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Effects of salmon calcitonin treatment on serum and synovial fluid bone formation and resorption markers in osteoporosis patients

Hasan ATBİNİCİ[1], Serkan SİPAHİOĞLU[2], Nurten AKSOY[3], İslam BAYKARA[2], Uğur Erdem IŞIKAN[2]

[1]Şanlıurfa State Hospital, Department of Orthopedics and Traumatology, Şanlıurfa, Turkey;
[2]Harran University Faculty of Medicine, Department of Orthopedics and Traumatology, Şanlıurfa, Turkey;
[3]Harran University Faculty of Medicine, Department of Medical Biochemistry, Şanlıurfa, Turkey

Objective: This study aimed to evaluate the effects of salmon calcitonin, and calcium and vitamin D treatment on bone mineral density, serum and synovial fluid bone formation and resorption markers in patients with osteoporosis.

Methods: The study was completed with twenty-five osteoporosis patients divided into two groups: The 15 patients comprising Group I (1 male and 14 females; mean age: 67.0±12.0) were administered calcitonin treatment in addition to calcium and vitamin D. The 10 patients in Group II (3 males and 7 females; mean age 68.0±16.0) were administered calcium and vitamin D only. Serum and synovial fluid calcium phosphorus, alkaline phosphatase, calcitonin, C-telopeptide (CTx), N-telopeptide (NTx) and sialoprotein levels, and bone densitometries were determined at the beginning and at the end of one year of treatment.

Results: In the calcitonin and calcium and vitamin D treatment group (Group I), femoral neck density scores were decreased and vertebrae scores were increased after one-year treatment. Both scores were increased in the non-calcitonin group (Group II). In Group I, synovial fluid levels of calcitonin, sialoprotein and NTx were decreased, and synovial fluid CTx levels showed no change. The only decrease that was statistically significant was that in calcitonin levels. In Group II, synovial fluid calcitonin levels were decreased, synovial fluid CTx levels were increased and synovial fluid NTx and sialoprotein level were unchanged. These changes were not statistically significant. Serum changes in the parameters were not statistically significant in either group.

Conclusion: In osteoporosis, salmon calcitonin treatment affects synovial fluid bone formation and absorption marker levels. Advanced studies are needed to evaluate the mechanisms by which this takes place, and to explain the relationship between osteoporosis and articular cartilage metabolism.

Keywords: CTx, densitometry; NTx; osteoporosis; salmon calcitonin; synovial fluid.

Osteoporosis is known to be asymptomatic until fractures occur, and therefore detection of fracture risk is crucial in their prevention. As an easily applied and inexpensive method, measurement of bone mineral density (BMD) is accepted as the gold standard today. This method provides static information about a dynamic

Correspondence: Serkan Sipahioğlu, MD. Harran Üniversitesi Tıp Fakültesi, Ortopedi ve Travmatoloji Anabilim Dalı, Yenişehir, Şanlıurfa, Turkey.
Tel: +90 505 – 533 23 60 e-mail: serkans@harran.edu.tr

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structure in which there is osteoblastic and osteoclastic activity. However, most medications which slow down bone destruction also slow down bone turnover, and as a result, measurement of osteoblastic and osteoclastic markers provides more rapid and accurate information about the efficacy of a drug than BMD measurement. In addition, while BMD measurement provides local and static information only about the measured region, measurement of osteoclastic markers provides a systemic and dynamic result. Consequently, it determines the need for initiating treatment before bone mineral density decreases and fracture risk increases.[1-3]

The normal values of osteoblastic and osteoclastic parameters in synovial fluid are not known and how osteoporosis treatment affects these parameters is not clear. No study was found evaluating the relationship between the two in the literature review. This study aimed to reveal the relationship between osteoporosis and joint cartilage and synovial fluid metabolism, and to identify more specific parameters for osteoporosis diagnosis and osteoporosis treatment effectivity in relation to synovial fluid.

