

Treatment of Established Osteoporosis in Postmenopause

POSTMENAPOZAL HASTALARDA YERLEŞMİŞ OSTEOPOROZİS'İN TEDAVİSİ

Bilge ŞENER*, Serdar OĞUZ*, İlker GÜNYELİ*, İclal ÇETİNDAG*

* Zekai Tahir Burak Woman Health Education and Research Hospital, Ankara, TURKEY

Summary

Objective: In this prospective open randomized study, we tried to determine the effectiveness of different treatment modalities in established osteoporosis in postmenopausal women.

Materials and Method: This study was conducted for one year at Zekai Tahir Burak Woman Health Education and Research Hospital Ankara Turkey. 104 women with established osteoporosis enrolled into the study at Menopause Clinic between June 1998-February 1999. Before the treatment, all patients undergone a diagnostic bone-density scan. The lumbar spine bone mineral density measurements of the patients in the study group was -2.5 SD below of T-score. We generate randomization numbers by a computer and we allocate the patients into three groups according to the treatment modalities. Group-I comprising of 39 women, received conjugated estrogen 0,625 mg/daily+ medroxyprogesterone acetate 2,5 mg/daily and elemental calcium 1000 mg/daily continuously for one year. Group-II comprising of 35 women received continuously intranasal calcitonin 200 IU/daily and elemental calcium 1000 mg/day for one year. Group-III comprising of 30 patients received both treatments together. 29 patients discontinued the treatment and 75 patients completed one year treatment period. Bone mineral densities were evaluated before the therapy and at the end of the one year treatment and a comparison was made among the three groups.

Results: In Group -I, the mean BMD of lumbar spine was reduced 0.04 ± 0.05 % but on the other hand the mean BMD of lumbar spine was increased 0.04 ± 0.03 % in Group-II and 0.07 ± 0.04 % in Group-III.

Conclusion: It was concluded that in established osteoporosis calcitonin has the ability to increase BMD at lumbar spine eventhough no statistically significant difference was detected between the three treatment modalities.

Key Words: Established osteoporosis,
Bone mineral density,
Hormone replacement therapy,
Calcitonin, Calcium

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Özet

Amaç: Biz, bu prospektif randomize çalışmada postmenapozal kadınlarda yerleşmiş osteoporozis'in tedavisinde farklı tedavi modalitelerinin etkinliği araştırdık.

Materyal ve Metod: Bu çalışma Zekai Tahir Burak Kadın Sağlığı Eğitim ve Araştırma hastanesinde yaklaşık 1 yıllık bir sürede organize edilmiştir. Haziran 1998 ve Şubat 1999 tarihleri arasında menapoz kliniğine başvuran ve yerleşmiş osteoporozis tanısı konulan 104 postmenapozal kadın çalışmaya dahil edildi. Tedavi öncesinde tüm hastalara tanısal amaçlı kemik dansite taraması yapıldı. Çalışmaya alınan hastaların, lomber vertebra kemik mineral dansite ölçümlerinde; T skorları - 2,5 SD'nin altındaydı. Hastalar bilgisayar kayıtlarından randomize olarak seçilip tedavi modalitelerine göre 3 gruba ayrıldı. Grup 1 hastalar : 0,625 mg/gün konjuge östrojen ve 2,5 mg/gün Medroksiprogesteron asetat ve bunlara ilaveten 1 yıl boyunca 1000 mg/gün elementer Ca alan 39 hastadan oluşmaktadır. Grup 2 hastalar continue şekilde 200 IU/gün intranasal kalsitonin'e ilaveten 1000mg/gün elementer Ca alan 35 hastadan oluşmakta ve son olarak Grup 3 hastalarda her 2 tedavi protokolünü alan 30 hasta çalışmaya dahil edildiler. Çalışmaya katılan hastalardan 29 'u tedaviyi yarıda bırakırlarken kalan 75 hasta 1 yıllık tedavi protokolünü tamamlamışlardır. Kemik mineral dansiteleri tedavi öncesi ve 1 yıllık tedaviyi takiben değerlendirildi ve bu 3 grup arasında karşılaştırma yapıldı.

Sonuçlar: Grup I hastalarda lomber vertebranın ortalama BMD'sinde azalma saptanırken ($0,04 \pm 0,05$ %) diğer taraftan Grup II hastalarda ($0,04 \pm 0,03$ %) hastalarda ve Grup III hastalarda ($0,07 \pm 0,04$ %) lomber vertebra ortalama BMD'sinde artma saptandı.

