Original scientific paper

Effects of Raloxifene on Changes in Bone Density

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A B S T R A C T

Raloxifene hydrochloride therapy effectiveness in bone mineral density (BMD) changes compared to calcium and vitamin D3 therapy over a 2-year period. Case-control study: a group of 254 women was prescribed raloxifene (raloxifene hydrochloride) together with calcium and vitamin D3 while other group of 254 women used calcium and vitamin D3 therapy. BMD was measured at the hip, spine and forearm at the beginning and at the end of the 2-year period. Treatment with raloxifene resulted in a 3.7% increase in BMD at the spine in 98% of examinees. A 1.2% BMD increase was shown in 75% of examinees at the hip. A 1.2% decrease in BMD at forearm shown in 93% of examinees using raloxifene. The calcium and vitamin D3 therapy led to an increase in BMD in 58% examinees at the spine, in 56% at the hip and in 38% at the forearm, which was significantly lower than in women using raloxifene. Among women using calcium and vitamin D alone an average BMD decrease of 1.2% was registered on 42% of examinees at the spine, 2.6% decrease on 46% of examinees at the hip and 4.2% decrease on 35% of examinees at the forearm. Treatment with raloxifene resulted in a significant increase in BMD at the spine with odds ratio (OR 5.85, $p<0.05$) compared with calcium and vitamin D3 alone. There was no statistically proven increase in BMD at either the hip (OR 0.015) or forearm (OR 0.122).

Key words: *bone mineral density, osteoporosis, raloxifene, vitamin D3, calcium*

Introduction

One of the most represented metabolic diseases of the bone in the world is osteoporosis; its incidence is equal as that of cardiovascular and malignant diseases. It is known that risk of developing osteoporosis and severe complications as fractions increase with age. World population structure is getting older and by that the risk of fractures tends to increase. Fractures of the spine, forearm and the hip are the most frequent. Commonly induced by postmenopausal osteoporosis fractures of the spine are frequent in middle-aged women. Fractures of the hip, which are commonly induced by senile osteoporosis, are linked with: high mortality (25%), high long-term loss of function (25%) and lesser quality of life (50%)[1–3].

Society is trying to deal and coup with osteoporosis with raising awareness and education, acquiring and developing diagnostic tools, as well as developing new drugs and treatments. Currently on the market there is a variety of medications to prevent osteoporotic fractures.

Raloxifene is a first drug from the group of selective estrogen receptor modulators that has proven its efficiency in prevention and treatment of postmenopausal osteoporosis[4,5]. Its effects on 76% decrease of breast cancer incidence[6] and reduction of the overall cardiovascular risk is well known[7–13]. It is confirmed that raloxifene significantly decreases vertebral and non-vertebral fracturing[14,15].

Aim of this scientific paper is to determine changes in the bone mineral density in a case control study of group postmenopausal women who were prescribed raloxifene, calcium and vitamin D3 and a group of those who were prescribed only calcium and vitamin D3. Both groups of women were compatible by age, BMD, BMI and age of starting menopause. Study was done in a 2-yrs period.

Subjects and Methods

All examinees were split into two statistically equal groups – for further details see Table 1.

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TABLE 1
CLINICAL CHARACTERISTICS OF THE STUDY GROUPS

Variables	N (%) of postmenopausal women	
	Study group (n=254)	Control group (n=254)
Age, X±SD	56.1±7.9	56.1±7.9
Menarche, X±SD	14.7±2	14.4±1.7
Menopause, X±SD	47.8±5.7	47.9±5.2
Family history of osteoporosis	4 (1.57)	5 (1.96)
Immobility	7 (2.7)	8 (3.1)
Body mass index (BMI), X±SD	29.3±4.5	28.3±4.1
Smoking	30 (11.8)	32 (12.6)
Milk consumption < 500 ml	60 (23.6)	58 (22.8)
Serum Calcium, X±SD	2.7±2.4	2.4±0.2
Serum Phosphorus, X ±SD	1.1±0.3	1.1±0.6
Serum Alkaline Phosphatase, X±SD	69.2±22	73.5±26.4
Urine Calcium, X±SD	5.7±3.2	5.7±3.6
Urine Phosphorus, X±SD	24.4±15.4	23.9±10.1
Total Cholesterol, X±SD	6.6±1.5	6.1±1.2
Tryglicerids, X±SD	1.9±1.6	1.8±0.8