Patients and methods

A total of 103 volunteer osteoporosis patients aged between 50 and 75 years who had not been treated before and who were admitted to our outpatient clinic between 2008 and 2010 were included in the study. Criteria for exclusion from the study were as follows: malignancy, acute infection, chronic obstructive pulmonary disease, use of corticosteroids, history of renal, hepatic, gastrointestinal disease and traumatic compression fracture, onset of menopause before 40 years of age, other metabolic or inflammatory diseases, alcohol consumption, and use of medications that could influence osteoporosis.

Osteoporosis was diagnosed with DEXA (dual energy X-ray absorptiometry) in 2 regions; lumbar and femoral (gr/cm^2). T and Z scores were also recorded. Diagnosis of osteoporosis was made based on the WHO criterion of T score on femur neck and lumbar BMD being under -2.5. Patients with secondary osteoporosis were also excluded from the study.

All participants were administered 2500 mg calcium carbonate and 880 IU vitamin D for a period of one year. Patients who in addition received 200 IU salmon calcitonin (Miacalcic 200 IU 2x14 nasal spray once daily) were accepted as Group 1 (n=15), and patients who received calcium and vitamin D3 only were accepted as Group 2 (n=20). All calcitonin-containing nasal sprays were removed from the market by the Turkish Ministry of Health in 2012 as their benefits were not considered to outweigh their risks in long term use, and due to observations of their relationship with minimally increased malignancy risk. Our study was completed before this decision was made, and is not relevant to this decision.

Ethics committee approval was obtained prior to the study, and patients provided written informed consent. Physical examination of all patients was done, and height and weight measurements taken for calculation of body mass index (BMI = weight-kg/ height-m^2). The mean BMI of Group 1 was 26.0±9.90, and 29.8±7.00 for Group 2. Knee joint synovial fluid was obtained under sterile conditions after sterile staining had been done with povidone iodine. Venous blood samples were obtained from the antecubital region and sent to the biochemistry laboratory for measurement of baseline, blood and synovial fluid calcium, phosphorus, alkaline phosphatase, calcitonin, C-telopeptide, N-telopeptide and sialoprotein.

All participants were recommended lifestyle changes such as a balanced and calcium-rich diet, regular exercise, cessation of smoking and alcohol, sunlight exposure and some in-house modifications in addition to medical treatment. Both groups were invited to 3- and 6-month controls, when their medications were checked. Outpatient clinic controls were done at the 12th month, when venous blood and knee joint synovial fluid samples were obtained and BMD measurements were done again. Care was taken to take BMD measurements on the same device at baseline and at the 12th month. Patients who could not attend the controls due to death or the other causes were dropped from the study, and it was completed with 15 patients in Group 1 and 10 patients in Group 2.

Statistical analysis was done using the SPSS 11.5 package program (SPSS for Windows, 11.5, SPSS Inc. USA). The Mann-Whitney U test was used for comparison of inter-group data, the Wilcoxon test was used for comparison of data before and after medication, and chi-square test was used for distribution of gender according to groups. Results were shown as median ± IQR. A p level of <0.05 was accepted as statistically significant.

Results

L1-4 BMD values in Group 1 patients had increased by 14.2%, while femur neck BMD values had decreased by 17.6% at 12th month controls. These changes were not found to be statistically significant ($p>0.05$) (Table 1). L1-4 BMD values of Group 2 patients had increased by 16.2%, while femur neck BMD values had increased by 32.1% at 12th month controls. These changes were not found to be statistically significant ($p>0.052$) (Table 1).

Table 1. Serum values and densitometry results.

	Group 1			Group 2			p
	Before treatment	After treatment	p	Before treatment	After treatment	p	
Alp (U/L)	86.0±50.0	96.0±44.0	0.307	91.8±31.9	91.5±26.7	0.285	0.605
Calcitonin (pg/ml)	2.60±0.10	2.50±1.50	0.629	2.50±1.35	2.80±1.80	0.221	0.683
CTx (ng/ml)	0.23±0.48	0.23±0.31	0.932	0.21±0.56	0.32±0.25	0.799	0.397
NTx (nM BCE)	11.3±23.7	24.5±27.4	0.061	26.3±20.3	43.5±16.4	0.014	0.023
Sialoprotein (ng/ml)	3.10±3.50	3.00±2.10	0.532	1.65±0.57	1.70±0.57	0.905	0.071
Femur density (gr/cm^2)	-1.70±1.60	-2.00±-1.40	0.975	-1.40±1.62	-0.95±1.17	0.123	0.196
Vertebra density (gr/cm^2)	-2.80±0.60	-2.40±-1.10	0.222	-3.40±0.70	-2.85±1.82	0.052	0.531

Table 2. Synovial fluid valuess.