Tartışma: Her ne kadar yerleşmiş osteoporozisli hastalarda kalsitonin, lomber vertebra BMD'sini arttırmada oldukça başarılı bulunmuş olsada her 3 grup arasında istatistiksel olarak anlamlı bir fark tespit edemedik.

Anahtar Kelimeler: Yerleşmiş osteoporoz,
Kemik mineral dansitesi,
Hormon replasman tedavisi,
Kalsitonin, Kalsiyum

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Osteoporosis is a disorder of decreased bone mass, microarchitectural deterioration, and fragility fractures. Osteoporosis is perhaps the widest-ranging social, physi-

cal, and economic impact of estrogen deficiency and a major age-related disease affecting millions of people throughout the world, especially women (1). An essential

element in preventing osteoporosis is the achievement of normal peak bone mass. Postmenopausal bone loss is the major determinant of osteoporosis. A loss of one standard deviation gives rise to enhanced twofold risk of spine fractures or a 2.5 fold risk of hip fracture (2). Medical treatment of woman with established osteoporosis may decrease the incidence of future fractures. As people live longer, age-related diseases increasingly present problems.

Osteoporosis complicated by fracture is a condition that is difficult and often disappointing to treat. It is therefore important to identify and treat the women with established osteoporosis before the disorder has reached a more advanced stage (3)

Riggs and Melton have suggested that women at high risk may be identified through an analysis of risk factors for osteoporosis and that these patients should then have further studies, including measurements of bone mass (4).

It is not yet certain whether or not there is any effective treatment once established osteoporosis has been diagnosed (1). In this condition, the ideal therapy should stimulate bone formation and increase bone mass sufficiently to decrease the occurrence of new fractures (5).

Estrogen therapy is the drug of choice for preventing bone loss in women after the menopause. Estrogen, by inhibiting bone resorption, reduces bone loss at all skeletal sites. The effects of estrogen persist as long as the therapy continues (5).

Calcitonin decreases further bone loss at vertebral and femoral sites in established osteoporosis but its effect on fracture frequency has not been published. The effect of calcitonin is greater in patients with high turnover osteoporosis (5).

The importance of an adequate calcium intake at all stages of life is well established. However, a high calcium intake will not substitute for estrogen therapy in blunting the accelerated bone loss during the climacteric period. Maintenance of an adequate calcium intake is also necessary in elderly subjects (5). Women with low bone mass, high urinary bone collagen breakdown products, and/or major risk factors should consider hormone replacement therapy or a selective estrogen receptor modulator, or antiresorptive agents such as calcitonin and bisphosphonates.

The purpose of our study was to evaluate the results of treatments in established osteoporosis with three main modalities. The study enrolled 75 patients in whom the bone mineral densities were detected before and after one year of treatment.

Materials and Methods

Between June 1998-June 1999, 975 bone mineral densitometric measurements in spontaneous and surgical

postmenopausal women were performed at Zekai Tahir Burak Woman Health Education and Research Hospital Menopause Center. When the patients had a -2.5 SD below T-score than they were diagnosed as established osteoporosis. 123 established osteoporotic women were detected. Of these 19 women were excluded from the study because of a malignant, gastrointestinal, metabolic disease or a drug intake that is known to affect calcium metabolism. 104 women were informed verbally in accordance with Helsinki Declaration II and all gave their informed consent. 8 patients from the first group, 11 patients from the second group discontinued their treatments because of the cancer fear and 10 patients from the third group excluded from the study because they did not use their medicines regularly with the recommended dose and they skipped their control visits. 75 patients completed the one year treatment programme.

After an initial examination, the women were randomly allocated to one of the three treatment groups by a computer.

Group- I: Conjugated estrogen (CE) 0,625 mg (Premarin) + Medroxyprogesterone acetate (MPA) 2,5 mg (Farlutal) + 1000mg calcium (Calcium Sandoz) daily continuously.

Group-II: Nasal Calcitonin (Miacalcic) 200 IU/daily, with one puff in the morning and one before bedtime and 1500mg calcium daily continuously. (In order to check compliance, the patients were asked to bring their used bottles at each visit).

Group- III: Conjugated estrogen (CE) 0,625 mg + MPA 2,5 mg + Nasal calcitonin as mentioned above and 1000mg calcium daily continuously

1000 mg. Calcium carbonate was prescribed to the women in Group-I, while 1500 mg. calcium carbonate was given to Group-II because they did not receive any hormonal replacement.

Initial clinical data of the three treatment groups are shown in Table 1.

No significant differences were found as regards of median age, body mass index in the three groups prior to the treatment.

The initial examination of the patients did not reveal any significant clinical, radiographic, biochemical differences among the three treatment groups.

