http://journals.bmsu.ac.ir/ijtmgh
Int J Travel Med Glob Health. 2014;2(3):101-105
IJTMGH
International Journal of Travel Medicine and Global Health
Original Article Open Access

Treatment of Osteopenic Menopause Women as a Public Health Problem with Nasal Calcitonin; an Original Study on Follow up Markers

Bita Najafian[1], Majid Shohrati[2], Amin Saburi[1], Zahra Abbasi[3], Gholam-Hossein Alishiri[4], Noushin Bayat[4,*]

1. *Pediatrics Department, Faculty of Medicine, Baqiyatallah University of Medical Sciences, Tehran, Iran*
2. *Chemical Injuries Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran*
3. *Tehran Medical Branch, Islamic Azad University, Tehran, Iran*
4. *Internal Medicine Department, Faculty of Medicine, Baqiyatallah University of Medical Sciences, Tehran, Iran*

[*]Corresponding Author: Noushin Bayat, MD, Internal Medicine Department, Faculty of Medicine, Baqiyatallah University of Medical Sciences, Tehran, Iran
Email: md.researcher@yahoo.com

Abstract

Introduction: Various therapeutic options such as Calcitonin are suggested for patients with low bone density. However, the efficacy remains uncertain in all patients. C-telopeptide of type I collagen (CTx) is the authentic bone marker which is recently used to assess the bone turnover. This study aimed at revealing the therapeutic effects of Calcitonin on osteopenic women via serum CTx and assessment of other biochemical markers.

Methods: we conducted a before-after clinical trial on menopause women with low bone mineral density (bone mineral density score less than 1.5 SD of peak bone mass) attending Baqiyatallah hospital clinic. They received 200 IU Calcitonin nasal spray, calcium (1000 mg) and vitamin D (400 IU). Then the serum CTx and other laboratory parameters were compared after a 6 months treatment. The data was analyzed using SPSS ver.16, paired T-test and regression model.

Results: The study population included 115 menopause women with the mean age of 58.75 ± 8.15 years. The CTx amount decreased significantly compared with that of the baseline level (3.203 ± 2.24 vs. 2.497 ± 1.657 Pmol/lit, P <0.001). Also, Bone Mineral Densitometry of spine increased significantly from 0.834±0.112 to 0.852±0.122 (P =0.003). Serum levels of PTH, Ca, AST, ALT and alkaline phosphatase total had also changed insignificantly (P >0.05).

Conclusion: Nasal spray of Calcitonin could be effective on the progression of osteoporosis by decreasing bone tissue turnover and improving the bone density. Further controlled-studies with a larger sample size and a longer duration of follow up are recommended.

Keywords: Bone Density, Osteoporosis, Calcitonin, Biological Markers

Article History: **Received:** 2 Jul 2014 **Revised:** 25 Jul 2014 **Accepted:** 1 Aug 2014
Cite this article as: Najafian B, Shohrati M, Saburi A, Abbasi Z, Alishiri GH, Bayat B. Treatment of osteopenic menopause women as a public health problem with nasal calcitonin; an original study on follow up markers. Int J Travel Med Glob Health. 2014;2(3):101-5.

1. Introduction

Osteoporosis (OPS) is an age related disorder characterized by low bone density (LBD) and a destruction in bone tissue micro-architecture which leads to an increase in the susceptibility of the pathologic fracture [1]. OPS is usually expected in post-menopause women over fifty years of age because of hormonal imbalance between bone tissue resorption and reconstruction. LBD is a worldwide therapeutic problem particularly in developed countries. Moreover, it can amplify the risk of bone fracture and therefore influence the overall community health [2, 3].

Nowadays, Dual X-ray Absorptiometry (DXA) is the most common technique for the evaluation of bone mineral densitometry (BMD). This technique assesses the quantity of bone tissue and is the gold standard for the diagnosis of LBD and OPS [4]. Some conditions such as osteoarthritis, osteomalacia, overlying metal objects, vascular calcification in the spine, previous gold therapy, and previous fracture of the hip, spine and wrist, and severe scoliosis can interfere with the BMD interpretation [5]. Evaluating the quality of the bone mineral tissue is necessary to estimate the efficacy of the treatment of LBD. Bone markers indicating bone turnover and remodeling are recently used for assessing the quality of the bone tissue. Bone turnover control the calcium homeostasis and replacement of part of bone with micro-fractures. During these processes, several products of bone resorption and formation release into the circulation and measuring their concentrations could estimate the rate of bone turnover [2].

