effect of Sodium alendronate plus Thyme on mean ionized calcium at different time interval
(*) :- Mean there is a significant difference



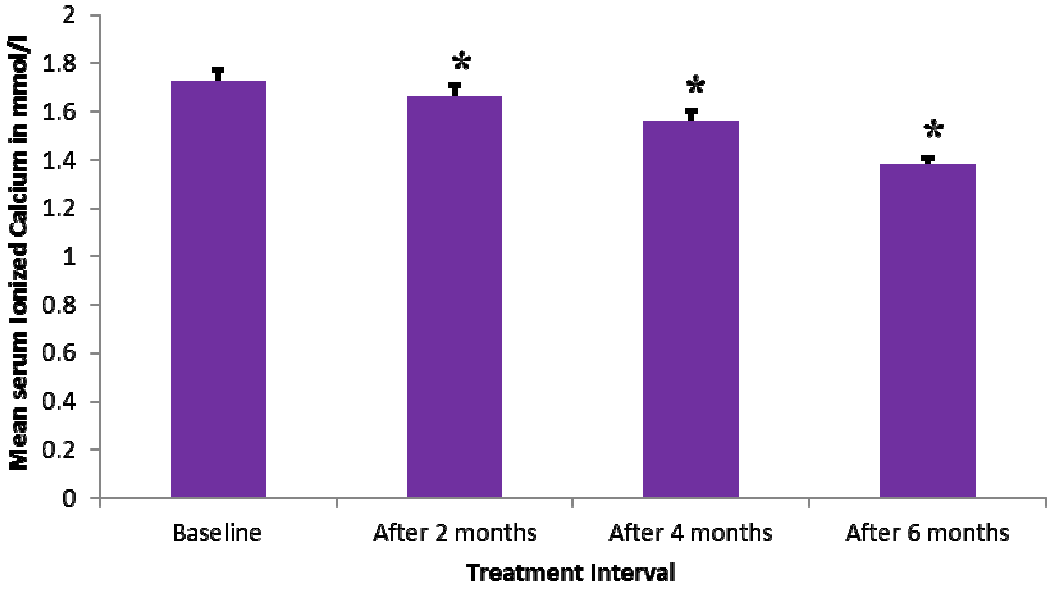
Figure(2):-A comparative effect of Sodium alendronate plus Thyme on mean ESR at different time interval
(*) :- Mean there is a significant difference



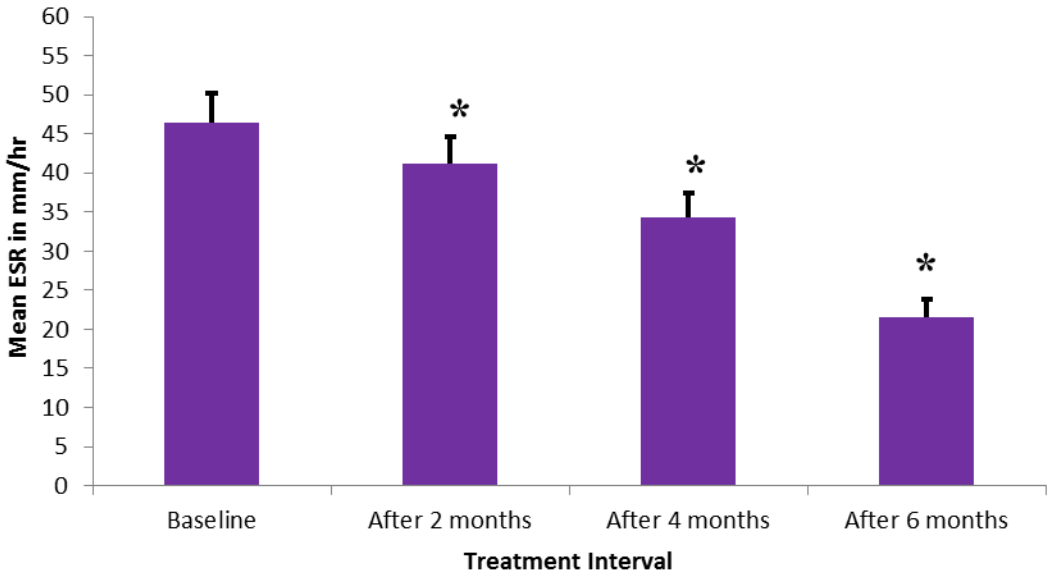
Figure(3):-A comparative effect of sodium alendronate plus Thyme on mean t score at different time interval
(*) :- Mean there is a significant difference