1. Study group was consisted of 254 women who had taken 60 mg of raloxifene (Eli Lilly Co. Ltd., Basingstoke, England), 1000 mg of calcium and 800 units of vitamin D3 per day over a 2-yr period.
2. Control group was consisted of 254 women who received only 1000 mg of calcium and 800 units of vitamin D3 per day throughout the same period.
3. The average age in both groups was 57 years. We monitored the effects on new vertebral and non-vertebral fractures. All women had been informed and had given their consent to the research by signing an informed consent form. Ethics Committee of the General hospital »Dr. Josip Benčević«, Sl.Brod approved this study Questionnaire handed out to examinees asked for information concerning daily intake of milk products, first and last menstrual period, family history of osteoporosis, tobacco intake and physical inactivity longer then 3 months. Before starting with the study/treatment examination of the BMD at the hip, vertebra and the forearm were conducted. Levels of calcium and phosphorus in the serum and 24h urine, alkaline-phosphatase, total cholesterol and tryglicerides were collected.

There was no statistically significant difference detected between of the control and study group after pre-treatment examinations. In both groups there was no vertebral fractures; during the 2-yr period every vertebral and non-vertebral fracture was reported. In the study group there were 9 fractures of the forearm, while in the control group 10 forearm fractures were detected. In both groups, during 2-yr period wasn't fractures of the hip and the vertebra detected.

BMD was measured by dual-energy X-ray absorptiometry with QDR 4500 densitometer (Hologic, Beresford, MA, USA) and the results were expressed in g/cm^2; for both groups at the beginning and end of the 2-year period.

Mean percentage changes in BMD at the both groups were determined and odds ratio (OR) was calculated. The statistical significance was tested using the chi square test and set to $p<0.05$. All statistics were performed using Statistica for Windows software, Version 6.0 (Tulsa, OK, USA).

Results

Raloxifene improved the spinal bone density in 98% of examinees. Hip BMD increased in 75% of cases whereas a decrease in density occurred at the forearm in 93% of examinees. The spine BMD increased from 0.807 g/cm^2 (±0.103) to 0.836 (±0.298), which was a 3.7% increase. BMD increased at the hip, from 0.813 (±0.125) to 0.821 (±0.09) that represented a 1.2% increase. However, the forearm BMD decreased from 0.615 (±0.071) to 0.541 (±0.073) that was a 1.2% decrease.

Calcium and vitamin D3 therapy led to an increase in BMD in 58% of examinees at the spine from 0.791 (±0.025) to 0.800 (±0.011) which is an 1.2% increase.

In 56% of examinees increase at the hip is 0,9% – from 0.783 (±0.025) to 0.790 (±0.014). In the forearm increase is an 0.8% in 38% of examinees- from 0.601 (±0.021) to 0.605 (±0.006).

A decrease in BMD was manifested in 42% of examinees at the spine area, 46% at the hip, and 35% at the forearm area. A decrease in BMD at the spine, hip and forearm was 1.6%, 2.6% and 4.2%, respectively (Table 2).

There were significantly more examinees with significant increase in bone density of the spine among raloxi-

TABLE 2
EFFECTS OF RALOXIFENE THERAPY AND CALCIUM AND VITAMIN D THERAPY ON BMD IN THE HIP, SPINE AND FOREARM THROUGHOUT A 2-YEAR PERIOD

Site of measuring	Time	Study group BMD (g/cm^2) X±SD	Control group BMD (g/cm^2) X±SD
Spine	In the begining	0.807±0.103	0.791±0.025
	After 2-yrs	0.836±0.298	0.800±0.011
Hip	In the begining	0.813±0.125	0.783±0.025
	After 2-yrs	0.821±0.821	0.790±0.014
Forearm	In the begining	0.615±0.615	0.580±0.501
	After 2-yrs	0.541±0.073	0.556±0.451

fene group than among women using calcium and vitamin D3 alone, while in hip and the forearm the difference was not significant. Chi-square values of 24.67 ($p<0.05$) for spinal BMD with OR 5.58 and CI 95% (1.535–53.967) were calculated. For the hips the χ^2 value was 43.14 with OR 0.0105 and CI 95% (0.0160–0.896), for the forearm the χ^2 value was 27.86 with OR 0.122 and CI 95% (0.0021–0.0568).

