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A comparative effect of calcium with vitamin D3 and simvastatin in treatment of postmenopausal women with osteoporosis

Qayssar Joudah Fadheel
Al-Kufa University, faculty of Pharmacy , Department of Pharmacology and Toxicology , Iraq

ABSTRACT

Osteoporosis is a disease where reduced bone strength enhances the risk of a broken bone. It is the most common cause for a broken bone among the elderly. Bones that are commonly break include the bones of the forearm ,the back bones , and the hip. Until a broken bone happens there are typically no symptoms. Bones may weaken to a degree that a break may occur with minor stress or spontaneously. Chronic pain and a reduced ability to accomplish normal activities may occur following a broken bone. The aim of this study was to assess the efficacy of simvastatin in treatment of postmenopausal women with osteoporosis and compare it's effect with calcium plus vitamin D3 . Twenty four postmenopausal women with osteoporosis were randomly divided into two groups(each group include twelve women) , in addition to apparently healthy group include twelve postmenopausal women without osteoporosis considered as a control group .The duration of treatment was 6 months . First group was given simvastatin tablet 20mg once daily, second group was given calcium plus vitamin D3(calcium 600mg plus vitamin D3 500 I.U.) once daily .The following parameters were measured for two groups at baseline and at 6 months intervals bone mineral density(BMD) and T-score , total cholesterol , and triglyceride . There were a significant increase in BMD, T- score in group treated with simvastatin after 6 months as compared with baseline and with group treated with calcium plus vitamin D3 . Also there were a significant reduction in mean serum total cholesterol and triglyceride in group treated with simvastatin e and group treated with calcium with vitamin D3 after six months as compared with baseline($P<0.05$) .

Keywords: simvastatin, calcium with vitamin D3, osteoporosis, BMD, TG

*Corresponding Author Email: joudahqayssar@yahoo.com
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INTRODUCTION

Osteoporosis is a progressive skeletal disease characterized by the bones become thin, brittle, weak, and prone to fracture. Osteoporosis literally means "porous bones." Thinning of the bones are caused by loss of bone mineral density [1]. Calcium and other minerals contribute to the bone density that assist in strengthen and protect bones[2]. In women, estrogen loss following menopause is particularly correlated with rapid resorption and loss of bone mineral density. Postmenopausal women are therefore at greatest risk for osteoporosis and subsequent fractures[3]. The major risk factors for osteoporosis are(age over 65 ,female gender , menopause , tobacco and excessive alcohol use , low body weight ,family history of fractures associated with osteoporosis, decrease level of vitamin D3)[4].Treatment include lifestyle modifications Dietary Factors. Diet plays an important role in both preventing and speeding up bone loss in men and women. Calcium and vitamin D deficiencies are risk factors for osteoporosis. Other dietary factors may also be harmful or protective for certain people. A combination of calcium and vitamin D can reduce the risk of osteoporosis. (For strong bones, people need enough of both calcium and vitamin D5,6. Exercise is very important for slowing the progression of osteoporosis. Although mild exercise does not protect bones, moderate exercise (more than 3 days a week for more than a total of 90 minutes a week) reduces the risk for osteoporosis and fracture in both older men and women. Exercise should be regular and l Limit alcohol consumption. Excessive drinking is associated with brittle bones. Limit caffeine consumption. Caffeine may interfere with the body's ability to absorb calcium. Quit smoking. The risk for osteoporosis from cigarette smoking appears to diminish after quitting. Medications includes two types of drugs are used to prevent and treat osteoporosis which are antiresorptive drugs[7]. Antiresorptives include bisphosphonates, selective estrogen-receptor modulators (SERMs), and calcitonin. Bisphosphonates are the standard drugs used for osteoporosis[8,9]. Denosumab is a newer type of antiresorptive[10.] These drugs block resorption (preventing bone break down), which slows the rate of bone remodeling, but they cannot rebuild bone[11]. Because resorption and reformation occur naturally as a continuous process, blocking resorption may eventually also reduce bone formation. *Anabolic (Bone-Forming) Drugs*. Drugs that rebuild bone are known as anabolics[12]. The primary anabolic drug is low-dose parathyroid hormone (PTH), which is administered through injections. This drug may help restore bone and prevent fractures. PTH is still relatively new, and long-term effects are still unknown. Fluoride is another bone-building drug, but it has limitations and is not commonly used. Both types of drugs are effective in preventing bone loss and fractures, although