Serum osteocalcin, procollagen I carboxyterminal propeptide and bone-specific alkaline phosphatase (ALP) are the bone-formation (ossification) markers. The bone resorption markers include urinary hydroxyproline, urinary deoxypyridinoline, urinary pyridinoline, collagen type I cross-linked N-Telopeptide (NTx), and collagen type I cross-linked C telopeptide (CTx) [6, 7]. Various protocols have been suggested for the treatment of osteoporosis aiming at inhibiting the progression of the disease and reducing the risk of fractures. Monitoring the usefulness of this treatment is highly important and bone resorption markers could be of great benefit for this purpose. Bone biomarker could indicate the efficacy of early treatment before changes in the BMD are

presented [5].

Since two decades ago Calcitonin has been suggested for the treatment of OPS as the anti-resorptive therapy (nasal spray or injection form). It inhibits osteoclastic activity [8-11] and also therapeutic effects on OPS and LBD are investigated through BMD. Also, there are few studies which examined the effects of calcitonin on the bone density using bone resorptive markers [2, 12]. The aim of this investigation was to study the early impact of nasal spray of Calcitonin on the BMD and CTx as the new marker of bone resorption in postmenopausal women with the LBD.

2. Methods

2.1. Study Design and Participants

We evaluated 115 post menopause women referring to a rheumatology clinic affiliated to the Baqiyatallah University in 2009-2010. The cases with the BMD at any sit of measurement with a T score<-1.5 SD, had no evidence for secondary LBD, no sufficient response to the pharmacological doses of vitamin D and Calcium during the past 6 months before the treatment was recruited.

The patients who had had a previous treatment with prednisone or other medication interfering bone metabolism such as estrogen or progesterone, bisphosphonates, calcitonin and present or previous history of nasal polyps or a nasal septal perforation were excluded from the study.

Those with secondary osteopenia and other bone disorders or other medical conditions such as hyperthyroidism, hyperparathyroidism, previous malignancy were also excluded. This was done based on the patient's history, whole body physical examination, usual laboratory tests, and, if necessary, hormone assessment and further investigations for suspected patients. The ethics committee of the Baqiyatallah University had approved the study's protocol. All the participants filled out a consent form before enrolling in the investigation. Patients' compliances were observed throughout the investigation by phone calls.

2.2. Bone Mineral Density (BMD) Measurement

The BMD was evaluated by dual-energy X-ray absorptiometry (Norland Company, USA) at the lumbar spine (L_2-L_4) and femoral neck. The BMD was assessed both at the baseline and six months later (at the end of the study).

2.3. Treatment Protocol

The patients received 200 IU intranasal salmon Calcitonin (Nasocalcin spray nasal 200 micro/puff, prepared by Sinadaru, Tehran, IR.Iran) daily plus Calcium tablet (1000 mg) and vitamin D (400 IU) for six months. All patients were visited every two months for efficacy and probable adverse events.

2.4. Biochemical and Bone Resorption Markers

Urine and blood samples were collected at the baseline and six months post-treatment for biochemical bone marker assessment. Serum and 24-hour urinary Calcium levels, serum and 24-h urinary Phosphorus levels, parathormone (PTH) serum levels, and serum alkaline phosphatase were analyzed for the evaluation of Calcium homeostasis.

Biochemical markers were assessed at the baseline and at the end of the treatment period for all of the patients. These makers included cell blood count, serum calcium (Ca), serum phosphorus, creatinine (Cr), albumin, blood urea nitrogen (BUN), electrolyte (sodium (Na) and potassium (K)) and liver aminotransferases. Non-fasting serum and urine samples were collected in the morning for measuring biochemical markers. The patients were also asked to avoid smoking. Bone resorption was estimated by determining the serum level of C-telopeptide of type-I collagen (CTx). CTx measurements were made by ELISA (One Step CTx ELISA, Denmark) in a single laboratory.

