Reproductive Medicine; *Endocrinology and Infertility*

Effectiveness of Different Treatment Modalities in Postmenopausal Women with Osteopenia and Osteoporosis

Berfu DEMİR[1], Enis ÖZKAYA[1], Nilgün ÖZTÜRK[2], Burak KARADAG[1], Ali HABERAL[1]

Ankara, Turkey

OBJECTIVE: The aim of this study was to evaluate the efficacy of different antiresorptive agents and hormone therapy (HT) on T score and to compare their effectiveness with each other.

STUDY DESIGN: Medical records of 1073 postmenopausal women were reviewed. Patients were classified into four groups; hormone therapy, antiresorptive therapy (AT), combined HT and AT and control. Groups were evaluated with their response to treatment modality by measuring the changes on T score. Also, patients of HT and AT groups were compared with each other according to the effectiveness of the treatment on T score changes.

RESULTS: Treatment related increase in T score was significantly different in HT-AT and AT groups compared with the HT group (P=0.001, P=0.001). Within the HT group (estrogen: 170, estrogen-progestin: 234, tibolone: 136) the alteration on T score was statistically significant compared to the control group (P=0.001, P=0.001, P = 0.001). Within the AT group (etidronate: 165, alendronate: 94, risedronate : 11, calcitonin: 10) all agents were significantly different compared to the control group according to the alterations on T score (P=0.001, P=0.001, P=0.001, P = 0.001). When the change in T score was compared, the alendronate group was significantly different than the etidronate group (P=0.001).

CONCLUSION: Hormone therapy combined with AT and AT alone was found to be superior to HT in terms of increments in T score values in postmenopausal women with osteopenia and osteoporosis.

Key Words: Menopause, Bone mineral density, Hormone therapy, Antiresorptive treatment

Gynecol Obstet Reprod Med;15:3 (153 - 156)

Introduction

Osteoporosis is a chronic and progressive disorder in which both environmental and genetic factors play role. In this disorder, having more osteolysis than osteogenesis causes abnormality in micro-architecture of bone, and results in a decrease in bone mass.[1] Osteoporosis is an asymptomatic state which may cause important morbidities and even may result in mortality. Low bone mineral density (BMD) is an independent risk factor for subsequent fracture.[2] Risk for spine fracture increases 2.3-fold for each decrease of 1 SD in age-adjusted BMD at spine.[3]

Type and duration of therapy are as important as diagnosis of osteoporosis. Estrogen deficiency in both surgical and spontaneous menopause is the major risk factor in osteoporosis development.

Bisphosphonates are accepted antiresorptive agents that are widely used for the treatment of postmenopausal osteoporosis. Etidronate is the first generation bisphosphonate. It is classified as nonnitrogen containing bisphosphonate according to the new classification. The advantage of this treatment is its cost-effectiveness and sequential use. Alendronate and risedronate are nitrogen containing bisphosphonates. Alendronate sodium, a second generation bisphosphonate and antiresorptive agent, was developed as an intervention to reduce vertebral and nonvertebral fractures in postmenopausal women.[4] Risedronate is a third generation bisphosphonate with antiresorptive activitiy, decreases vertebral and nonvertebral fracture risk in postmenopausal osteoporosis.[5]

Salmon calcitonin is one of the first available antiresorptive agents. However, improvement on BMD is less pronounced with calcitonin compared to bisphosphonates. It was found to be effective only in lumbar spine BMD.[6]

Tibolone is a steroid hormone and its three metabolites have estrogenic, gestagenic and weak androgenic effects on the different target organs. As expected, there is an increase of BMD comparable to that of HT.[7]

[1]Department of Obstetrics and Gynecology, Etlik Zübeyde Hanım Maternity & Women's Health Teaching and Research Hospital, Ankara

[2]Department of Obstetrics and Gynecology, İzmit Acıbadem Hospital, İzmit

Address of Correspondence: *Berfu Demir*
ODTU Lojmanları 34/4
Orta Dogu Teknik Universitesi
Ankara
demirs@isbank.net.tr

Submitted for Publication: *23.07.2009*
Accepted for Publication: *14.08.2009*

The aim of this study was to evaluate the efficacy of different antiresorptive agents and HT on T score changes and to compare their effectiveness with each other. T score changes were measured by BMD.

Material and Method

One thousand and seventy-three postmenopausal women who were followed in menopause outpatient clinic were included in the study. All cases were evaluated according to age, type of menopause whether spontaneous or surgical, years on menopause, treatment modality and its duration. Women who had amenorrhea for one year and women with previous history of bilateral oophorectomy were accepted as menopause. Women were evaluated to confirm menopause with their initial hormone levels; low estradiol (E_2 <25 pg/ml) and high follicle stimulating hormone (FSH >40 mIU/ml) serum levels.