they may cause different types of side effects[13]. The United States Preventive Services Task Force (USPSTF) recommends that these drugs should be prescribed only to patients who have been diagnosed with osteoporosis[14]. Mundy et al. first reported evidence showing that statins may have anabolic effects on bone, in which statins stimulated significant new bone formation in rodents [15]. Statins act on the mevalonate pathway in osteoblasts and enhance the expression of the bone morphogenic protein-2 (BMP-2), which is an important growth factor for osteoblast differentiation. It is believed that BMP-2 upregulation mediates the bone forming effect of statins. Additionally, statins act on the same pathway upstream of the bisphosphonates in osteoclasts via the inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, leading to decreased protein prenylation, which is essential for a normal osteoclast function [16].

MATERIALS AND METHOD

Patients

This is a randomized prospective clinical trial study. It was conducted in Merjan Teaching Hospital in DXA unit which present in Rheumatology department. The study was conducted between August 2015 and January 2016 . Dual-energy x-ray absorptiometry (DXA) is currently the criterion standard for the evaluation of BMD [17,18] Peripheral DXA is used to measure BMD at the wrist; it may be most useful in identifying patients at very low fracture risk who require no further workup.

DXA provides the patient's T-score, which is the BMD value compared with that of control subjects who are at their peak BMD. [19-22] .World Health Organization (WHO) criteria define a normal T-score value as within 1 standard deviation (SD) of the mean BMD value in a healthy young adult. Values lying farther from the mean are stratified as follows [21]:-

- T-score of –1 to –2.5 SD indicates osteopenia
- T-score of less than –2.5 SD indicates osteoporosis
- T-score of less than –2.5 SD with fragility fracture(s) indicates severe osteoporosis

Normal triglyceride less than 150mg/dl and normal total cholesterol less than 200mg/dl

Sample size

The sample of the study include 24 postmenopausal women suffering from Osteoporosis) .They divide into two groups, each group include 12 patient. The duration of treatment is 6 months.

Study Groups

Group I: - received calcium with vitamin D3(calcium hydrogen phosphate 600mg and vitamin D3 500 I.U.) one tablet daily .

Group **II**:-received simvastatin 20 mg one tablet daily.

All the following parameters were measured for all groups at baseline and after 6 months treatment (BMD, T- score, total cholesterol , triglyceride) .

Data collection

The method of collecting information depend on direct(personal) interview in a specific room attached to unit DXA 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. lnc. 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 AND DISCUSSION

Anthropometry

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

Mean± SEM (Group I I)	Mean± SEM (Group I)	Anthropometric data
59.9±1.86	56.15±1.84	Age(year)
82.95±4.06	81.2±2.54	Weight(kg)
154.6±1.52	152.4±1.22	Height(cm)

Between the two groups included in this study, there were no significant difference in anthropometric data as shown in tab Demographic distribution in healthy and patients with osteoporosis

Table 2: Mean of the age, weight, and height among healthy and patients with osteoporosis

Demographic data	Healthy(control)	Patients with osteoporosis	P-value
Age(years)	60.25±1.62	58.13±1.42	N.S.
Weight(Kg)	79.12±2.16	78.18±3.14	N.S.
Height(cm)	158.18±1.28	156.16±1.16	N.S.

expressed in Mean± SEM

Effect of the two treatment regimen on Bone mineral density, T- score, Total cholesterol, Triglyceride

There were a significant reduction in mean serum triglceride , total cholesterol in group treated with calcium plus vitamin D3 after 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, bone mineral density(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 triglyceride, total cholesterol in group treated with simvastatin 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 calcium plus vitamin D3 more efficacious than simvastatin in treatment of postmenopausal osteoporosis than as shown in table(3).

Table 3: Percentage of patients remain osteoporosis and patients show improvement in bone health (osteopenia) after the end of treatment .

