TREATMENT OF OSTEOPOROSIS IN PATIENTS WITH RHEUMATOID ARTHRITIS: SODIUM FLUORIDE OR CALCITONIN

Mowla K.
Department of Internal Medicine, Ahwaz Jundishapur University of Medical Sciences
Accepted:*5th July 2004* ***Received:****12th Sep. 2005*

Abstract
Historical controversy and lack of controlled clinical trial study comparing the effects of sodium fluoride and calcitonin therapies in osteoporosis of patients with RA made us to conduct this study to clarify which one of the above treatments would be more useful and effective in the treatment of osteoporosis.
From subjects who turned to Ahwaz Rheumatoid Arthritis Clinic during 2000, all women who met the American College of Rheumatology (ACR) 1987 criteria for RA (7), WHO 1994 criteria for osteoporosis (8) and signed the written consent were enrolled into the study. Considering these inclusion criteria, 70 women were enrolled into the study. They were randomized into two groups. Age, BMI (body mass index) and BMD (bone mineral density) were the adjusted variables during randomization. Thirty-four patients were treated with 20 mg sodium fluoride daily and 36 patients with 200 units nasal calcitonin per day. All patients were treated for 12 months.
Patients who received Fluoride showed significant higher BMD in femoral neck (0.74 vs. 0.65, $p<0.01$) and in lumbar spine (0.90 vs. 0.79, $p<0.05$) than who received calcitonin after 12 months of therapy.

Keywords:
Osteoporosis, Sodium Fluoride, Calcitonin

Introduction
Osteoporosis is a very common disorder, which result in an increase in fracture risk. It is a skeletal disorder characterized by low bone density and microarchitectural deterioration of bony tissue (1). In the rheumatoid arthritis (RA) population osteoporosis is more often found than in the normal population (2), and both inflammation and corticosteroids (3) have been identified as independent risk factors for osteoporosis.
Calcitonin is a naturally occurring hormone, which inhibits bone resorption, decrease osteoclast formation and osteoclast attachment. In a randomized trial of nasal spray salmon calcitonin in postmenoposal women with established osteoporosis, a dose of 200 International Unit (IU) daily significantly reduced the risk of new vertebral fractures and the lumbar spine bone mineral densitometry (BMD) increased significantly (4).
Some studies have suggested that sodium fluoride therapy may be an effective treatment for vertebral osteoporosis however, in 1991, Duell and Chesnut reported exacerbation of RA after the initiation of sodium fluoride therapy (5). Six years later, Adachi et al. reported the results of a randomized double blind placebo controlled trial regarding the fluoride therapy in prevention of RA induced bone loss. They showed the lumbar spine BMD increase in about 80% of patients treated with fluoride compared to 44% of patients treated with placebo. They concluded that the fluoride therapy

Email: Mowla_ K@yahoo.com

is well tolerated and increased vertebral bone mass in patients with RA (6).
This historical controversy and lack of controlled clinical trial study comparing the effects of these two types of treatment in osteoporosis of patients with RA made us to conduct this study to clarify which one of the above treatments would be more useful and effective in the treatment of osteoporosis.

Materials & Methods

From subjects who turned to Ahwaz Rheumatoid Arthritis Clinic during 2000, all women who met the American College of Rheumatology (ACR) 1987 criteria for RA (7), WHO 1994 criteria for osteoporosis (8) and signed the written consent were enrolled into the study. Considering these inclusion criteria, 70 women were enrolled into the study. They were randomized into two groups. Age, BMI (body mass index) and BMD (bone mineral density) were the adjusted variables during randomization.
Dual energy *x* ray absorptiometry (DXA) is the gold standard for assessing bone density, and the World Health Organization (WHO) definition of osteoporosis is based on this. Standardized BMD measurements at the left femoral neck and the lumbar spine L2-4 (anterior-posterior view) were performed.

All patients received 1000 mg calcium (Daru Pakhsh, Tehran, Iran), 400 units of vitamin D (Daru Pakhsh, Tehran, Iran), 7.5-10 mg prednisolon (Iran Hormone) and 150 mg chloroquin (Pars Daru- Iran) daily. They also received 7.5-10 mg methotrexate (Eloac - Austria) weekly. Thirty-four patients were treated with 20 mg sodium fluoride daily and 36 patients with 200 units nasal calcitonin per day. All patients were treated for 12 months. Each of them was visited every two months to be asked about their treatments. The DXA measurements were expressed as BMD (g/cm^2). The mean values were expressed with standard deviations (SD). Student's t-test and paired t-test were employed to compare values between and within groups. P values less than 0.05 were considered significant.

Results

Table 1 shows the patients' characteristics for various demographic and related variables in both groups. Table 2 shows the BMD values for the different measurement sites before and after treatment. Patients who received fluoride showed significant higher BMD in femoral neck (0.74 vs. 0.65, $p<0.01$) and in lumbar spine (0.90 vs. 0.79, $p<0.05$) than who received calcitonin after 12 months of therapy. Individual BMD values before and after the treatments are shown in Fig.1 (A, B)

Table 1: Patients' characteristics for various demographic and related variables

Variables	Group 1 (n=34)	Group 2 (n=36)	All (n=70)
Age (years)	55.67	60.83	58.32
Weight (kg)	65.73	62.05	63.84
Height (cm)	152.45	156.20	154.30

Table 2: BMD values for the different measurement sites before and after treatment.

