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ORIGINAL ARTICLE

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The effectiveness of calcitonin on chronic back pain and daily activities in postmenopausal women with osteoporosis

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Abstract The aim of this study was to investigate the effect of nasal calcitonin on chronic back pain and disability attributed to osteoporosis. The study design involved three groups of osteoporotic postmenopausal women suffering from chronic back pain. Group I consisted of 40 women with vertebral fractures, group II of 30 women with degenerative disorders and group III of 40 patients with non specific chronic back pain and without abnormality on plain X-rays. Pain intensity was measured using a numerical rating scale (NRS) and disability due to back pain was measured using the Oswestry disability questionnaire. The patients were randomly assigned to receive, for three months, either 200 IU intranasal salmon calcitonin and 1,000 mg of oral calcium daily (groups IA, IIA, IIIA) or 1,000 mg of oral calcium daily (groups IB, IIB, IIIB). Repeated measures ANOVA showed that there were no significant time, group or interaction effects for pain intensity and disability in any of the groups studied. Mean Oswestry and NRS scores were reduced during the follow-up period in the groups IA, IIIA, but the differences between the two time points were not statistically significant. Intranasal calcitonin has no effect on chronic back pain intensity and functional capacity of osteoporotic women regardless of the presence of fractures, degenerative disorders or chronic back pain of non-specific etiology.

Keywords Calcitonin · Chronic back pain · Osteoporosis

Introduction

Osteoporosis is characterized by bone loss with consequent structural failure leading to bone fragility and fracture. Although the majority of osteoporotic patients suffer from back pain and physical disability, there is no clear evidence relating back pain to low bone mineral density (BMD) [23]. The most apparent reason for back pain in osteoporotic patients is vertebral deformities resulting from fractures [12, 28]. However, in this age group, other reasons may contribute to back pain such as concomitant degenerative disorders of the spine, and other non-specific factors [14].

The goal of treatment in osteoporosis is to prevent bone loss and fractures and to minimize pain and physical disability. A number of medications are available that prevent bone loss or enhance bone mass and strength. Among the antiresorptive agents currently used are estrogens, selective estrogen receptor modulators, calcitonin and bisphosphonates. It is generally accepted that calcitonin is an effective treatment not only in preserving or increasing bone mass but also in reducing fracture risk [4, 6]. Apart from its antiresorptive action

on bone, some claim that it has also an analgesic effect in patients with osteoporotic vertebral fractures [16, 24]. This analgesic property of calcitonin does not appear to be bone-specific, since it has been shown in patients suffering from pain of extraskeletal etiology such as migraine [11], phantom limb pain syndrome [13] and reflex sympathetic dystrophy [1]. However, the effect of calcitonin on chronic back pain and physical disability of patients suffering from BMD, with or without fractures, has not been studied.

The aim of this study was to investigate the effect of nasal calcitonin on chronic back pain and disability, in osteoporotic postmenopausal women.