2.5. Statistical Analysis

The data collated from women who completed the study period was used for statistical analysis. All quantitative variables' distribution were assessed by the Kolmogorov-Smirnov test and then represented as mean ± SD (standard deviation) and the qualitative variables are shown in percentages. Two-sample (Paired) t-test was used to compare the effect of the treatment on bone marker levels. Also the chi-square and two-tailed Wilcoxon test were used to compare the effect of the treatment on qualitative or non-parametric quantitative variables. Independent variables with a P.value ≤0.2 in the univariate analysis were entered into the multivariate linear regression model. All analyses were performed using SPSS ver.16 and P-values < 0.05 were considered statistically significant.

3. Results

The subjects included 115 menopause women with the mean age of 58.75 ± 8.15 years. No considerable adverse reaction of medications was seen among the patients. The mean age for menopause was 47.11±5.43 years and the mean year for the time of menopause was 12.32 ± 8.70 years. The mean of baseline BMI and weight were 27.48±4.10 kg/m^2 and 67.52±5.47 kg, respectively.

At the baseline measurement the BMD was 0.834±0.112 (g/cm^2) at the lumbar spine, 0.699±0.104 (g/cm^2) at the femoral neck, and the values for six months after the treatment were 0.852±0.122 (g/cm^2) and 0.708±0.100 (g/cm^2), respectively. This difference in the BMD of the lumbar spine was statistically significant (P=0.003) but it was not significant in femur's BMD (P=0.061). Changes in the BMD characteristics over the six month treatment period are presented in Table-1. In addition to the BMD of the spine, the T-score, the Z score and the standardized BMD of the spine changed significantly during the study. At the baseline, 55.3% of the patients suffered from lower back pain although this pain reduced to 3.5% (at the second month after beginning the treatment), 1.8% (at the 4th month) and 0% (at the 6th month) which was statistically significant (P<0.001). There was a significant increase in Ca level of 24-h urine compared to that of the baseline (from 216.968±114.683 to 270.871±155.477 with P=0.000). Cr level in 24-h urine altered from 0.93 ±0.35

to 1.08 ±0.37 that this difference was statistically significant. Also, the BUN at the baseline was 17.08 ±4.07 which significantly increased to 18.17 ±4.35 at the end of the study (P=0.043). Changes in serum levels of other biochemical markers were insignificant (Table-2). Serum levels of PTH, Ca, AST, ALT and Alkaline phosphatase total changed insignificantly (P>0.05).

The serum level of CTx significantly decreased from 3.203 ± 2.241 to 2.497 ± 1.657 Pmol/lit (P=0.001). By using linear regression, the CTx changes were adjusted for confounding variable and variable with the P.value less than 0.2 such as the age, duration of menopause, PTH, serum P, femur and spine BMD, 24-hours urine Cr, BUN and urine 24 hours Ca. There were no significant correlation with the CTx changes, although the mentioned factors were adjusted (P>0.05).

4. Discussion

According to the findings, all the characteristics of the densitometry of the lumbar spine and also the CTx changed significantly after administrating the nasal calcitonin spray and these changes were concomitant with the improvement of the clinical symptoms (back pain). There was no control group for generalizing the findings. However, we confirmed the efficacy of the nasal spray of the calcitonin on post-menopause women with LBD who were resistant to routine medications (Ca and vitamin D). It is expected to see an increase in BMD after one year of treatment but when we used full doses of treatment including Calcium-D in addition to nasal spray of calcitonin, its therapeutic impacts occurred in shorter periods.

Decrease in bone mass and especially osteoporosis (OSP) is a great community health problem throughout the world which is becoming increasingly prevalent even in developed countries. By the growth in the number of the old population the incidence of osteoporotic is increasing in the developing countries [6, 13, 14]. OPS is the main cause of hip and vertebral fractures and it is a major cause of pathologic fracture in elderly [15]. Previous studies claimed that almost 45% of all women will experience at least one osteoporotic fracture during their lifetime [16]. The substantial relationship between decrease in bone mass and increase in the mortality and morbidity rate was confirmed by some studies in which five percent reduction in BMD per year increased the hazard risk of death in men and women by 1.6 and 1.8 fold, respectively[15, 17, 18]. Also, the expenditure on health care and experiencing complicated OSP such as osteoporotic fractures are a great health problem throughout the world [1]. Therefore, an effective protocol for the prevention and treatment of OSP is highly imperative.

Various medications that approvingly alter bone metabolism are used both in the treatment and in the prevention programs.