Bone mineral density was measured anteroposteriorly at the level of L1-L4 by DXA method by Hologic 4500 QDR (Discovery). According to WHO criteria T score value lower than -2.5 SD and -1 to -2.5 SD were accepted osteoporosis and osteopenia, respectively.

Participants were divided into four groups according to treatment modalities: HT, antiresorptive therapy, combined HT and AT and control. Hormone therapy group was divided into three subgroups: Estrogen only (n=170), estrogen-progesterone group (n=234), and tibolone group (n=136). Also, antiresorptive therapy group were divided into four subgroups: etidronate group (n=165), alendronate group (n=94), risedronate group (n=11), calcitonin group (n=10).1000 mg elementary calcium and 800 IU vitamin D supplementation were given to all groups. Groups were evaluated with their response to treatment modality by measuring the changes on T score value. Also, patients with HT and AT were compared within each other according to their effectiveness on T score changes.

Result

Baseline and demographic characteristics were comparable in all four groups (Table 1). Duration of hormone therapy and bisphosphonate treatment were 21.8 months (10-160), and 11.2 months (8-107), respectively.

The treatment related increase in T score was significantly different in HT-AT and AT groups compared with the HT group (P=0.001, P=0.001). When HT-AT and AT groups were compared the change in T score was not statistically different (P=0.157) (Table 2).

Hormone therapy group was divided into three subgroups: Estrogen only (n=170), estrogen-progesterone group (n=234), and tibolone group (n=136). All treatment groups showed significantly different changes on T score compared with the control group (Estrogen group P=0.001, estrogen-progesterone group P=0.001, and tibolone group P=0.001) (Table 3).

Antiresorptive therapy group was divided into four subgroups: etidronate group (n=165), alendronate group (n=94), risedronate group (n=11), calcitonin group (n=10). All treatment groups showed significantly different changes on T score compared with the control group (etidronate group P=0.001, alendronate group P=0.001, risedronate group P=0.001, calcitonin group P=0.001). When all AT subgroups were compared with each other, only the T score change in the alendronate group was significantly different compared to the etidronate group (P=0.001) (Table 3).

Table 1: Baseline characteristics of control and treatment groups

	Control (n = 253)	HT (n = 540)	ART (n = 46)	HT+ART (n= 234)
Age (year)	48.4 ± 3.9	48.3 ± 3.9	47.8 ± 4.9	47.2 ± 5.1
Parity	3.0 (0-10)	3.0 (0-9)	4.0 (0-10)	4.0 (0-15)
Years since menopause	2 (0-16)	3.0 (0-25)	4.0 (0-29)	4.0 (0-25)
Menopause type				
Surgical	61 (24)	140 (26)	12 (26)	59 (25)
Natural	192 (76)	400 (74)	34 (74)	175 (75)
BMI (kg/m^2)	28.5 ± 4.1	29.2 ± 4.6	27.9 ± 4.6	28.0 ± 4.1
Smoking	45 (18)	75 (14)	4 (8)	28 (12)

Data are expressed as n (%), mean ± standard deviation, or median (min-max)

Table 2: Changes on T score value in control and treatment groups

T score value	Control (n = 253)	HT (n = 540)	ART (n = 46)	HT+ART (n = 234)
Pretreatment	-2.30±1.74	-0.64±1.02	-2.34±1.14	-2.12±1.04
Posttreatment	-2.20±1.06	-0.75±0.96	-2.30±0.82	-1.99±0.91

Data are expressed as mean ± standard deviation

Table 3: Effects of different agents on T score value

Treatment agents	T score value	
	Baseline	Posttreatment
Estrogen+progesterone (n= 234)	-1.39±1.23	-1.31±1.17
Estrogen (n=170)	-1.10±1.23	-1.22±1.07
Tibolone (n=136)	-1.30±1.36	-1.32±1.14
Etidronate (n=165)	-1.96±0.95	-1.90±0.87
Alendronate (n=94)	-2.49±1.16	-2.29±0.88
Risedronate (n=11)	-2.50±0.64	-2.15±0.73
Calcitonin (n=8)	-1.80±1.23	-2.05±1.48

Data are expressed as mean ± standard deviation

Discussion

In this study, the effectiveness of different treatment modalities were compared by measuring changes on T score values. The advantage of this study is the large number of patients with seven different treatment modalities, including combinations of some, assessed with

their responses to treatments. It is shown that patients' T score values with HT, AT and HT-AT increase significantly after treatment compared to control group. In the subgroup analysis, except for the alendronate group compared with the etidronate group, no significant difference in T score values was observed.