Group	Osteopenia (No. , %)	Osteoporosis (No. , %)
Calcium plus vitamin D3	(6, 50%)	(6, 50%)
Simvastatin	(5, 41.7%)	(7, 58.3%)

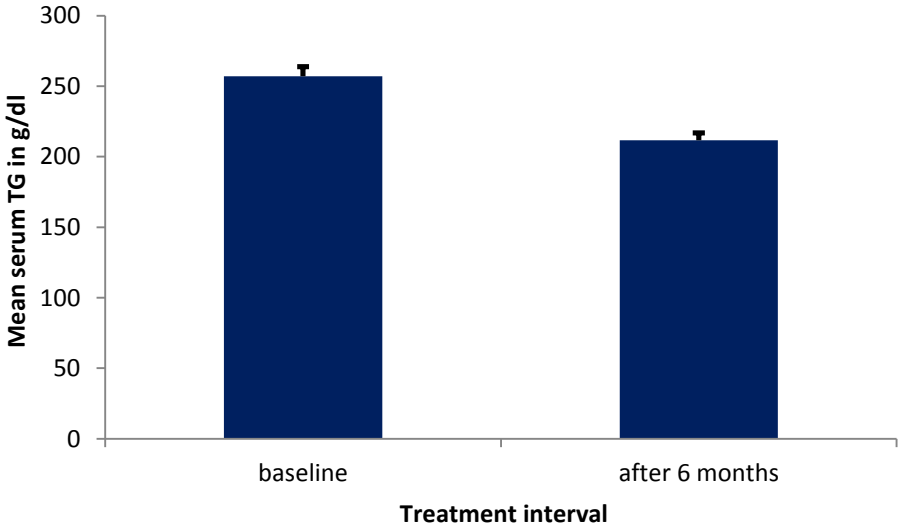

Figure 1: A comparative effect of calcium plus vitamin D3 on mean serum triglyceride at different time interval

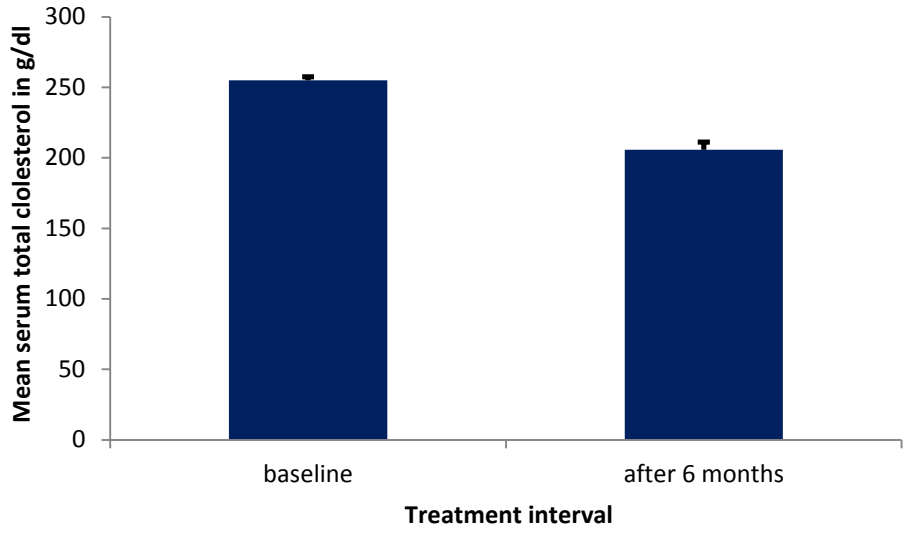

Figure 2: A comparative effect of calcium plus vitamin D3 on mean serum total cholesterol at different time interval