BMD (g/cm^2)	Group 1 (n=34)	Group 2 (n=36)
Before treatment		
Femoral neck	0.73	0.64
Lumbar spine	0.89	0.77
12 months after treatment		
Femoral neck	0.74	0.65
Lumbar spine	0.90	0.79

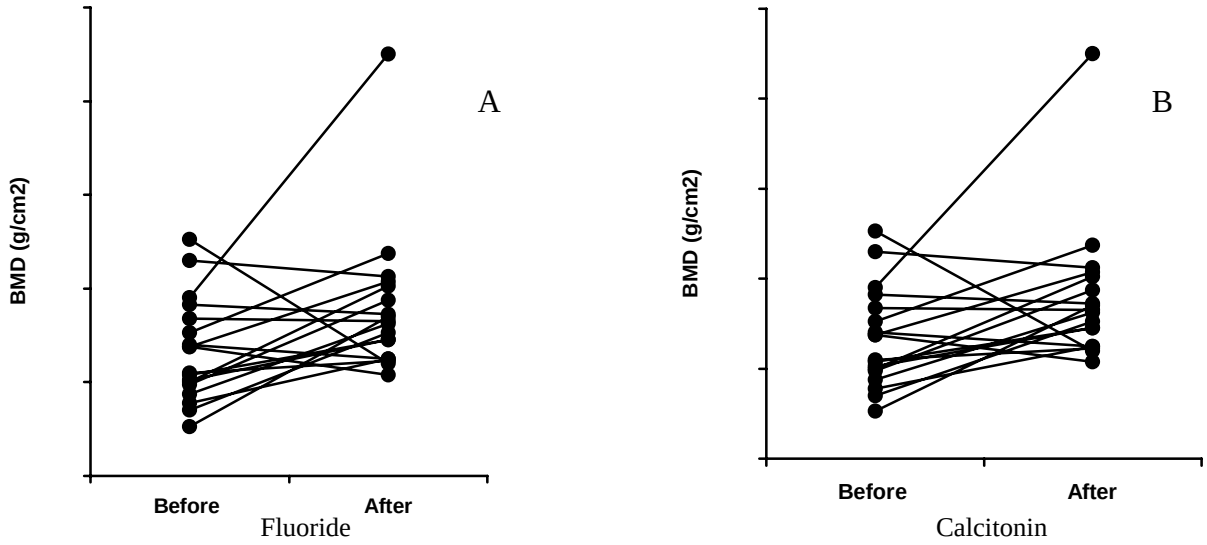

Fig. 1: Individual BMD values before and after the treatment.

Discussion

In the present study, we found that sodium fluoride increases BMD more than calcitonin in patients with RA and osteoporosis who received calcium and vitamin D, concurrently. A meta-analytic approach to corticosteroid-induced osteoporosis reported that vitamin D plus calcium is more effective than no therapy or calcium alone in the management of corticosteroid induced osteoporosis. There was a moderate beneficial effect of vitamin D plus calcium versus no therapy, or calcium alone, (from 9 trials, effect size = 0.60, 95% CI 0.34-0.85). In a comparison of vitamin D versus other osteoporosis therapies, bisphosphonates were more effective than vitamin D (from 6 trials, effect size = 0.57, 95% CI 0.09-1.05); calcitonin was similar in efficacy to vitamin D (from 4 trials, effect size = 0.03, 95% CI –0.39 to +0.45); and fluoride was more effective than vitamin D but there were only two trials (9). Cranney et al. reported that calcitonin appears to preserve bone mass in the first year of glucocorticoid therapy at the lumbar spine by about 3% compared to placebo (weighted mean difference at 12 months = 3.2%, 95% CI, 0.3-6.1), but not at the femoral neck. At 24 months, lumbar spine BMD was not statistically significant between groups. The authors stated that the protective effect may be greater for the treatment of patients who have been taking corticosteroids for more than 3 months (10). Bone loss from the lumbar spine, but not the femoral neck was prevented or reduced by treatment for one year with calcium plus calcitriol, with or without calcitonin, in the patients receiving corticosteroid therapy as reported by sambrook et al. In the second year of the study, when the patients received no calcium, calcitriol, or calcitonin, bone loss in the lumbar spine continued in the group that had received calcium alone, but not in the group that had received calcitonin and calcitriol. There was bone loss from the lumbar spine in the patients who had received calcium plus calcitriol in the second year, but this group received a higher cumulative dose of corticosteroid during that year than did the other groups. These results suggested that therapy should be extended in patients who continue to