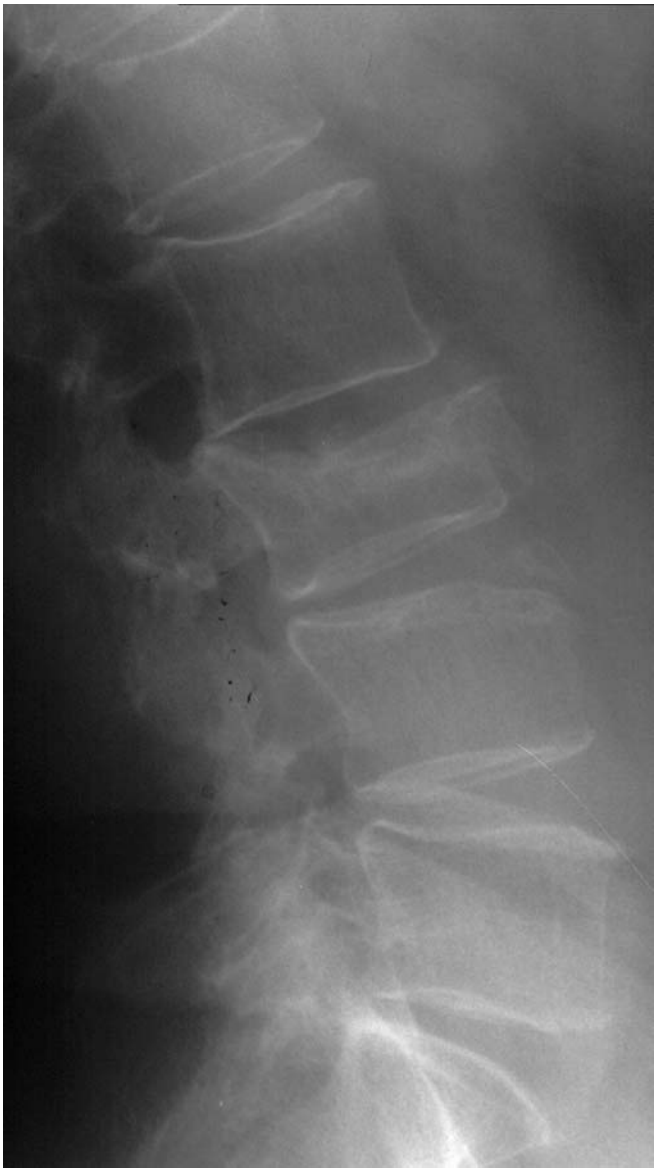

Fig. 1 Lateral X-ray of a patient with osteoporotic structural changes and low-back pain

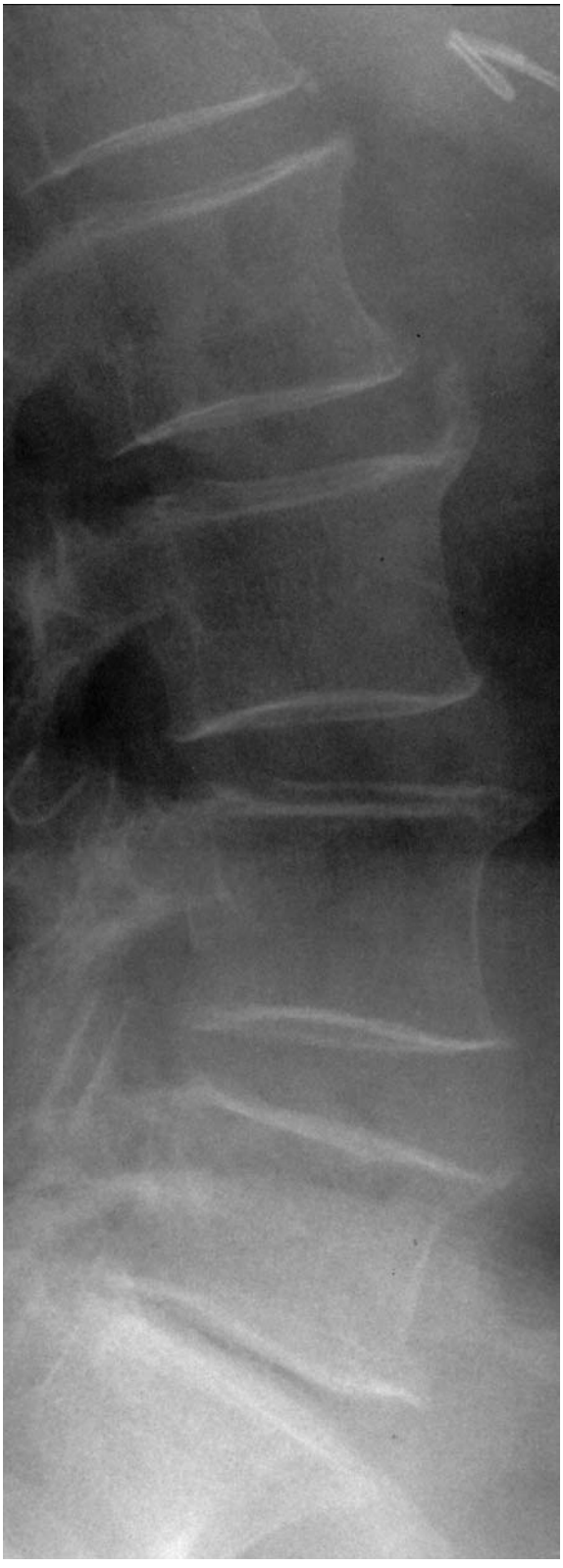

Fig. 2 Lateral X-ray of a patient with osteoporosis without fractures, but with concomitant radiographic evidence of disc degeneration and osteophytes

Patients and methods

This study involved three groups of postmenopausal women. Group I consisted of osteoporotic patients with one or more vertebral fractures without radiological evidence of degenerative disorders (Fig. 1). Group II consisted of osteoporotic patients with degenerative disorders at the lumbar spine, such as degenerative spondylosis and spondylolisthesis, (Fig. 2). Group III consisted of osteoporotic patients without radiographic evidence of vertebral deformities, degenerative disorders or other demonstrable condition, by means of plain radiographic imaging, causing chronic back pain (Fig. 3). All the patients were suffering from chronic back pain of at least 3 months duration.