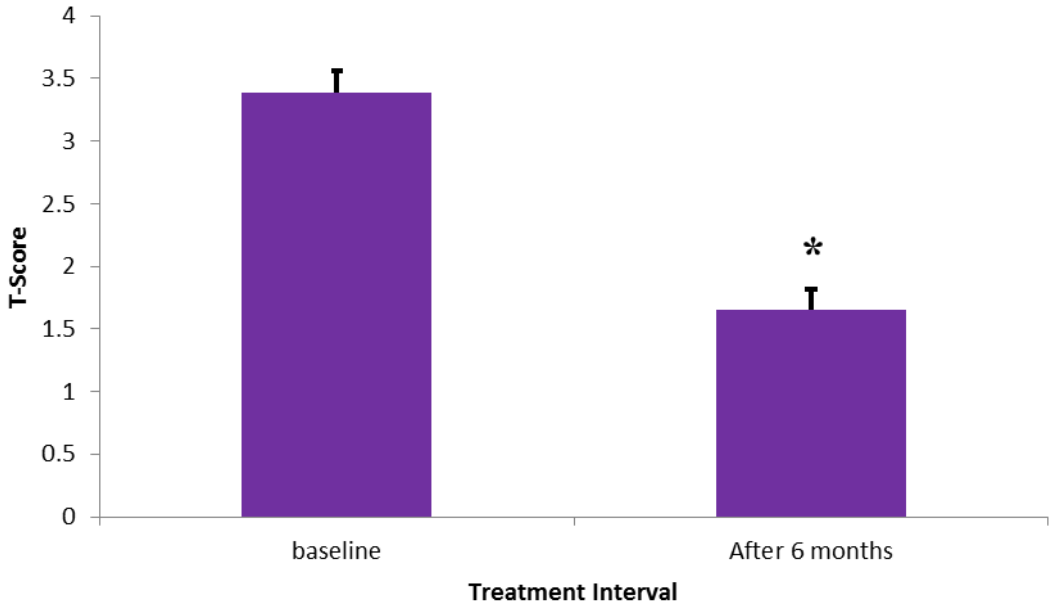
Figure(4):-A comparative effect of Sodium alendronate plus Thyme on mean BMD at different time interval
(*) :- Mean there is a significant difference



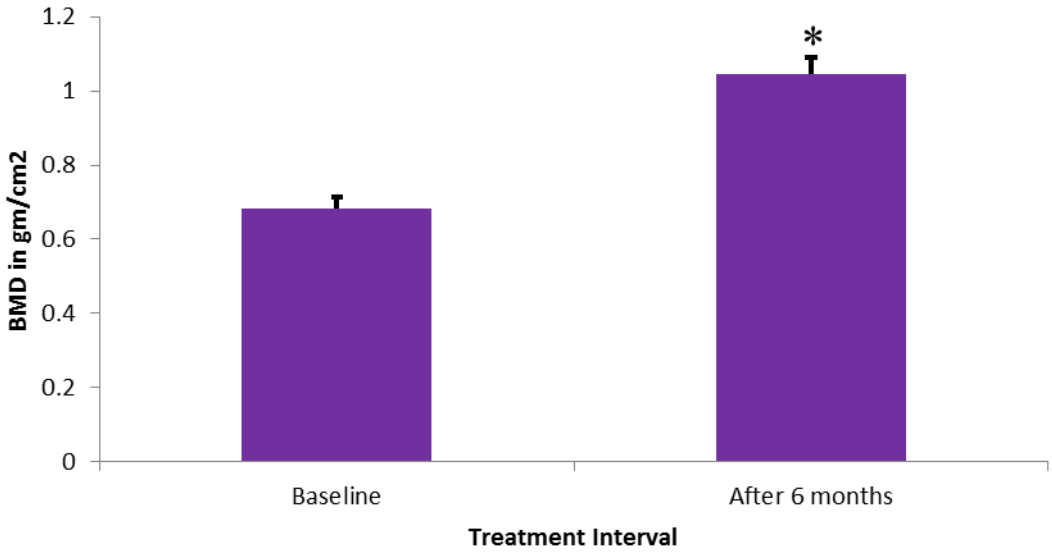
Figure(5):-A comparative effect of Sodium alendronate on mean serum ionized calcium at different time interval
(*) :- Mean there is a significant difference



Figure(6):-A comparative effect of Sodium alendronate on mean ESR at different time interval
(*) :- Mean there is a significant difference



Figure(7):-A comparative effect of Sodium alendronate on mean t Score at different time interval
(*) :- Mean there is a significant difference



Figure(8):-A comparative effect of Sodium alendronate on mean BMD at different time interval
(*) :- Mean there is a significant difference

Discussion

According to a clinical practice guideline by the American College of Physicians, because of the significant disability, morbidity, mortality, and expenses associated with osteoporotic fractures treatment is aimed at fracture prevention(26). Preventive measures include modification of general lifestyle factors, such as increasing weight-bearing and muscle-strengthening exercise, which have been linked to fractures in epidemiologic studies, and ensuring optimum calcium and vitamin D intake as adjunct to active antifracture therapy(27) . Medical care includes the administration of adequate calcium, vitamin D, and anti-osteoporotic medication such as bisphosphonates,(28) parathyroid hormone (PTH), raloxifene, and estrogen(29) . In addition, potentially treatable underlying causes of osteoporosis such as hyperparathyroidism and hyperthyroidism should be ruled out or treated if detected. Surgical care includes vertebroplasty and kyphoplasty, which are minimally invasive spine procedures used for the management of painful osteoporotic vertebral compression fractures. However, there may be an increased risk of adjacent level vertebral fractures after these procedures(30,31) .