After 2 to 5 years HT resulted in an increase in BMD 3.5 to 6.8% at lumbar spine.[8,9,10] Hormone therapy improves bone density and reduces bone fractures, however positive effect of HT on bone loss seems to come out when the treatment is administered at menopause and for a continuous period of time.[11] The effect of HT is restricted to the period of estrogen use and disappears when it is stopped.[12]

Alendronate 10 mg/day, compared to control has been shown to increase BMD after two to three years of treatment, by 5.6% (95% CI 4.8 to 6.39) in the lumbar spine.[13] For vertebral fractures, a significant 45% relative risk reduction (RRR) was found (RR 0.55, 95% CI 0.45 to 0.67). This result was statistically significant for both primary prevention with 2% absolute risk reduction and secondary prevention with 6% absolute risk reduction. Also, statistically significant reductions in nonvertebral, hip and wrist fractures were observed for secondary prevention.[14]

Risedronate treatment 5 mg/day, relative to control, presented an increment on BMD after 1.5 to three years of treatment by 4.54% (95% CI 4.12 to 4.97) in the lumbar spine.[15] Risedronate treatment 5 mg/day has been associated with a statistically significant reduction for vertebral fractures with 39% RRR (RR 0.61 95% CI 0.50 to 0.76). Absolute risk reduction is 5%. Also, statistically significant antifracture efficacy was observed in nonvertebral and hip areas.[16]

Etidronate, relative to control, increased bone density after three years of treatment in the lumbar spine by 4.06% (95% CI 3.12 to 5), in the femoral neck by 2.35% (95% CI 1.66 to 3.04) 17. For Etidronate, a significant relative risk reduction of 47% in vertebral fractures (RR 0.53, 95% CI 0.32 to 0.87) and a 5% absolute risk reduction were demonstrated.[18]

Calcitonin treatment resulted in an increase of BMD in the lumbar spine by 3%19. Antifracture efficacy was observed only in the vertebrae.[20]

Combined therapy alendronate or risedronate and HT has shown a favorable effect on BMD compared with either agent alone.[21,22] However, HT combined with bisphosphonate should be considered in women who had a new fracture or significant bone loss under ongoing HT.[23]

The disadvantage of this study is that the data of antifracture efficacy is not presented. Another disadvantage may be the heterogeneity of baseline T score values in groups and subgroups; even though the changes are compared in the study, baseline states of patients may affect the response.

According to the results of this study, HT-AT and AT alone were found to be superior to HT alone with respect to increments in T score values in postmenopausal women with osteopenia and osteoporosis.

Postmenopozal Osteopeni ve Osteoporoz Tedavisinde Farklı Tedavi Modalitelerinin Etkinliği Çalışması

AMAÇ: Farklı antirezorptif ajanların ve hormon tedavisinin (HT) T skoru üzerine etkisi araştırıldı.

GEREÇ VE YÖNTEM: Postmenopozal 1073 hasta çalışmaya dahil edildi. Hastalar aldıkları tedavilere göre HT, antirezorptif, HT ve antirezorptif tedavi kombine ve kontrol grubu olarak dört gruba ayrıldılar. Tedaviye yanıt T skorundaki değişimle değerlendirildi. Ayrıca hormon tedavisi ve antirezorptif tedavi grubunda alt grup analizi yapıldı.

BULGULAR: Antirezorptif ve kombine tedavi alan grupta HT grubuna kıyasla anlamlı fark saptandı (P = 0.001, P = 0.001). Hormon tedavisi (östrojen:170, östrojen-progestin: 234, tibolon:136) grubunda kontrol grubuna göre T skorundaki değişim anlamlı idi (P = 0.001, P = 0.001, P = 0.001). Antirezorptif tedavi (etidronat: 165, alendronat: 94, risedronat:11, kalsitonin: 10) alan grupta da kontrol grubuna göre anlamlı değişim saptandı (P = 0.001, P = 0.001, P = 0.001, P = 0.001) . Alt grup analizinde T skorundaki değişim sadece alendronat ve etidronat arasında bulundu (P=0.001).

SONUÇ: Postmenopozal osteopeni-osteoporozlu olgularda, hormon tedavisi ve antirezorptif tedavi kombinasyonu tek ajan tedaviye kıyasla T skoru üzerinde daha etkilidir.