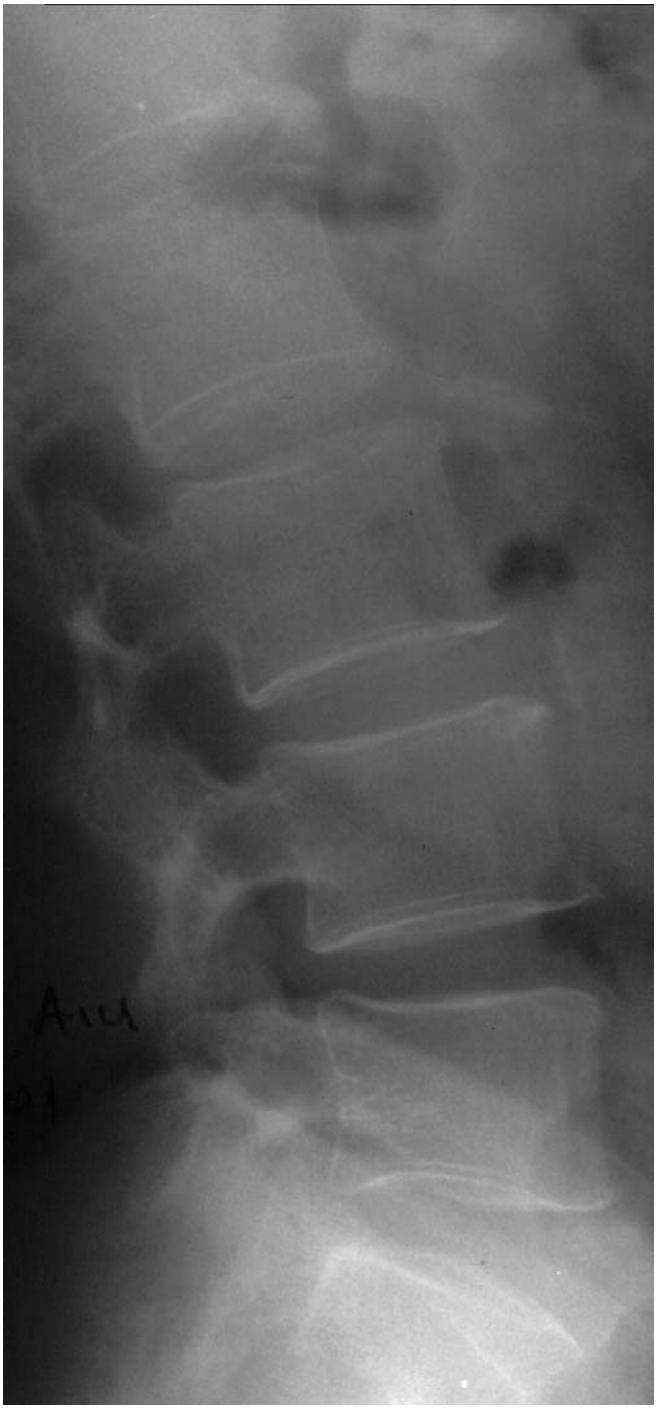

Fig. 3 Radiographic imaging (lateral view) of an osteoporotic patient with non-specific low-back pain

Bone mineral density (BMD), was measured at the lumbar spine and femoral neck (Hologic QDR-1,000 plus Waltham, MA, USA). The coefficient of variation was 0.8% for anteroposterior spine measurements and 1.3% for femoral neck [5]. Women were considered as "having osteoporosis" if their BMD value was 2.5 standard deviations (SD) below the normal mean for young age, according to the WHO definition [30]. Anteroposterior and lateral plain radiographs of the lumbar spine and lateral radiographs of the thoracic spine were obtained at a standardized tube to film distance. The presence and the type of vertebral fractures were assessed morphometrically. Anterior (A), middle (M), posterior (P) heights of the vertebral body and posterior height of the nearest adjacent normal vertebra (PC) were calculated from T4 to L4. Vertebral fractures were defined if the ratio of heights of A/P, M/P, P/PC, were 3 SD below the normal mean, according to McCloskey method [21]. The presence of degenerative changes were evaluated radiologically. Degenerative spondylosis was considered if there were narrowing of the intervertebral space, subchondral sclerosis of the adjacent vertebral body and osteophyte formation [33]. Spondylolisthesis was defined as the greater than 3 mm forward displacement of one vertebra, in relation to the vertebra below [31].