The bone mineral contents of the lumbar spine were detected in all of the patients before and after one year of treatment using a X-ray densitometer (HOLOGIC-QDR-1000TM). The bone mineral density of the spine were calculated in vertebra L₂, L₃, L₄ (6).

Table 1. Initial clinical data in three treatment groups

Mean±SD	Group-I (n=29)	Group-II (n=29)	Group-III (n= 17)	P
Age (year)	53,8±0,5	55,8±0,9	53,9±0,8	NS
BMI (Body mass index)	41,4±0,8	44,3±1,4	43±1,3	NS
Years since menopause	7,3±0,6 ^a	8,5±1,2	7,9±1,4	=0,01
Gravidity	5,7±0,7	5,2±0,6	2,9±0,4	NS
Parity	3,4±0,5	2,8±0,3	2,9±0,4	NS
Abortus	1,6±0,4	1,9±0,3	1±0,5	NS
D&C	0,5±0,2	0,4±0,3	1,4±0,8	NS
BMD (g/cm ²)	0,842±0,046 ^b	0,798±0,024	0,725±0,033	<0,05

a= Group-I vs. Group-II

b= Group-I vs. Group-III

Table 2. Ca⁺⁺ and P levels before and after the treatment

Mean±SD	Group-I	Group-II	Group-III	P
Ca ⁺⁺ (mg/dl) (before treatment)	9,4±0,2	9,4±0,4	9,4±3	NS
Ca ⁺⁺ (mg/dl) (after treatment)	9,3±0,3	9,3±0,3	9,2±0,4	NS
P (mg/dl) (before treatment)	3,5±0,6	3,5±0,5	3,2±0,9	NS
P (mg/dl) (after treatment)	3,5±0,8	3,5±0,7	3,4±0,7	NS

Table 3. Alkaline phosphatase and fU Hpr/Cr levels before and after the treatment

Mean±SD	Group-I	Group-II	Group-III	P
Alk. phos. (U/L) (before treatment)	172±12	178±10	176±13	NS
Alk. phos. (U/L) (after treatment)	180±10	176±12	180±11	NS
FU Hpr/Cr (mg/g) (before treatment)	30,4±1,0	34,0±1,6	33,0±1,1	NS
FU Hpr/Cr (mg/g) (after treatment)	28,0±1,0	30,8±1,0	30,2±1,1	NS

Estradiol (E₂) levels were measured with double antibody RIA method by using RSL direct 1-125 estradiol 17 β kits (ICN Biomedicals, Inc. Diagnostics Division. USA).

Serum calcium was measured by atomic absorptiometry and the serum phosphate by photometry. Serum alkaline phosphatase was measured enzymatically, according to Scandinavian recommendations (7). Fasting urinary hydroxyproline was measured by spectrophotometry and corrected for creatinine excretion.

The significances of differences within groups during the one year period were tested using student's t-test for paired data whereas changes between groups were tested by one-way analysis of variance. A p-value lower than 0,05 was considered significant.

The average changes per year were calculated by accumulating all values after starting to the treatment.

Results

No differences in serum calcium, phosphorus, alkaline phosphatase and fasting urine hydroxyproline were

observed among three treatment groups at the end of the study. (Table 2,3)

In Group-I, the mean BMD of lumbal spine was reduced 0,04±0,05% and was increased 0,04±0,03% in Group-II. and 0,07±0,04% in Group-III. But there was no significant difference in any of the treatment modalities (Table 4).

In our study, in group-I and group-III, the estradiol levels were 12,5±1,8 pg/ml. and 21,7±6,5 pg/ml. respectively at the beginning of the treatment. At the end of one year of the treatment they were found to be 90±7,4 pg/ml. and 90,8±19,8 pg/ml. respectively (Table 5).

Discussion

Postmenopausal osteoporosis is a disorder characterized by reduced amounts of bony tissue per unit volume of bone and by increased susceptibility to fractures. Osteoporosis and its associated problems are common clinical disorders and a major public health problem in all over the world, affecting as many as one out of two women in aged population.

