Original Article

Effects of Raloxifene Hydrochloride on Bone Mineral Density and Serum Lipids in Kuwaiti Postmenopausal Women with Osteoporosis

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ABSTRACT

Background: Osteoporosis is currently a major cause of mortality, morbidity, and medical expense worldwide. **Aim:** This study was designed to detect the effect of raloxifene hydrochloride on bone mineral density (BMD) and serum lipids in Kuwaiti postmenopausal women with osteoporosis. **Subjects and Methods:** Eighty postmenopausal women, who received raloxifene 60 mg with calcium 500 mg and 200 IU Vitamin D daily for 2 years were included in this prospective study which was conducted from August 2011 to August 2013 after informed consent and approval of the study by hospital ethical committee. BMD measured by dual-energy X-ray absorptiometry (DXA) and serum lipids were assessed before and after the treatment to detect the effect of raloxifene on BMD and on serum lipids. Unpaired *t*-test was used to compare lumbar spine, total hip BMD and serum lipid values before and after the raloxifene treatment. **Results:** Lumbar spine and total hip BMD were significantly increased from 0.92 (3.8) and – 0.83 (5.6); respectively before treatment to 3.21 (5.4) and 1.62 (7.4); respectively 2 years after treatment. Also, Ward`s triangle and trochanter BMD were significantly increased from 1.53 (6.6) and – 1.4 (6.4); respectively to 4.84 (9.3) and 1.78 (8.5); respectively. Total cholesterol and low-density lipoprotein cholesterol were significantly decreased from 5.15 (4.5) and 3.82 (4.6) mmol/L; respectively before treatment to 3.57 (3.4) and 2.56 (3.7) mmol/L; respectively 2 years after treatment. While, changes in high-density lipoprotein cholesterol and triglycerides after treatment were statistically insignificant. **Conclusions:** Raloxifene appears to be an effective, well tolerated option for treating osteoporosis in Kuwaiti postmenopausal women, suitable for long term use with favorable effect on serum lipid profiles.

KEY WORDS: Bone mineral density, lipid metabolism, osteoporosis, postmenopausal, raloxifene

INTRODUCTION

Reduced estrogen in postmenopausal women accelerates bone loss and estrogen replacement therapy can prevent bone loss.[1-3] Long-term estrogen use (without concurrent use of progestin) has been reported to cause an increased risk of endometrial cancer.[4,5] Raloxifene hydrochloride is one of estrogen receptor modulator acting as an estrogen agonist in bone and as antagonist in breast and uterus.[6] Postmenopausal women with osteoporosis receiving raloxifene showed significant increase in bone mineral density (BMD) and reduced incidence of subsequent vertebral fractures.[7-11]

Raloxifene does not stimulate the endometrium of breast.[12,13] Osteoporosis is a major cause of morbidity worldwide[14,15]

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Therefore, it is important to investigate therapies for prevention and treatment of osteoporosis in postmenopausal women. Previous studies, suggest that long term use of raloxifene has favorable effect on serum lipid.[7,10,16] So, this study was designed to detect the effect of raloxifene hydrochloride on BMD and serum lipids in Kuwaiti postmenopausal women with osteoporosis.

SUBJECTS AND METHODS

Randomly selected eighty postmenopausal women, who received raloxifene 60 mg (Eli Lilly and Company, Indianapolis, USA) with calcium 500 mg and 200 IU Vitamin D daily for 2 years were included in this prospective study after informed consent, approval of the study by hospital ethical committee to compare changes in lumbar spine, total hip BMD and serum lipids before and after raloxifene treatment.

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Postmenopausal women free of severe or chronically disabling conditions, had their last menstrual period at least 2 years before start of raloxifene, had a T-score for femoral neck or lumbar spine BMD measurements ≤ 2.5, without previous treatment affecting BMD or affecting serum lipids, without fractures were included in this study.