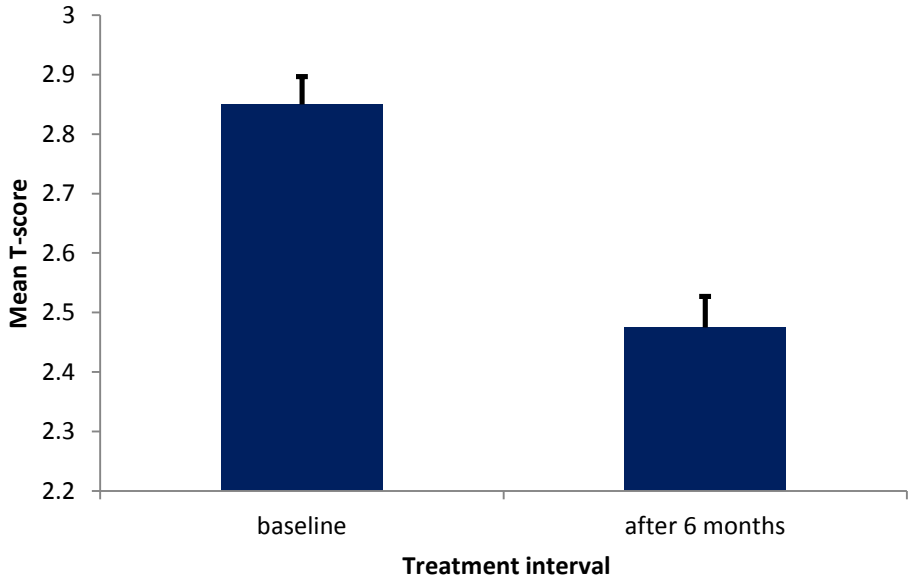

Figure 3: A comparative effect of calcium plus vitamin D3 on mean T-score at different time interval

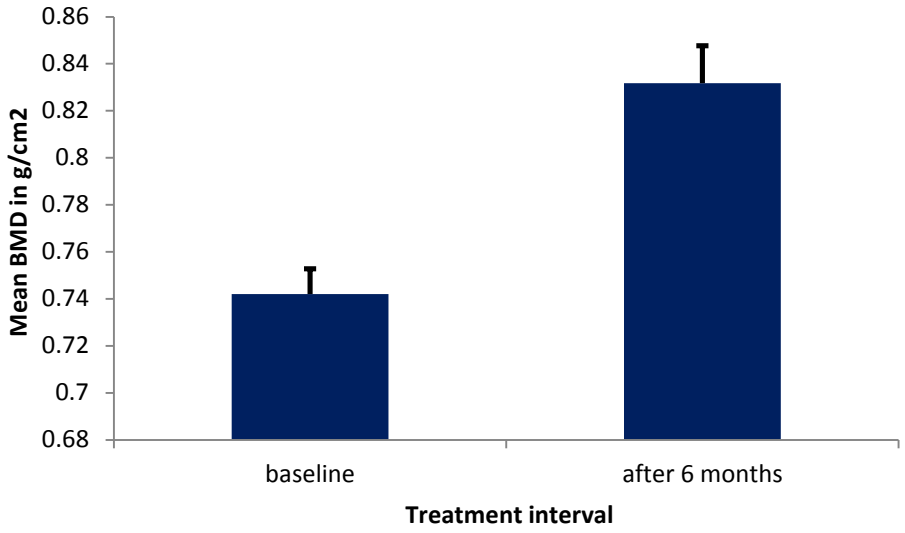

Figure 4: A comparative effect of calcium plus vitamin D3 on mean bone mineral density at different time interval