receive corticosteroid therapy (11).There appeared to be some persistent benefit of calcitonin in the following year, in a manner consistent with studies in patients receiving long-term corticosteroid and parenteral calcitonin therapy (12). Although the long-term bioavailability of nasal calcitonin is uncertain, nasal and intramuscular calcitonin alone may both reduce vertebral-bone loss in corticosteroid-treated patients (13). This is in agreeing with our results which indicate a light effect of calcitonin on bone loss. Although fluoride increases bone mass, the newly formed bone may have reduced strength. To assess the effect of fluoride treatment on the fracture rate in osteoporosis, Riggs et al. conducted a four-year prospective clinical trial in 202 postmenopausal women with osteoporosis and vertebral fractures who were randomly assigned to receive sodium fluoride (75 mg per day) or placebo. All received a calcium supplement (1500 mg per day). As compared with the placebo group, the treatment group had increases in median bone mineral density of 35 percent in the lumbar spine (predominantly cancellous bone), 12 percent in the femoral neck, and 10 percent in the femoral trochanter (sites of mixed cortical and cancellous bone), but the bone mineral density decreased by 4 percent in the shaft of the radius (predominantly cortical bone). The number of new vertebral fractures was similar in the treatment and placebo groups (163 and 136, respectively; P not significant). Fifty-four women in the fluoride group and 24 in the placebo group had side effects sufficiently severe to warrant dose reduction; the major side effects were gastrointestinal symptoms and lower-extremity pain. They conclude that fluoride therapy increases cancellous but decreases cortical bone mineral density and increases skeletal fragility. Thus they reported that the fluoride-calcium regimen is not effective treatment for postmenopausal osteoporosis (14).

However, we had no side effect with fluoride in our study and it was effective to increase BMD.

In conclusion, we found that sodium fluoride increases BMD more than calcitonin in patients with rheumatoid arthritis and osteoporosis who received calcium plus vitamin D. However, we suggest a more comprehensive clinical trial to find out whether fluoride reduced bone loss is effective on reducing the risk of bone fracture or not.

Conclusion

We found that sodium fluoride increases BMD more than calcitonin in patients with rheumatoid arthritis and osteoporosis who received calcium plus vitamin D. However, we suggest a more comprehensive clinical trial to find out whether fluoride reduced bone loss is effective on reducing the risk of bone fracture or not.

Referneces

1) Christodoulou C, Cooper C. What is osteoporosis? Postgrad Med J 2003; **79**:133-138.

2) Haugeberg G, Uhlig T, Falch JA, Halse JI, Kvien TK. Reduced bone mineral density in male rheumatoid arthritis patients: frequencies and associations with demographic and disease variables in 94 patients in the Oslo County Rheumatoid Arthritis Register. Arthritis Rheum 2000;**43**:2776–84.

3) Verhoeven AC, Boers M. Limited bone loss due to corticosteroids; a systematic review of prospective studies in rheumatoid arthritis and other diseases. J Rheumatol 1997;**24**:1495–503.

4) Chesnut CH, Silverman S, Andriano K, *et al.* 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**:267–76.

5) Duell PB, Chesnut CH. Exacerbation of rheumatoid arthritis by sodium fluoride treatment of osteoporosis. Arch Intern Med. 1991; **151(4)**: 783-4.

6) Adachi JD, Bell MJ, Bensen WG, Bianchi F, Cividino A, Sebaldt RJ, Gordon M, Ioannidis G, Goldsmith C. Fluoride therapy in prevention of rheumatoid arthritis induced bone loss. J Rheumatol. 1997; **24(12)**:2308-13.

7) Arnett FC et al. The ARA revised criteria for the classification of rheumatoid arthritis. Arthritis rheum 1988; **31**: 315-324.

8) WHO Study Group. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Geneva: World Health Organization, 1994.

9) Amin S, La Valley MP, Simms RW, Felson DT. The role of vitamin D in corticosteroid-induced osteoporosis – a meta-analytic approach. *Arthritis and Rheumatism* 1999; **42(8)**: 1740-1751.

10) Cranney A, Welch V, Adachi JD *et al.* Calcitonin for preventing and treating corticosteroid-induced osteoporosis [updated 27 October 1999]. Cochrane Database of Systematic Reviews. *Cochrane Library*, 2001 Issue 4.

11) Sabrook et al. Prevention of Corticosteroid Osteoporosis -- A Comparison of Calcium, Calcitriol, and Calcitonin. New Engl J Med 1993; **328**: 1747-52.

12) Luengo M, Picado C, Del Rio L, Guanabens N, Monsterrat JM, Setoain J. Treatment of steroid-induced osteopenia with calcitonin in corticosteroid-dependent asthma: a one-year follow-up study. Am Rev Respir Dis 1990;**142**:104-107.

13) Montemurro L, Schiraldi G, Fraioli P, Tosi G, Riboldi A, Rizzato G. Prevention of corticosteroid-induced osteoporosis with salmon calcitonin in sarcoid patients. Calcif Tissue Int 1991;**49**:71-76.

14) Riggs et al. Effect of fluoride treatment on the fracture rate in postmenopausal women with osteoporosis. New Engl J Med 1990; **322**: 802-809.