Table 4. BMD levels before and after the treatment

Mean±SD	Group-I	Group-II	Group-III	P
BMD (g/cm ²) (before treatment)	0,842±0,046	0,798±0,024	0,725±0,033	S
BMD (g/cm ²) (after treatment)	0,831±0,021	0,825±0,030	0,766±0,027	NS
BMD difference	-0,010±0,047	+0,026±0,028	+0,040±0,030	NS
BMD ↑ (%)	-0,04±0,05	0,04±0,03	+0,07±0,04	NS

Table 5. E₂ levels before and after the treatment

Mean±SD	Group-I	Group-II	Group-III	P
E ₂ (pg/ml) (before treatment)	12,5±1,8 ^a	-	12,5±1,8 ^a	NS
E ₂ (pg/ml) (after treatment)	90,0±7,4	-	90,8±19,8	NS
E ₂ difference	+77,4±7,6	-	+69,1±21,7	NS
E ₂ ↑ (%)	9,3±1,2	-	11,6±6,6	NS

a= before vs.after p<0.05

The high frequency of falls in advanced age contributes significantly to the likelihood of hip and other fractures in the elderly. Spine fractures are common causes of pain, deformity, loss of height and disability. Osteoporosis affects approximately 28 million Americans and costs about 14 billion a year (8). The treatment of osteoporosis is still a challenge (9). Important principles of management are still considered to be maximizing peak bone mass and prevention of postmenopausal bone loss by estrogen replacement therapy (10,11,12) and if the therapy is started early enough, it will clearly decrease bone turnover and significantly reduce the number of fractures later in life (13-15). Some studies indicate that one year of treatment with estrogen+progesterone increases bone mass in postmenopausal osteoporotic women (16). But due to the potential long-term adverse effect and to negative attitudes toward estrogen therapy, it is not acceptable by all women. Furthermore many women would find it inconvenient to start estrogen therapy 8 to 10 years after menopause. Calcitonin may, therefore be suitable as an alternative treatment for these women (17) where it has an excellent long-term safety record, but its effectiveness in preventing fracture remains to be fully demonstrated (18).

In some osteoporotic patients, a calcitonin regimen produces a substantial increase in bone mass and arrests vertebral deterioration (19,20). In others, there may be a delayed skeletal response, with a decrease in the annual rate of bone loss but no increments in bone mass demonstrable for 18 to 24 months (21).

Chesnut et al reported that the use of 200-IU dose of salmon calcitonin nasal spray significantly reduced the risk of new vertebral fractures by 33% compared with placebo. They also pointed out significant lumbar spine bone mineral density increase from baseline (22). In our study, the

three groups did not differ significantly in any of the initial values. After 1 year of treatment there were minimal increases in group-II and group-III and a minimal decrease in group-I, whereas the changes were not significant. We think that the different results of this two studies could arise from the selection of the patients and treatment duration. The degree of osteoporosis of patients enrolled in the study, the duration of established osteoporosis, the time between the menopause and the onset of the treatment seemed to be the major factors in determining the answer of the treatment. On the positive side calcitonin may have analgesic effects separate from its effects on bone remodelling (23).

In osteoporotic patients who have a reduced bone mass, the aim of therapy must be not only the prevention of further bone loss but also the restoration of bone mass previously lost.

Therapeutic agents such as oral calcium, calcitonin and estrogen primarily inhibit bone resorption. Each of these agents, when given as the sole therapy, presumably, has primarily a prophylactic benefit of preventing bone loss rather than a restorative value of replacing bone mass previously lost. Conversely, severe osteoporosis can be satisfactorily treated with combinations of drugs (9).

The dose of estrogen appears to be the factor that determines whether or not skeletal effects will be seen. Circulating estradiol levels between 50 and 100 pg/ml. appear to be sufficient to reduce bone turnover. Such levels are seen after treatment with conjugated equine estrogen 0,625 mg/day or transdermal estrogen 50 µg/day.

It is often believed that when 20% of the bone mass has been lost the fracture risk increases seriously. Women with a moderate degree of osteoporosis with a BMD averaging 25% below that of premenopausal women may be a

more realistic target group for treatment (24). This might be the reason why we did not find any significant increase in BMD.

We can say that nasal calcitonin might be effective alternative for treatment of established osteoporosis when HRT is contra-indicated or when there is reluctance to use hormonal treatment. The prevention and treatment plan should be individualized for each patient, taking into account personal preferences, risk factors for osteoporosis and fracture, concomitant diseases and drug therapies, efficacy and tolerance of osteoporosis therapy, quality of life, life expectancy, finances, and health insurance coverage.

We concluded that all three treatment modalities prevented bone loss furthermore, but they did not increase the bone mass significantly. We believe that the bone mineral density should be measured at beginning of the menopause and if its below the normal level, early and effective treatment modalities must be given to these women as early as possible and sustain over a long period. This may be a more realistic therapy.

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Yazışma Adresi: Dr.Serdar OĞUZ

Dr.Zekai Tahir Burak Kadın Hastalıkları ve
Doğumevi Eğitim ve Araştırma Hastanesi, ANKARA
oguzjs@yahoo.com