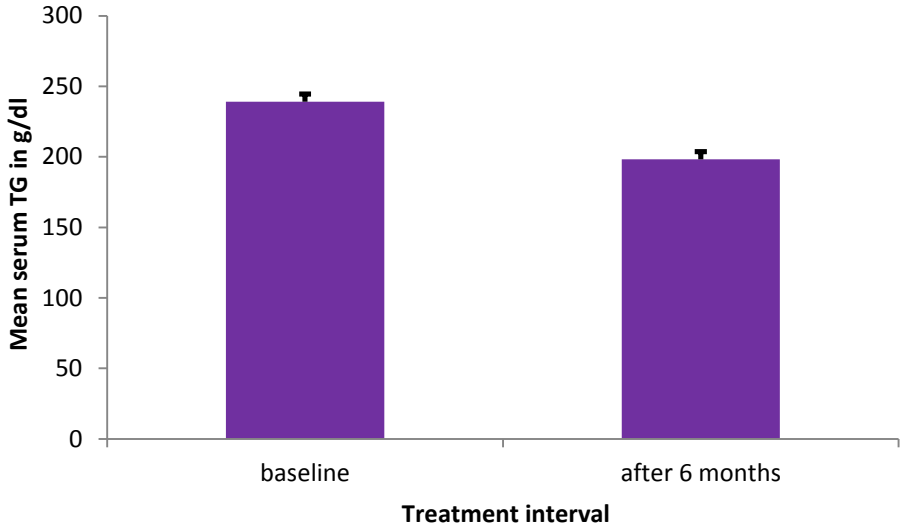

Figure 5: A comparative effect of simvastatin on mean serum triglyceride at different time interval

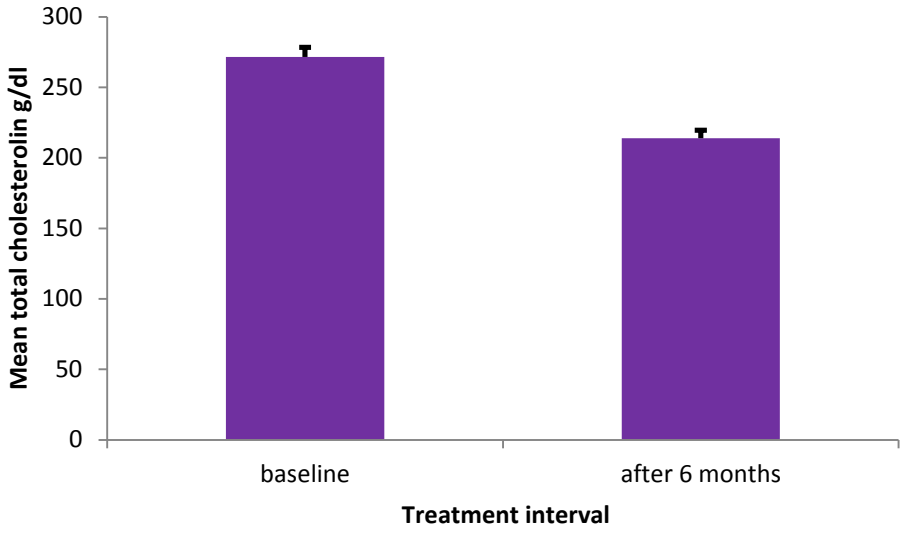

Figure 6: A comparative effect of simvastatin on mean serum total cholesterol at different time interval

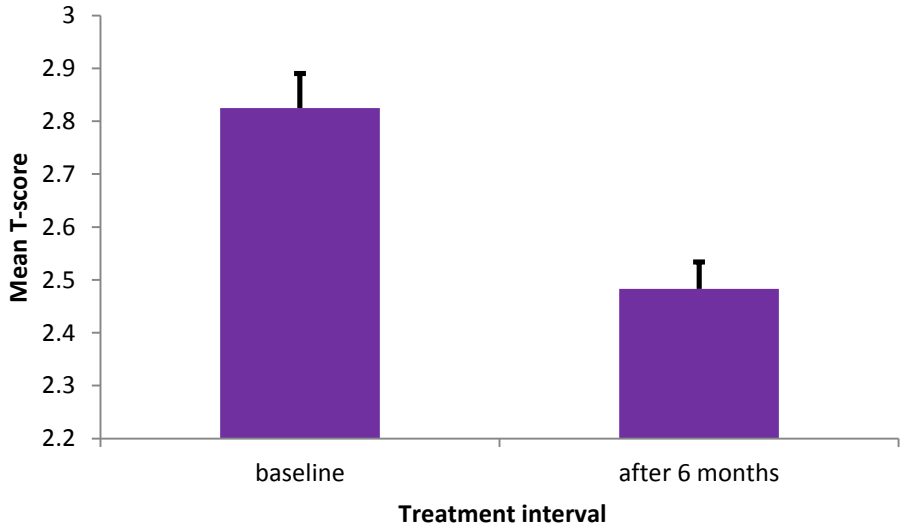

Figure 7: A comparative effect of simvastatin on mean T-score at different time interval