Table 1. Bone densitometry findings before and after treatment

Variable	Mean	SD	P.value
BMD before spine	0.8344	0.11211	0.003
BMD after spine	0.8521	0.12242	
SBMD before spine	890.68	123.85	0.005
SBMD after spine	907.02	132.65	
T-score spine before	-1.7265	0.70923	0.001
T-score spine after	-1.5796	0.75216	
Z-Score Spine before	-1.1059	0.67621	0.008
Z-Score spine after	-1.0035	0.75800	
BMD femur before	0.6994	0.10449	0.061
BMD femur after	0.7082	0.10034	
SBMD Score femur before	783.92	99.58	0.346
SBMD Score femur after	786.18	100.65	
T-Score femur before	-2.3309	0.79607	0.601
T-Score femur after	-2.3106	0.74536	
Z-Score femur before	-.7671	0.79358	0.069
Z-Score femur after	-.7026	0.75137	

BMD: Bone Mineral Density, SBMD; Standardized BMD, SD; Standard Deviation. Bold is Statistically Significant.

Table 2. Lab findings before and after treatment

Variable	Before (Mean± S.D)	After (Mean± S.D)	P.value	Normal Range
PTH	64.75±35.43	56.71±27.23	0.090	14.0 - 66.0 pg/mL
Serum Ca	9.47±0.59	9.41±0.52	0.513	8.8-10.0 mg/dL
Serum P	3.82±0.47	3.96±0.65	0.099	2.7-4.8 mg/dL
Serum Alk-ph	206.824±73.581	194.904±58.521	0.515	<350 U/L
Cr in Urine 24 h	0.93±0.35	1.08±0.37	**0.003**	0.6-1.8 mg/day
P in Urine 24 h	0.915±0.52	0.83±0.75	0.595	0.4-1.3 g/day
Ca in Urine 24 h	216.968±114.673	270.871±155.477	**0.000**	<300 mg/day
BUN	17.08±4.07	18.17±4.35	**0.043**	6-21 mg/dL
Cr	0.96±0.18	0.97±0.14	0.786	<1.5 mg/dL
ALT	20.98±11.51	20.81±11.33	0.886	11-35 U/L
AST	20.75±7.05	20.64±8.78	0.910	15-35 U/L

PTH; Parathormone, Ca; Calcium, P; Phosphorus, Alk-ph; Alkaline Phosphatase, Cr; Creatinine, h; hours, BUN; Blood Urea Nitrogen, ALT; Alanine Aminotransferases, AST; Aspartate Aminotransferases. Bold is Statistically Significant.

These medications are divided into three groups; stimulators of bone formation, inhibitors of bone resorption, and agents with heterogeneous effects. Most are used in the prevention programs and the treatment of OSP by inhibiting bone resorption [2, 5]. Calcitonin is approved for the treatment of OSP, low bone density and other disorders involving increased bone turnover as an inhibitor of bone resorption for almost 25 years. But the nasal type of Calcitonin has been recently confirmed. The present study is the first from Iran to assess the efficacy of nasal Calcitonin in post-menopausal women with osteopenia in a randomized trial scheme with the measurement of the CTx. Our results on the baseline serum CTx measurement in 115 post-menopause women revealed a decrease in the bone turnover in osteopenic patients after using 200 IU nasal Calcitonin and a stabilized level of bone loss in elderly patients. However, our study showed an increase in spine BMD compared with femoral BMD and this is similar to previous trials.

Previously, Calcitonin had been certified for the treatment of OSP but recent studies clarified the efficacy of nasal form of Calcitonin [19]. Monitoring and tracking the response to the treatment in patients with OSP is an important and challenging issue. BMD by DXA for this purpose is a reliable marker, but this test cannot measure the bone turnover accurately. On the other hand, when significant changes appear in the BMD, the bone density will increase to at least 3-5%. Moreover, DXA is not suitable for tracking in short-term periods. Also, the decrease in the fracture frequency due to therapy is much greater than that justified by the raise in bone density. Therefore, the bone biomarkers have propounded for early detection of the efficacy of the treatment [20]. Traditional biochemical markers of bone turnover such as alkaline phosphates (ALP) have a valuable role in assessing the bone formation and mineralization but are not specific to bone tissue. Recently, the value of new biomarkers such as C telopeptide of type I collagen was explained for predicting bone turn over during the course of treatment [21].