Pain intensity was measured using an 11-point numerical rating scale (NRS) [32]. The scale rates ranged between 0, representing "no pain" and 10 representing "the most severe pain". Functional status of the patients was measured using the Oswestry disability questionnaire [3, 27].

All patients had a detailed medical history and a complete physical examination. They also had laboratory tests including complete blood cell count (WBC), erythrocyte sedimentation rate (ESR), C reactive protein (CRP), liver enzymes, plasma concentrations of calcium, phosphate creatinine and bone-specific alkaline phosphatase. Patients with renal failure, liver disease, hyperparathyroidism, intestinal maladsorption and malignant disease were excluded from the study. None of the patients included in the present study was under treatment or had a history of long-term therapies of anti inflammatory drugs (NSAID), glucocorticoids, myorelaxants, and antidepressant drugs. Patients with radiological evidence of coexistence vertebral fractures and degenerative disorders at the lumbar spine were also

excluded from the study. The majority of the patients had previously received treatment for osteoporosis; however, the washout period was at least 3 months.

To study the effect of calcitonin on chronic back pain and disability, a randomised study was performed. Block (or restricted) randomisation was used to keep the number of patients in the different groups closely balanced. The patients of each group were randomly assigned in 1:1 ratio to receive either 200 IU intranasal salmon calcitonin and 1,000 mg oral calcium daily (groups IA, IIA, IIIA), or 1,000 mg oral calcium daily (groups IB, IIB, IIIB), for 3 months. Patients completed the Oswestry questionnaire and reported the pain intensity reference, at the initial visit to our department, prior to the treatment, and 3 months later. During the treatment no analgesic or anti inflammatory drugs were allowed for more than 4 days. Compliance of the patients was evaluated once a month after a phone contact. All participating patients gave an informed consent at the beginning of the study. The protocol was accepted by the ethics committee of the university hospital.

Summary descriptive statistics are given as mean ± standard deviation. Repeated measures ANOVA with time as the within factor at two levels (baseline and 3 months), treatment at two levels (calcitonin and placebo) and type at three levels (vertebral fractures, degenerative disorders, and non-specific back pain) was used to assess changes over time between the groups and types. The interaction effects between factors was also assessed. In case of significant findings post-hoc Bonferroni adjusted tests were used to pinpoint differences.

Results

Two patients, one from the group IIB and another from the group IIIB, discontinued the calcium treatment after 2 months due to enteric disturbance. Both patients completed the Oswestry questionnaire, reported the pain intensity reference and data were included in our results. There have been no cases on anti-inflammantory or analgesic treatment in the days immediately preceding physical disability and pain intensity assessments. Table 1 shows the characteristics of the study population at baseline. No statistically significant differences in age, weight, height, body mass index (BMI) or BMD at the lumbar spine and femoral neck were detected between groups IA and IB, IIA and IIB, IIIA and IIIB.

Table 2 shows the effect of calcitonin plus calcium and calcium alone in disability at the beginning and at the end of the 3 months treatment. Repeated measures ANOVA showed that there were no significant time, group, or interactive effects for Oswestry and NRS scores. Mean Oswestry and NRS scores were reduced during the follow-up period in the groups IA and IIIA, but the differences between the two time points were not statistically significant. On the contrary, a non-significant increase in Oswestry disability score was observed after the 3 months treatment with calcitonin in patients with degenerative disorders (group IIA). Moreover, there was no remarkable effect of calcitonin plus calcium or calcium alone in any of the activities described by the Oswestry questionnaire (sitting, sleeping, walking, lifting, standing, travelling, lifting social life). Figure 4 and 5 show no statistically significant differences of NRS scores between the groups of calcium alone and calcitonin plus calcium at two time points. In the above figures there is evidence of a high degree of overlap between baseline and 3 months box plots, indicating absence of time and group effects.