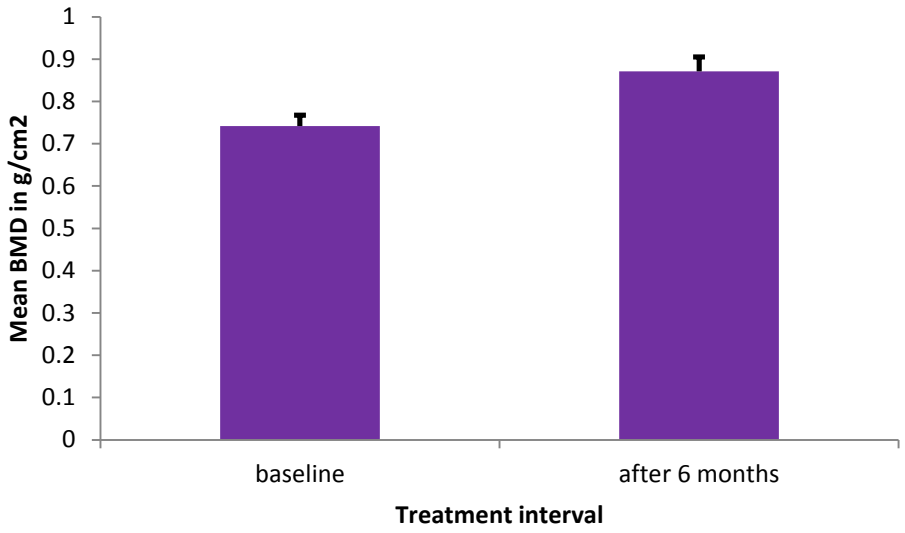

Figure 8: A comparative effect of simvastatin on mean bone mineral density at different time interval

DISCUSSION

Osteoporosis is the condition in which a low bone mass and altered microarchitecture of the bone leads to increased risk of fracture. Traditionally, osteoporosis has been classified into primary and secondary osteoporosis. Primary osteoporosis refers to osteoporotic conditions which are not related to other chronic illnesses and is usually associated with aging and decreased gonadal function, such as decreased level of estrogen, whereas secondary osteoporosis is the type of osteoporosis caused by other health problems. Disuse is one of the many reasons inducing bone loss and resulting in secondary osteoporosis[23] .

Effect of simvastatin on different parameters of the present study

The present study show a significant reduction in mean serum triglyceride, total cholesterol after 6 months treatment with simvastatin as compared with baseline as shown in figure(5,6) .These findings were in line with findings of study by (Nissen SE ,et al., they were stated that single dose daily 20mg simvastatin tablet taking by hyperlipidemic patient at night may be effectively result in reduction of serum lipid profile including total cholesterol and triglyceride[24]. The results of current study show a significant increase in mean T-score, BMD after 6 months treatment with simvastatin as compared with baseline figure(7,8) .These findings were had similarity with findings of studies by Skoglund et al. recently reported that statins enhance the net bone formation and improve the healing of fractures in mice [25]. In addition, in vitro studies have shown that statins increase bone density via enhance the osteoblastic synthesis of BMP-2 and promote osteoblastic differentiation in a mouse osteoblastic cell line [26], in a human