Few investigations have been conducted on the effect of the therapy of OSP on new biochemical markers. In these studies, significant decrease was found in the levels of biomarkers of bone turnover. Srivastava et al [12] performed a clinical trial using 200 IU Calcitonin nasal spray with calcium (500 mg) and vitamin D (200 IU) on elderly osteopenic women. They reported significant reduction in serum CTx levels, two, four, and six months after therapy compared with the baseline, and after four and six months compared with controls. Also, they declared that the maximum reduction in serum CTx level from baseline of 33% was seen at six months. In the present study the decrease in the serum CTx level after six months of treatment was 22% although the target population and treatment protocol were alike. This difference might be due to the difference between the ages of the patients. Tanko et al revealed that oral Calcitonin can reduce the CTx level even three months after treatment [22]. In another study carried out by Trovas et al 200 IU intranasal Calcitonin was used daily for 12 months and showed significant improvements in lumbar BMD and a decreased level of the CTx among men with idiopathic OSP [10]. This study altered femoral BMD insignificantly which this finding is consistent with the results of our study. In other studies the role of nasal Calcitonin was discussed on other biomarkers such as Crosslaps and NTx confirming the anti-resorptive effect of nasal Calcitonin [2, 23]. On the other hand, it seems that CTX, in comparison with BMD, can be a more useful biomarker for observing bone hormonal imbalance between bone tissue resorption and re-construction in a short-term follow up.

In our study, a rise in BUN and the serum creatinine level were seen along with an increase in the urinary calcium excretion after using Calcitonin. The reason was probably because of insufficient consumption of water when calcium was being excreted. Further investigations should be done in order to focus on the effect of Calcitonin on renal function.

One of the limitations of this study was the short term duration of follow up and not being able to observe long-term effects of nasal Calcitonin beyond six months although we observed the therapeutic effect of nasal calcitonin in the spine BMD and CTX in a 6-month follow up. Therefore, we recommend performing further studies on the effect of nasal Calcitonin on the CTx level covering more than six months. Moreover, we did not have a control group for overruling the impacts of the nationality or the race on clinical or para-clinical findings. By the way, the results of this study and other similar studies indicated that 200 IU intra-nasal Calcitonin daily could effectively inhibit bone tissue resorption, prevent the progression of the disease, and improve the bone density.

Acknowledgments

The authors thank all participants for their kind collaboration and cooperation.

Authors' Contributions

All authors involved in all steps including design, data gathering, analyzing the data and manuscript preparation.

Financial Disclosure

This manuscript was prepared from a well-rounded study that an initial part of the result was published in another language (Persian) but this manuscript was prepared originally and the main sections was written with a different pattern. Also, more patients were reported in the manuscript in compared to the previous ones.

Funding/Support

This project was supported by the Sinadaru Company and the chemical injury research center of the Baqiyatallah University of medical sciences but these centers did not interfere in any stage of the study from design to interpretation of the results.