	Group 1			Group 2			p
	Before treatment	After treatment	p	Before treatment	After treatment	p	
Phosphorus (mg/dl)	4.00±1.00	4.50±0.50	0.608	4.25±0.62	3.50±1.50	0.201	0.103
Alp (U/L)	30.0±27.0	30.0±20.0	0.859	30.0±13.5	30.0±16.3	0.439	0.765
Calcitonin (pg/ml)	3.16±1.30	2.60±2.20	0.013	5.33±8.06	4.12±7.10	0.221	0.048
CTx (ng/ml)	0.50±0.18	0.50±0.34	0.932	0.34±0.20	0.46±0.28	0.541	0.723
NTx (nM BCE)	5.00±5.10	3.20±3.30	0.233	6.55±1.25	6.55±2.07	0.760	0.461
Sialoprotein (ng/ml)	6.60±3.40	5.40±4.40	0.955	3.85±3.10	3.80±2.17	0.441	0.978

In Group 1, synovial fluid calcitonin values had decreased by 17.7%, and this difference was statistically significant (p=0.013) (Table 2). A decrease was seen in synovial fluid calcitonin values in Group 2, but the change was not statistically significant (p=0.221) (Table 2).

The differences in synovial fluid, sialoprotein, phosphorus, ALP, CTx, NTx values were not found statistically significant at the end of one year treatment in Group 1 patients (p>0.05) (Table 2). Serum NTx values were increased at the end of one year treatment in Group 1, but the difference was not found statistically significant (p>0.05). The differences in serum sialoprotein, phosphorus, ALP, Ca, calcitonin and CTx values after treatment were not found significant after treatment in Group 1 (p>0.05) (Table 1).

The differences in synovial fluid sialoprotein, phosphorus, ALP, CTx and NTx values were not found statistically significant after treatment in Group 2 (p>0.05) (Table 2). In Group 2, baseline serum NTx values had increased by 65% following one year treatment and this difference was found statistically significant (p=0.014). The differences in serum sialoprotein, phosphorus, ALP, Ca, calcitonin and CTx values after treatment was not found significant after treatment in Group 2 (p>0.05) (Table 1).

Synovial fluid and serum values of Group 1 and Group 2 were compared at the end of one year treatment. A statistically significant difference was found between synovial fluid calcitonin and serum NTx values (p<0.05) (Tables 1 and 2). No significant difference was found between densitometry measurements, synovial fluid phosphorus, ALP, CTx, NTx, sialoprotein values and serum phosphorus, ALP, Ca, calcitonin, and sialoprotein values at the end of one year treatment (Tables 1 and 2). Synovial fluid and calcium values of the same groups could not be evaluated as their levels were too low to be measured.

Discussion

Many methods measuring the mass, density and mineral content of bone are currently available. Bone density measurements are accepted as significant data, indicating the physiological and pathological condition of the bone and determining fracture risk, and are accepted as the gold standard in osteoporosis diagnosis because they are easily applied and inexpensive. The influence of bone destruction in preventing treatment to increase BMD has been proven in previous studies.[1,4-6] When compared to bone density measurement, serial measurement of osteoclastic markers provides faster and accurate information about the efficacy of medication. Therefore re-measurement of an osteoclastic marker measured before treatment has been suggested as a useful method in

assessment of drug efficacy.[7,8] An increase of measured values to premenopausal levels is accepted as sufficient to eliminate the need for treatment.[9]

Knowing the markers for osteoblastic and osteoclastic activity in healthy individuals may be pioneer for further assessments. With this in mind, the study aimed to determine the influence of calcitonin medication, an osteoclastic activity inhibitor, on osteoblastic and osteoclastic activity markers in synovial fluid and serum and BMD. No studies were encountered in the literature investigating synovial fluid parameters for determining the effectiveness of osteoporosis treatment, so for this purpose, we compared synovial fluid, serum and bone mineral density results at baseline and after one year treatment. The aim was twofold: To reveal the relationship between joint cartilage metabolism and osteoporosis and osteoblastic and osteoclastic activity parameters , and to lead the way for future studies on this issue.