Effect of Sodium alendronate plus Thyme on different parameters of the present study

The present study show a significant reduction in mean serum ionized calcium after 2,4,6 months treatment with sodium alendronate + thyme as compared with baseline mean serum ionized calcium .These results were in a line with the results of study by Cosman et al.,(32) , as they were given alendronate in combination with teriparatide hormone to postmenopausal osteoporosis for one year, they were reported that the elevated serum ionized calcium in osteoporosis was decrease because of alendronate stop bone matrix loss and teriparatide increase bone formation and help to mobilize calcium from the circulation to the bone, in our study given alendronate in combination with thyme do the same function because of alendronate stop bone loss and thyme is a good anabolic agent that increase bone formation and mobilize calcium from the circulation to the bone .

The results of current study show a significant decreased in mean serum ESR after 2,4,6 months treatment sodium alendronate + thyme as compared with baseline mean ESR . These results were in a line with the results of study by Nishizawa et al.,(33), in this study Fifty-four postmenopausal women with back pain were treated with alendronate (5 mg/day or 35 mg/week) and ECT (intramuscular, 20 units a week) (the ALN+ECT group), and 180 women without obvious back pain were treated with ALN alone (5 mg/day or 35 mg/week) (the ALN group), The doses indicated in the parentheses above are the doses used in Japan for the treatment of postmenopausal women with osteoporosis and have been recognized as being safe and Effective(34), the duration of treatment 6 months ,biochemical markers were assessed such as serum ALP, ESR, they were found that serum ALP, ESR, were elevated before treatment and reduce after treatment, and the efficacy of combination treatment is more than single treatment, the interpretation for his variation were that in osteoporosis there were a loss of bone ALP and release of proinflammatory cytokines that initiate osteoclast activity and mediate bone resorption , thus this lead to increase serum ALP and ESR because ESR is a marker of inflammation, therefore treatment withis combination reduce osteoclast activity and had a role in increase osteoblast activity, so this lead to suppression of proinflammatory cytokines and mobilization of serum ALP to the bone , so decrease the elevated level of serum ALP, these findings were in accordance with findings of presentr study, because of alendronate inhibit osteoclast activity, so help to suppress proinflammatory cytokines, and ESR level was decrease.

There were a significant increase in mean T score, BMD after 6 months treatment with sodium alendronate + thyme as compared with baseline mean T score, BMD. These findings were had similarity with findings of study by Black et al.,(35), they were reported that the use of alendronate in combination with teriparatide for treatment of postmenopausal osteoporosis reduce bone removal and enhance bone mineral density , the interpretation for this were that alendronate was prevent loss of bone matrix by inhibiting osteoclast activity, and teriparatide enhance osteoblast activity , and thus increase bone formation, in present study, the combination of alendronate and thyme were had similar effect, alendronate decrease bone loss and thyme was anabolic agent that increase bone mineral density by increase osteoblast activity (36) .

Effect of Sodium alendronate on different parameters of the present study

In the present study there were a significant reduction in mean serum ionized calcium after 2,4,6 months treatment with sodium alendronate as compared with baseline mean serum ionized calcium . This finding was in accordance with that revealed by Royer et al.,(37) were demonstrated that alendronate inhibit osteoclastic bone resorption and are effective in the treatment of hypercalcemia due to conditions causing increased bone resorption and malignancy-related hypercalcemia .

The present study show a significant reduction in mean ESR after 2,4,6 months treatment with sodium alendronate as compared with baseline mean ESR .The value of ESR in patient with osteoporosis, pregnancy, RA is high as compared with normal. It is a very common hematology test, and is a non-specific test of inflammation (38) . In present study the results of ESR were in accordance with results of Gregório et al., (39), they were stated that ESR should be assessed for all patients with osteoporosis as a marker of inflammation because of the inflammation has a major influence on bone metabolism and this lead to increase bone resorption and risk of fracture. All medication including bisphosphonates inhibit osteoclast activity lead to reduce inflammation (40) .

The present study show a significant increase in mean T-score ,BMD after 6 months treatment with sodium alendronate as compared with baseline mean T score, BMD . These results were similar to results of study by Luckey et al.,(41), they were stated that weekly doses of alendronate 70 mg is associated with a 4.7% increase in mean BMD values at the spine, 1.3% at the femoral neck and 2.9% at the total hip in postmenopausal women and results of Yan et al.,(42), they were reported that increase in mean BMD (4.87% at the spine, 2.47% at the femoral neck, and 2.56% at the total hip) , this increments in BMD by alendronate due to that it's inhibit bone resorption and help to move calcium from the circulation to the bone, thus maintain calcium balance in bone and T scores increased because of T scores compare a patient’s bone density to that of a healthy 30-year-old of the same gender. The more negative the number, the less dense the bones(43) .

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