Discussion

Raloxifene increases total bone density, especially at the spine. Some authors indicate increase of the bon density at the hip as well[13–16]. Results of our research were similar to those of earlier conducted research. We detected a slight improvement of the BMD at the hip and forearm. During the period of the study we detected no fractures of the hip. In the study group we have registered 9 and in the control group 10 fractures of the forearm, which difference was not statistically significant. In this age group of our examinees we found no fractures of the spine, probably due to raloxifene therapy. Monitoring the effects of these therapies in a longer period of time probably would have shown significant difference between vertebral and non-vertebral fractures. Significant differences of the efficiency of preventing fractures weren't and could not have been detected due to the younger age of women in study group.

Raloxifene improved significantly spine bone density. A 2.4% increase in BMD at the lumbar spine and hip and a 2% increase in total bone mass following 2 years of therapy was previously reported[14]. Etinger et al.[15] found a 2.6% increase in BMD at the spine and a 2.1% increase in BMD at the hips following 36 months of therapy. Zheng et al.[16] found an increase of 2.3% in BMD at the spine and 2.5% at the hip area. Our results were consistent with most of these previously conducted studies on Caucasian or Asian women.

Our study showed insignificant positive effects of vitamin D and calcium therapy on the spine only, while a decrease in bone density at hip and forearm was revealed. However, the BMD decrease at forearm was lower among this group of women. Evidence by other researchers has shown how intake of calcium and vitamin D prevented the risk of bone density decrease at all areas[17].

Our study had several limitations, the most important of them being the case-control design of the study. More relevant data, with possibility of definite conclusion could be yielded through a prospective randomized study. However, our place of work lacks organization and financial potentials for that kind of investigation. It would also be interesting to prospectively investigate the risk of fractures in these two groups of women.

Irrespective of age, raloxifene has advantages in patients who have a higher risk of breast and endometrial cancer, as well as those with medium hypercholesterolemia[10]. Raloxifene therapy is the good solution for both treatment and prevention of early postmenopausal osteoporosis**.**

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UTJECAJ RALOKSIFENA NA PROMJENE KOŠTANE GUSTOĆE

S A Ž E T A K

Kroz dvije godine je uspoređen utjecaj raloksifen hidroklorida (raloksifena) na promjenu koštane gustoće (BMD) u odnosu na kalcij i vitamin D3. »Case control« studija je obuhvaćala dvije skupine po 254 žene, od kojih su jedne kroz 2. godine uzimale raloksifen, kalcij i vitamin D3, a druge samo kalcij i vitamin D3. Koštana gustoća je mjerena na kuku, kralješnici i podlaktici na početku i nakon 2. godine terapije. Tretman raloksifenom je povećao koštanu gustoću za 3,7% na kralješnici kod 98% ispitanica. Povećanje gustoće na kuku je bilo 1,2% kod 75% ispitanica. Pad koštane gustoće je bio za 1,2% na podlaktici kod 93% ispitanica uz raloksifen. Terapija kalcijem i vitaminom D3 je povećala koštanu gustoću kod 58% ispitanica na kralješnici, 56% na kuku i 38% na podlaktici što je značajno niže u odnosu na skupinu liječenu raloksifenom. U skupini liječenoj kalcijem i vitaminom D3 zabilježen je prosječni pad koštane gustoće na kralješnici za 1,2% kod 42% ispitanica, na kuku za 2,6% kod 46% ispitanica te za 4,2% na podlaktici kod 35% ispitanica. Terapija raloksifenom značajno povećava koštanu gustoću na kralješnici (OR 5.85, $p<0.05$) u odnosu na terapiju samo kalcijem i vitaminom D3. Nema statističke značajnosti u povećanju koštane gustoće na kuku (OR 0.015) ni podlaktici (OR 0,122).