Calcitonin treatment was shown to increase spine BMD and significantly reduce spinal fracture risk in the long term.[10] Overgaard showed that spinal fracture risk is reduced by two-thirds in calcitonin-receiving patents. [11] Among osteoclastic activity inhibiting drugs, salmon calcitonin is known to be the least effective treatment on BMD.[12] It was observed to have less effect on dose-dependent BMD increase compared to bisphosphonates, and the increase was observed to be more prominent in lumbar spines.[11,13] Femur neck BMD values did not show significant change in follow-ups of calcitonin-receiving patients in the study by Hejdova et al. on the influences of alendronate and calcitonin in 50 patients. [14] Calcitonin was shown to be ineffective on BMD of the proximal femur and in reduction of femur fracture risk beside spinal fracture in the Prevention of Recurrent Osteoporotic Fracture (PROOF) study.[15] Calcitonin was shown to have an analgesic effect in addition to osteoporosis treatment in painful spinal fractures. [16] It was shown to reduce the pain from osteoporotic spinal compression fracture faster than placebo, but this analgesic effect could not be shown in different spinal pathologies.[17,18] The inconsistency between BMD and fracture risk was shown in the QUEST (Quantitative Effects of Salmon Calcitonin Treatment) trial. In this two-year trial, they observed that trabecular microstructure was preserved in iliac crest bone biopsies obtained from calcitonin-receiving patients, but observed different results in osteoclastic activity-inhibiting treatment in different bones. This study also shows the absence of a linear correlation between BMD and fracture risk.[10] In our study, BMD increase was higher in Group 1 (the calcitonin-using group), but the difference was statistically insignificant due to the small number of patients. An increase was also observed in Group 2 (the calcium and vitamin D-using group). However, the 36% increase in femur neck was seen to be related to an abnormal value in one patient, and it was found statistically insignificant.

When NTx values at baseline and after one year treatment were compared in both groups, mean values were seen to increase after medical treatment. This increase was found statistically insignificant in Group 1 and statistically significant in Group 2. Elevation of NTx, an osteoclastic marker, was not found consistent with the literature, as a decrease was anticipated. However, less NTx elevation in Group 1 and this being statistically insignificant may be evaluated as the osteoclastic activity-reducing effect of calcitonin. In addition, it was suggested that the literature studies being conducted with urinary rather than serum levels could lead to a difference with regard to NTx metabolism. Colpan et al. reported a progressive decrease in 3rd and 6th month urinary NTx levels in 50 patients who were administered calcitonin treatment.[19] Presence of a significant decrease in the early period also may suggest its being a parameter that could be used for assessment of treatment effectiveness during this period. Srivastava et al. detected a significant reduction in only 6th month NTx values among 2,4 and 6. month NTx values of the patient who received calcitonin treatment for 6 months.[20] Trovas et al. reported calcitonin as an effective treatment in males also, as they detected a reduction in urinary NTx following one year calcitonin treatment in male idiopathic osteoporosis patients.[21] In the present study, examining NTx values only at the end of one year may be a limiting factor for determining change, and the lack of change in synovial fluid NTx values in both groups after treatment indicates that synovial fluid is not affected by treatment. Further studies are required to evaluate the relationship between serum and urinary NTx levels, as the literature studies are conducted on urinary levels.