Discussion

Several studies have focused on the analgesic effect of calcitonin in osteoporotic patients with vertebral fractures [25, 16]. However, there are no data regarding the analgesic effect of intranasal calcitonin on chronic back pain and disability in women with osteoporosis, without vertebral fractures.

The mechanisms of the analgesic effect of calcitonin is not yet fully understood. Experimental studies have shown that calcitonin may inhibit prostaglandins synthesis or interfere with the calcium flux between neural tissue and cerebrospinal fluid [2].

Table 1 Baseline characteristics of the study groups

Treatment	*n*	Age (years)	BMD(LI-L4) (g/cm^2)	(Femoral neck) (g/cm^2)	BMI (kg/m^2)
Calcitonin + calcium					
Group IA	20	65 ± 6.1	0.700 ± 0.07	0.606 ± 0.06	28.7 ± 4.8
Group IIA	15	62.6 ± 6.4	0.740 ± 0.03	0.663 ± 0.07	30.6 ± 5.3
Group IIA	20	60.8 ± 4.6	0.727 ± 0.07	0.739 ± 0.10	27.2 ± 4.3
Calcium alone					
Group IB	20	66.1 ± 5.1	0.677 ± 0.13	0.608 ± 0.06	29.1 ± 3.1
Group IIB	15	62.8 ± 4.1	0.751 ± 0.06	0.658 ± 0.07	32.2 ± 6.7
Group IIB	20	61.9 ± 5.7	0.731 ± 0.07	0.731 ± 0.07	28.9 ± 3.7

BMD bone mineral density, *BMI* body mass index

Table 2 Effects of treatment on Oswestry score

Group	Type	Time	Mean	Std.Error	95% Confidence Interval	
					Lower bound	Upper bound
Calcitonin and Calcium	IA	Baseline	37	3.7	29.7	44.2
		3 Months	35.1	3.6	28	42.1
	IIA	Baseline	32.7	4.2	24.5	41.2
		3 Months	35.4	4.1	27.2	43.5
	IIIA	Baseline	36	3.7	29.4	43.9
		3 Months	31.4	3.6	22.2	36.3
Calcium alone	IB	Baseline	31.5	3.7	24.2	38.7
		3 Months	31.9	3.6	24.9	39
	IIB	Baseline	29.9	4.2	21.5	38.2
		3Months	32.3	4.1	24.1	40.5
	IIIB	Baseline	29	3.7	21.8	36.3
		3 Months	32.1	3.6	25	39.1

Experimental and preclinical studies have supported the theory that calcitonin may have a direct action on specific receptors in the central nervous system [9, 29]. Calcitonin receptors are located in areas of brain responsible for pain transmission and modulation such as mesencephalon and periaqueductal gray matter [7]. Moreover rising of H-endorphines plasma levels has been observed in patients given salmon calcitonin [22]. Beta-endorphins belong to the family of endogenous opioids and are produced by the pituitary gland [15]. The analgesic role of circulating B-endorphines is however uncertain [8]. Experimental studies in animals suggest that calcitonin binding sites exist in the pituitary gland [20] and might interfere with its secretory function.

The treatment of osteoporotic women with back pain is usually focused on prevention of bone loss, fractures rates, and reduction of back pain and disability. Pamidronate may have an analgesic effect on chronic back pain in the presence of vertebral osteoporotic fractures [10]. However, intravenous pamidronate has not been widely used in clinical practice and its effect on bone density and fractures risk has not been sufficiently studied.

Nasal administration of calcitonin is effective in preventing bone mass loss and decreasing the incidence of vertebral fractures [4]. Additional clinical evidences suggest that calcitonin may have analgesic properties in acute and chronic back pain due to osteoporotic vertebral fractures. Intranasal salmon calcitonin was shown to be equally effective as its intramuscular or rectal administration in decreasing acute pain and improving functional capacity in postmenopausal women with