Anahtar Kelimeler: Menopoz, Kemik mineral densitesi, Hormon replasmanı, Antirrezorptif tedavi

References

1. NIH Consensus Development panel on Osteoporosis Prevention, Diagnosis, and Therapy. Osteoporosis prevention, diagnosis, and therapy JAMA 2001; 285: 785-95
2. Ng MYM, Sham PC, Paterson AD, Chan V, Kung AWC Effect of environmental factors and gender on the heritability of bone mineral density and bone size. Annals of Human Genetics 2006; 70: 428-438
3. Marshall D, Johnell O, Wedel H Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ 1996; 312:1254-1259
4. Cranney A, Wells G, Willan A, Griffith L, Zytaruk N, Robinson V, Blavk D, Adachi J, Shea B, Tugwell P, Guyatt G Metaanalysis of Alendronate for the treatment of postmenopausal women. Endocrine Reviews 2002; 23(4): 508-516
5. Reginster JY. Prevention postmenopausal osteoporosis

with pharmacological therapy: practice and possibilities. J Int Med 2004; 255: 615-628

6. Chesnut CH 3rd, Azria M, Silverman S, Engelhardt M, Olson M, Mindeholm L Salmon calcitonin: a review of current end future therapeutic indications. Osteoporosis Int 2008; 19: 479-91
7. Von Holst T Alternatives to hormone replacement therapy: raloxifene and tibolone. Z Arztl Fortbild Qualitatssich 94(3): 205-9
8. Wells G, Tugwell P, Shea B, Guyatt G, Peterson J, Zytaruk N, Robinson V, Henry D, O'Connell D, Cranney A (2002) Meta-analyses of therapies for postmenopausal osteoporosis. V. Meta-analysis of the efficacy of hormone replacement therapy in treating and preventing osteoporosis in postmenopausal women. Endocr Rev 2000; 23:529-539.
9. Effects of hormone therapy on bone mineral density: results from the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial. The Writing Group for the PEPI. JAMA 1996; 276:1389-1396.
10. Cauley JA, Robbins J, Chen Z, for the Women's Health Initiative Investigators. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. JAMA 2003; 290:1729-1738.
11. Torgerson DJ, Bell-Syer SE Hormone replacement and prevention of nonvertebral fractures. J Am Med Assoc 2001; 285: 2891-2897
12. Tremollieres FA, Pouilles JM, Ribot C Withdrawal of hormone replacement therapy is associated with significant vertebral bone loss in postmenopausal women. Osteoporos Int 2001; 12:385-390.
13. Cranney A, Wells G, Willan A, Griffith L, Zytaruk N, Robinson V, Black D, Adachi J, Shea B, Tugwell P, Guyatt G Meta-analysis of therapies for postmenopausal osteoporosis. II. Meta-analysis of alendronate for the treatment of postmenopausal women. Endocrine Rev 2002; 23(4): 508-16
14. Wells GA, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, Coyle D, Tugwell P Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women Cochrane Database Syst. Rev. 2008; 23(1)
15. Cranney A, Tugwell P, Adachi J, Weaver B, Zytaruk N, Papaicannou A, Robinson V, Shea B, Wells G, Guyatt G. Meta-analysis of therapies for postmenopausal osteoporosis. III. Meta-analysis of risedronate for the treatment of postmenopausal women. Endocrine Rev 2002; 23(4): 517-23
16. Wells GA, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, Coyle D, Tugwell P Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women Cochrane Database Syst. Rev. 2008; 23(1)
17. Cranney A, Guyatt G, Krolicki N, Welch V Griffith L, Adachi JD A meta-analysis of etidronate for treatment of postmenopausal osteoporosis. Osteoporosis Int 2001; 12(2): 140-51
18. Wells GA, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, Coyle D, Tugwell P Etidronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women Cochrane Database Syst. Rev. 2008; 23(1)
19. Overgoard K, Riis BJ, Christiansen C, Podenphant J, Johansen JS Nasal calcitonin for treatment of established osteoporosis. Clin Endocrinol 1989; 30: 435-42
20. Chesnut CH 3rd, Silverman S, Andriano K, Genant H, Gimona A, Harris S, Kiel D, LeBoff M, Maricic M, Miller P, Moniz C, Peacock M, Richardson P, Watts N, Baylink D. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the Prevent Recurrence of Osteoporotic Fractures Study. PROOF study group. Am J Med 2000; 109:267-276.
21. Bone HG, Greenspan SL, McKeever C, Bell N, Davidson M, Downs RW, Emkey R, Meunier PJ, Miller SS, Mulloy AL, Recker RR, Weiss SR, Heyden N, Musliner T, Suryawanshi S, Yates AJ, Lombardi A. Alendronate and estrogen effect in postmenopausal women with low bone mineral density. Alendronate/Estrogen Study Group. J Clin Endocrinol Metab 2000; 85:720-726.
22. Harris ST, Eriksen EF, Davidson M, Ettinger MP, Moffett Jr AH Jr, Baylink DJ, Crusan CE, Chines AA. Effect of combined risedronate and hormone replacement therapies on bone mineral density in postmenopausal women. J Clin Endocrinol Metab 2001; 86:1890-1897.
23. Pinkerton JV, Dalkin AC Combination therapy for treatment of osteoporosis: A review. Am J Obstet Gynecol 2007; 197(6): 559-565