Postmenopausal women with abnormal uterine bleeding, suspected, or history of carcinoma of the breast or estrogen-dependent neoplasia as endometrial cancer, history of cancer within the previous 5 years, history of deep venous thrombosis, bone disorders other than osteoporosis, treatment with any medications affecting bone metabolism, liver diseases, impaired kidney functions were excluded from this study.[1]

Bone mineral density was measured by DXA using Hologic QDR-2000 to test 4 sites (L1-L4) of the lumbar spine at a posterio-anterial position and 4 sites of the left hip (femoral neck, Ward`s triangle, trochanter, and intertrochanter) by radiologist who was blinded to patient`s data. Serum lipids including; total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides were also assessed before and after raloxifene treatment. Outcome measures changes in lumbar spine, total hip BMD and serum lipids before and after raloxifene treatment.

Sample size justification

The required sample size was calculated using G* Power software version 3.17 for sample size calculation (*Heinrich Heine Universität, Düsseldorf, Germany), setting the α-error probability at 0.05, power (1−βerror probability) at 0.95% and effective sample size (*w*) at 0.5. The effective size (*w*) was calculated as follows: $w = \sqrt{X^2 / N}$, Where X^2 is the Chi-square test and *N* is the total sample size. The number of participants needed to produce a statistically acceptable figure was 80 women. Assuming a 10% drop during follows up process, and so the number of women included in the beginning of this study was 88 and it was completed with 80 women.

Statistical analysis

Data were collected, tabulated then statistically analyzed using the Statistical Package for Social Sciences computer software version 18(Chicago, IL, USA). Numerical variables were presented as mean and standard deviation (±SD), while categorical variables were presented as number (*n*) and percentage (%). Unpaired *t*-test was used to compare lumbar spine, total hip BMD and serum lipid values before and after raloxifene treatment. A difference with a $P < 0.05$ was considered statistically significant.

RESULTS

Eighty eight women were included in the beginning of this study and it was completed with 80 women (5 women were lost during follow up visits and 3 women decided to stop raloxifene early after 2 months of administration because of its side effects). Mean age of the studied population was 64.4 (6.5) years (range: 58.5-68.5 years), mean weight was 56.2 (6.9) kg (range: 45.4-62.5 kg), mean height was 164.5 (3.1) cm (range: 157.5-173.2 cm), mean body mass index was 23.7 (5.7) kg/m^2 (range: 22.5-28.5 kg/m^2), mean years since menopause was 5.3 (7.6) (range: 2.5-7.2 years) and 33.75% (3/80) of the studied population were cigarette smoker.

Lumbar spine and total hip BMD were significantly increased from 0.92 (3.8) and − 0.83 (5.6); respectively before treatment to 3.21 (5.4) and 1.62 (7.4); respectively 2 years after treatment ($P < 0.01$ *S* (95% confidence interval [CI]; −3.74 to − 0.83) and 0.01 (95% CI; −4.49 to − 0.40); respectively). Also, Ward`s triangle and trochanter BMD were significantly increased from − 1.53 (6.6) and − 1.4 (6.4); respectively to 4.84 (9.3) and 1.78 (8.5); respectively ($P = 0.01$ (95% CI; 5.82 to − 0.79) and < 0.01 (95% CI; −5.52 to − 0.83; respectively) [Table 1 and Figure 1].

Total cholesterol and LDL-C were significantly decreased from 5.15 (4.5) to 3.82 (4.6) mmol/L; respectively before treatment to 3.57 (3.4) and 2.56 (3.7) mmol/L; respectively 2 years after treatment ($P = 0.01$ (95% CI; 0.33-2.82) and 0.5 (95% CI; −0.04-2.56); respectively). While, changes in HDL-C and triglycerides after treatment were statistically insignificant [Table 2 and Figure 2].