osteosarcoma cell line [27]and in murine embryonic stem cells [28].These results are consistent with previous observations showing that the statins enhanced osteogenesis in MC3T3-E1 cells (a clonal pre-osteoblastic cell line derived from mouse calvaria) [29]and murine embryonic stem cells [30].Ohnaka et al. reported the stimulatory effect of statin on the osteocalcin mRNA expression level in primary culture of human osteoblasts prepared from femur bone fragments[31]. All these results and our findings are in good agreement with the concept that statin may differentiate the osteoblasts. This beneficial influence of simvastatin on the bone metabolism might allow the statins to become an effective anabolic agent for treating osteoporosis. To the best of the authors' knowledge, there is no report on the effects of statins on cell growth and proliferation. The implications of these findings are as yet uncertain. Several mechanisms have been suggested to be involved in a bone formation defect: a deficit in the bone marrow stromal cell populations, a decrease in the osteoblastic growth and/or function and a lower proliferation rate of the osteoblast precursors [32]. It is difficult to weigh the effects of the proliferation and differentiation on new bone formation; in our opinion, either factors are important. Although the statins have beneficial effects on the differentiation process, if the effects on cell growth and proliferation are considerable, the net effects would be less. Additional randomized, prospective, trials with the use of the appropriate statins, doses, and routes would solve these debates. In conclusion, this study found that the HMG-CoA reductase inhibitor, simvastatin, is able to increase the alkaline phosphatase activity, the osteocalcin expression level, and the deposition of minerals in human BMSCs. These results suggest that simvastatin has anabolic effects on the bone by promoting osteoblastic differentiation. However, the inhibitory function of the simvastatin on bone cell proliferation also demonstrated that it might interfere with new bone formation. In the process of osteogenesis in vivo, it is difficult to predict whether decreased proliferation or enhanced differentiation would contribute more in the presence of statins, and future studies will be needed to address this issue.

Effect of Calcium plus Vitamin D3 on different parameters of present study

The present study show a significant reduction in mean serum triglyceride, total cholesterol after 6 months treatment with calcium plus vitamin D3 as compared with baseline as shown in figure(1,2) .

An increase of low density lipoprotein cholesterol (LDL-cholesterol) and a reduction of high density lipoprotein cholesterol (HDL-cholesterol) levels have been associated with low BMD in postmenopausal women [33].

Lipid oxidation products such as minimally oxidized LDL-cholesterol promote arterial calcification, and its accumulation in the subendothelial space of skeletal bone arteries inhibits bone formation [34]. The hyperproduction of oxidized low density lipoprotein fraction of cholesterol stimulates atherogenesis and activates osteoblasts in the arterial pool, leading to the calcification of arterial plaque. However, the published results are controversial. It has been shown that plasma LDL-cholesterol level inversely correlated with BMD values, while low plasma triglyceride (TG) levels were associated with the presence of vertebral fractures in postmenopausal women[33-37].

Some studies found no association between serum lipid concentrations and BMD 38and other studies found even a positive relationship between them [37-40] .

The study of Sivas *et al.* [37] showed that serum lipids have an impact on vertebral fracture existence, rather than BMD alterations. The total cholesterol (TC), TG and LDL-C levels were lower in postmenopausal women who had at least one vertebral fracture. TC level was the strongest factor affecting vertebral fracture existence. And an increase of 1 mg/dl TC decreased the risk of vertebral fracture by 2.2%. In the study of Jeong *et al.* [41] after adjustment for clinical and laboratory covariates, the authors found a weak positive association between HDL-cholesterol and BMD at the lumbar spine only in postmenopausal women. This result is in accordance with the work of Yamaguchi *et al.* [33] but opposite to the results of the study by Adami *et al*[39], in which worse lipid profiles (lower HDL-cholesterol and higher LDL-cholesterol or TG) were associated with higher bone mass, although they could not provide a documented explanation. In conclusion, the correlation between lipid profile and BMD was neither consistent at all bone sites [41], nor from study to study. Further studies are needed to clarify this relationship and the underlying mechanism thus the results of these studies were in similarity with results of our study which stated that treatment of postmenopausal women suffer from osteoporosis with calcium plus vitamin D3 lead to decrease the level of total cholesterol and triglyceride and increase the bone mineral density and T-score as shown in figures(3, 4) . This fact were in line with Vonhurst[42] study which stated that nutrional habits had a positive effect on BMD, and in accordance with L'Abbe et al., [43] study, they were reported that calcium and vitamin D intake are the most important determinants of peak BMD, they also contribute to maximize the bone strength [44] .

CONCLUSION

Postmenopausal women with osteoporosis have increase T-score and decrease bone mineral

density in comparison with healthy , from the results of current study we conclude that simvastatin has a therapeutic effect on patients with osteoporosis as they lead to increase bone mineral density and decrease T-score but less efficacious than calcium plus vitamin D3.

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