The evaluation of serum CTx levels, used as an osteoclastic activity marker, showed that while no significant change was observed in Group 1, a significant increase was observed in Group 2. The absence of increase Ctx values in Group 1 may suggest that calcitonin is effective on osteoclastic activity in osteoporosis patients. Ofluoglu et al. reported a significant decrease in 78 patient who received calcitonin for 6 months compared to the placebo group.[22] Srivastava et al. showed that a decrease in serum NTx began to appear beginning from the 2nd month and reached maximum reduction at the 6th month in their calcitonin-receiving group. Therefore, serum NTx level is suggested for use in assessment of

treatment effectiveness in the early period.[20] Bruyere et al. proposed an association between spinal deformity index and urinary CTx and serum osteocalcin levels, and therefore urinary CTx may be used for assessment of possible spinal deformities.[23] Serum CTx was reported to be a parameter for use in assessment of male idiopathic osteoporosis treatment.[14]

Bone sialoprotein is an important part of non-collagen proteins of bone matrix structure, and has been shown to be synthesized in osteoblasts, osteocytes and osteoclasts in mineralized tissue. Thus, it is a protein which takes part in both osteoblastic and osteoclastic activity.[24] As it is synthesized in a restricted area in the body, it can be used as a unique marker for evaluation of bone metabolism. Störk et al. detected a 52% reduction in their study investigating sialoprotein changes in 82 osteoporosis patients who were receiving hormone replacement therapy, and reported that sialoprotein could be used for quantitative evaluation.[25] Serum levels were found to rapidly decrease following bisphosphonate treatment, suggesting that the protein is connected with osteoclastic activity.[26] Sialoprotein level was seen to decrease in the calcitonin-receiving group in our study also, but the decrease was not found statistically significant. A greater decrease in sialoprotein was seen in synovial fluid. Clinical and experimental studies conducted in a larger patient group are required to identify the mechanisms of this decrease.

Evaluation of the relationship between calcitonin treatment and serum and synovial fluid calcitonin levels revealed low serum and synovial fluid calcitonin levels at the end of one year in Group 1 patients. Only the decrease in synovial fluid values was statistically significant. This decrease suggests that calcitonin treatment may have an effect on calcitonin release by the thyroid gland and synovial fluid values may be affected more. However, it is not clear whether this effect is related to calcium and vitamin D or another common effect, as a decrease, although statistically insignificant, was detected in Group 2 also.

Osteoporosis is suggested to develop due to calcitonin insufficiency and therefore calcitonin administration is recommended. However, studies are also available indicating that there is no association between osteoporosis and calcitonin. Leggate et al. could not found an association in their study comparing basal calcitonin level and yearly BMD values, and advocated that osteoporosis development is not associated with calcitonin deficiency.[6] Serum calcitonin level may change also with diet. Kalu et. al reported that serum calcitonin level decreased in rats restricted for food intake, and that the amount of change is correlated with serum calcium levels.[27] Absence of significant changes in serum calcium and phosphorus levels can be within normal ranges in groups which receive calcitonin and not suggest that exogenous calcitonin is a factor in the reduction in calcitonin. Synovial fluid is affected more by these changes, and new studies are required to explain the mechanism of this effect.

Apart from their use in making a diagnosis, serum values of osteoblastic-osteoclastic markers are useful for evaluating the effectiveness of treatment and follow-up. Despite being more expensive than BMD measurements, there are advantages, such as increasing patient compliance and reliance on treatment due to earlier evaluation. We consider that measurement of these markers in synovial fluid would create a difference both technically and academically. In the literature, we could not encounter a study evaluating these parameters in synovial fluid. The present study may also be considered to indicate the normal values of synovial fluid CTx, NTx, calcitonin, sialoprotein, as they were examined at baseline. Synovial fluid calcitonin values only were seen to significantly decrease after treatment in Group 1, the calcitonin-receiving group, in this study, demonstrating that synovial fluid values are affected by osteoporosis and osteoporosis treatment. Further larger studies with longer follow-ups are required to investigate the relationship between osteoporosis and synovial fluid and joint cartilage metabolism. In addition to medications which inhibit osteoclastic activity, those which increase osteoblastic activity should also be evaluated and investigated.

Conflics of Interest: No conflicts declared.

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