Table 1: Lumbar spine, total hip bone mineral density of studied population before and after treatment

BMD	Mean (SD)		*P*, (95% CI)
	Pretreatment values	Posttreatment values	
Lumbar spine	0.92 (3.8)	3.21 (5.4)	0.002**, (−3.74 to −0.83)
Total hip	−0. 83 (5.6)	1.62 (7.4)	0.01**, (−4.49 to −0.40)
Femoral neck	−0.62 (6.3)	1.25 (8.8)	0.12*, (−4.24 to −0.51)
Ward's triangle	1.53 (6.6)	4.84 (9.3)	0.01**, (−5.82 to −0.79)
Trochanter	−1. 4 (6.4)	1.78 (8.5)	0.008**, (−5.52 to −0.83)

*Nonsignificant; **Significant. Test used: Unpaired *t*-test. BMD – Bone mineral density; CI – Confidence interval; SD – Standard deviation

Table 2: Lipids profile of studied population before and after treatment

Serum lipids (mmol/L)	Mean (SD)		*P*, (95% CI)
	Pretreatment values	Posttreatment values	
Total cholesterol	5.15 (4.5)	3.57 (3.4)	0.01**, (0.33 to 2.82)
High-density lipoprotein cholesterol	1.56 (2.5)	1.45 (3.3)	0.8*, (−0.80 to 1.02)
Low-density lipoprotein cholesterol	3.82 (4.6)	2.56 (3.7)	0.5**, (−0.04 to 2.56)
Triglycerides	2.34 (6.1)	1.56 (5.60)	0.4*, (−1.04 to 2.60)

*Nonsignificant; **Significant. Test used: Unpaired *t*-test. SD – Standard deviation; CI – Confidence interval

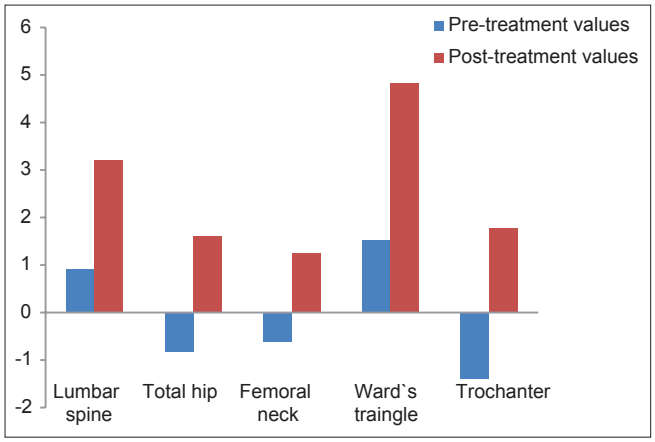

Figure 1: Lumbar spine, total hip bone mineral density of studied population before and after treatment

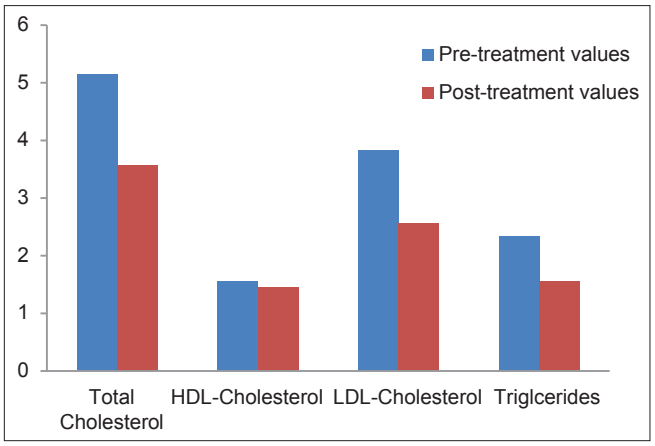

Figure 2: Serum lipids profile of studied population before and after treatment

Adverse effects recorded in this study over 2 years were; nasopharyngitis (18.75% (15/80) cases), muscle cramps (8.75% (7/80) cases), hot flushes (7.5% (6/80) cases), allergic dermatitis (6.25% (5/80) cases), diarrhea (3.75% (3/80) cases).

DISCUSSION

Eighty postmenopausal women, who received raloxifene 60 mg with calcium 500 mg and 200 IU Vitamin D daily for 2 years were included in this study. BMD and serum lipids were assessed before and after treatment to detect the effect of raloxifene on BMD and on serum lipids.

Lumbar spine and total hip BMD were significantly increased 2 years after raloxifene treatment. Also, Ward`s triangle and trochanter BMD were significantly increased 2 years after raloxifene treatment in this study.