References

1. Genant H, Cooper C, Poor G, Reid I, Ehrlich G, Kanis J, et al. Interim report and recommendation of the World Health Organization task-force for the osteoporosis. Osteoporos Int. 1999;10(4):259-64.
2. Ofluoglu D, Karadag-Saygi E, Canbulat C, Hakan Gunduz O, KUL-Panza E, Akyuz G. Early effect of nasal salmon calcitonin on the bone marker Crosslaps. Rheumatol Int. 2006;26(4):288-91.
3. Weiss M, Ben-Shlomo A, Hagag P, Rapoport M. Reference database for bone speed of sound measurement by novel quantitative multi-site ultrasound device. Osteoporos Int. 2000;11(8):688-96.
4. M.Blake G, Fogelman I. Bone densitometry and the diagnosis of osteoporosis. Seminars in Nuclear Medicine. 2001;31(1):69-81.
5. Kanis J, Delmas P, Burckhardt P, Cooper C, Torgerson D. Guidelines for diagnosis and management of osteoporosis. The European Foundation for Osteoporosis and Bone Disease. Osteoporos Int. 1997;7(4):390-406.
6. Brown J, Josse R, Scientific Advisory Council of the Osteoporosis Society of Canada. 2002 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. CMAJ 2002;12(167(10 Suppl)):S1-34.
7. Herrmann M, Seibel M. The amino- and carboxyterminal cross-linked telopeptides of collagen type I, NTX-I and CTX-I: A comparative review. Clinica Chimica Acta. 2008;393(2):57-75.
8. Chesnut C, Silverman S, Andriano K, Genant H, Gimona A, Harris S, 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(4):267-76.
9. Huusko T, Karppi P, Kautiainen H, Suominen H, Avikainen V, Sulkava R. Randomized, double-blind, clinically controlled trial of intranasal calcitonin treatment in patients with hip fracture. Calcif Tissue Int. 2002;71(6):478-84.
10. Trovas G, Lyritis G, Galanos A, Raptou P, Constantelou E. A randomized trial of nasal spray salmon calcitonin in men with idiopathic osteoporosis: effects on bone mineral density and bone markers. J Bone Miner Res. 2002;17(3):521-7.
11. Ellerington M, Hillard T, Whitcroft S, Marsh M, Lees B, Banks L, et al. Intranasal salmon calcitonin for the prevention and treatment of postmenopausal osteoporosis. Calcif Tissue Int. 1996;59:6-11.
12. Srivastava AK, Libanati C, Hohmann O, Kriegman A, Baylink DJ. Acute effects of calcitonin nasal spray on serum C-telopeptide of type 1 collagen (CTx) levels in elderly osteopenic women with increased bone turnover. Calcif Tissue Int. 2004;75(6):477-81.
13. Patni R. Normal BMD values for Indian females aged 20-80 years. J Midlife Health. 2010;1(2):70-3.
14. Acharya S, Srivastava A, Sen IB. Osteoporosis in Indian women aged 40–60 years. Arch Osteoporos. 2010;5:83-9.
15. Sanchez-Riera L, Wilson N, Kamalaraj N, Nolla JM, Kok C, Li Y, et al. Osteoporosis and fragility fractures. Best Practice & Research Clinical Rheumatology. 2010;24(6):793-810.
16. Brixen K, Abrahamsen B, Kassem M. Prevention and treatment of osteoporosis in women. Current Obstetrics & Gynaecology. 2005;15:251-8.
17. Bliuc D, Nguyen N, Milch V, Nguyen TV, Eisman JA, Center JR. Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. JAMA. 2009;301(5):513-21.
18. Nguyen N, Center J, Eisman J, Nguyen T. Bone loss, weight loss, and weight fluctuation predict mortality risk in elderly men and women. J Bone Miner Res. 2007;22(8):1147-54.
19. Mehta N, Malootian A, Gilligan J. Calcitonin for osteoporosis and bone pain. Curr Pharm Des. 2003;9(32):2659-76.
20. Delmas P, Eastell R, Garnero P, Seibel MJ, Stepan J; Committee of Scientific Advisors of the International Osteoporosis Foundation. The use of biochemical markers of bone turnover in osteoporosis. Committee of Scientific Advisors of the International Osteoporosis Foundation. Osteoporos Int. 2000;11 Suppl 6:S2-17.
21. Wekre LL, Eriksen EF, Falch JA. Bone mass, bone markers and prevalence of fractures in adults with osteogenesis imperfecta. Arch Osteoporos. 2011;6(1-2):31-8.
22. Tankó L, Bagger Y, Alexandersen P, Devogelaer J, Reginster J, Chick R, et al. Safety and efficacy of a novel salmon calcitonin (sCT) technology-based oral formulation in healthy postmenopausal women: acute and 3-month effects on biomarkers of bone turnover. J Bone Miner Res. 2004;19(9):1531-8.
23. Kaskani E, Lyritis G, Kosmidis C, Galanos A, Andypas G, Chorianopoulos K, et al. Effect of intermittent administration of 200 IU intranasal salmon calcitonin and low doses of 1alpha (OH) vitamin D3 on bone mineral density of the lumbar spine and hip region and biochemical bone markers in women with postmenopausal osteoporosis: a pilot study. Clin Rheumatol. 2005;24(3):232-8.
24. Bayat N, Shohrati M , Saburi A, Abbasi Z, Alishiri Gh , Najafian B. Effects of calcitonin nasal spray on serum bone resorptive marker CTX and other laboratory findings in osteopenic menopausal women: a clinical trial. Tehran Univ Med J. 2012;70(4):236-41