Liu *et al*., found that 12 months after treatment of postmenopausal women with raloxifene both lumbar spine and total hip BMD was increased significantly compared with the placebo (mean increase in lumbar spine BMD was 3.3 (4.8) and mean increase in total hip BMD was 1.4 (4.8) in the raloxifene group).[1]

Similar increases in lumbar spine and total hip BMD have been observed in response to raloxifene treatment in other clinical trials in postmenopausal women with osteoporosis.[8,9,16]

Increased lumbar spine and total hip BMD 2 years after raloxifene treatment in this study add further support to the idea that raloxifene acts as an antiresorptive agent on the skeletal system, preserving bone mass and an efficacious treatment option for osteoporosis.

Also, Abdelazim *et al*. and Khan and Fortier, concluded that raloxifene reduces the risk of vertebral fracture in postmenopausal women with osteoporosis.[8,9]

Healthy postmenopausal women with a BMD T-score at the lumbar spine or femoral neck between −1.0 and −2.5 or clinical risk factors for osteoporosis were randomly assigned to one of five groups (bazedoxifene 10, 20, or 40 mg/day, placebo, or raloxifene 60 mg/day) by Miller *et al*., to detect the efficacy and safety of three doses of bazedoxifene compared with placebo and raloxifene in prevention of postmenopausal osteoporosis.[17]

Miller *et al*., concluded that treatment with bazedoxifene as well as raloxifene prevented bone loss and reduced bone turnover and was generally well tolerated in postmenopausal women with normal/low BMD.[17]

Total cholesterol and LDL-C were significantly decreased 2 years after raloxifene treatment, while, changes in HDL-C and triglycerides after treatment were statistically insignificant in this study. Naves-Díaz *et al*., in their study to detect the effects of raloxifene on BMD, serum cholesterol concentrations and uterine endometrium in postmenopausal women concluded that long term use of raloxifene has favorable effect on serum lipid without a significant rise in triglyceride.[7]

Also, Oztas *et al*. and Grover-Páez *et al*., in their studies concluded that the long term use of raloxifene has favorable effect on serum lipid without a significant rise in triglyceride.[10,16]

The effects of raloxifene on serum lipids may explain the decrease in cardiovascular events observed in a subset of women with increased risk for cardiovascular events in the MORE study.[11]

Lost women during follow up visits and discontinuation of raloxifene due to side effects were faced as limitations during conduction of this study. Adverse effects of raloxifene recorded in this study were; nasopharyngitis, muscle cramps, hot flushes, allergic dermatitis, diarrhea, and were similar to adverse effects with recorded by Abdelazim *et al*. and Khan and Fortier, in their studies.[8,9]

The safety profile of raloxifene was confirmed by Naves-Díaz *et al*., Abdelazim *et al*., and Oztas *et al*.,[7,8,10] also, in this study, the continuous use of raloxifene for 2 years by Kuwaiti postmenopausal women with osteoporosis was well tolerated without any serious side effects.

Osteoporosis is skeletal disease characterized by decrease bone mineralization and increase bone fragility with subsequent increased risk of fractures.[18] Osteoporosis is currently a major cause of mortality, morbidity, and medical expense worldwide.

In this study, raloxifene increases lumbar spine, total hip, Ward`s triangle, trochanter BMD and decreases total cholesterol and LDL-C. Zheng *et al*., previously concluded that raloxifene increases lumbar spine and hip BMD in healthy postmenopausal women,[15] also, Liu *et al*., concluded that raloxifene increases lumbar spine, hip BMD and decreases biochemical markers of bone metabolism in postmenopausal women with osteoporosis, indicating that raloxifene provides an effective for the prevention and treatment of osteoporosis.[1]

Raloxifene appears to be an effective, well tolerated option for treating osteoporosis in Kuwaiti postmenopausal women, suitable for long term use with favorable effect on serum lipid profiles.

Large case controlled studies are needed to detect effect of raloxifene (cases) compared to control cases (not under effect of raloxifene) on BMD and serum lipids profile.

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