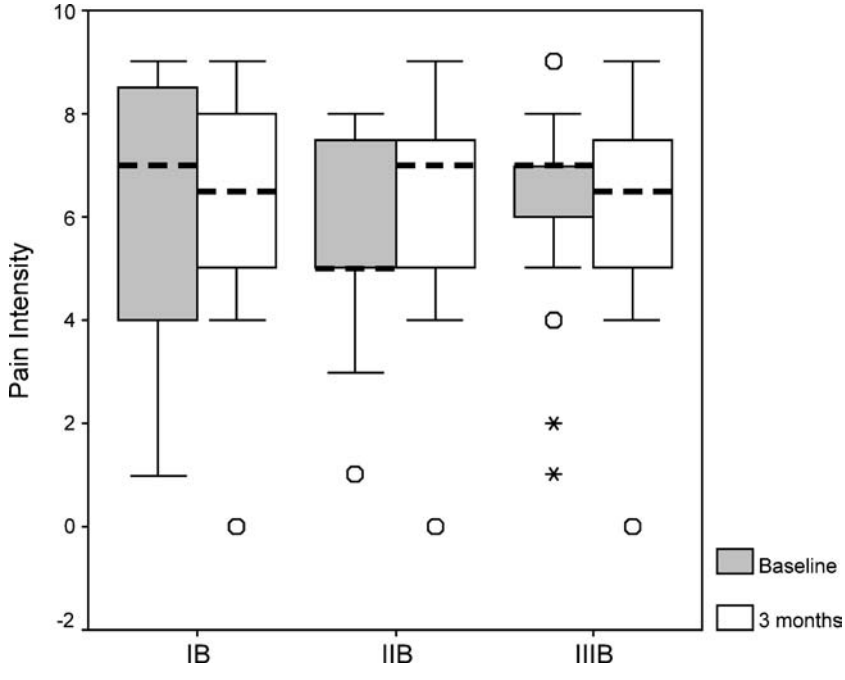

Fig. 4 Illustrate that calcium alone has no effect on chronic back pain. *Circles* indicate values that are potentially outliners (more than 1.51QR from the quartiles), while *asterisks* mark values that are extreme (more than 31QR's from the quartiles)

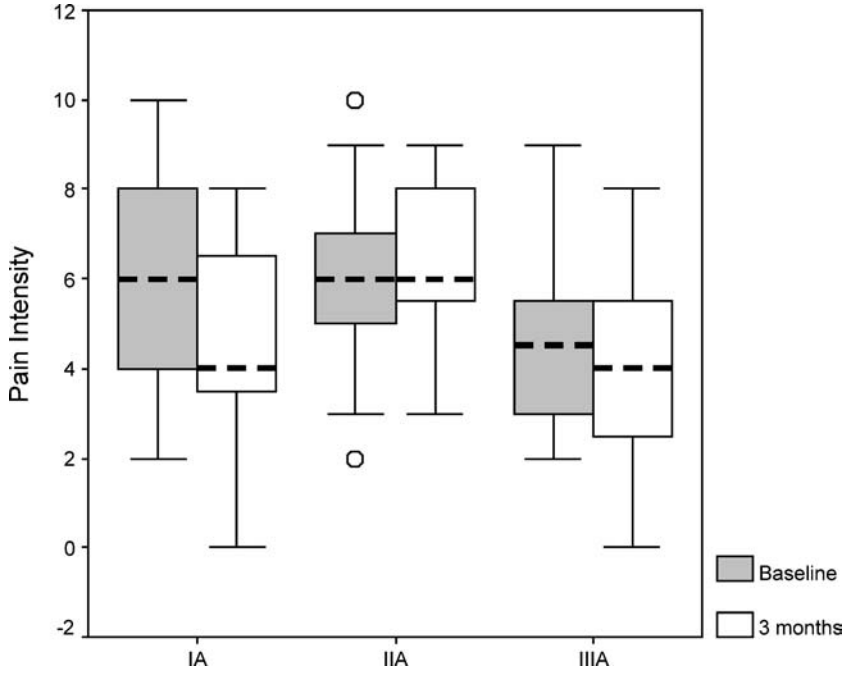

Fig. 5 Demonstrate that the combination of calcitonin and calcium had no convincing evidence that can improve chronic back pain in osteoporotic patients

recent vertebral fractures [16, 17, 26]. In a randomized study of recent vertebral fractures, calcitonin shows a marked decrease in pain intensity accompanied by early mobilization and gradual improvement of functional status [18]. Furthermore, it has been claimed that calcitonin is equally effective in chronic back pain due to osteoporotic vertebral fractures. Peichl et al. examined the effect of 200 IU intranasal salmon calcitonin on bone density, fracture rate and chronic pain in a group of 24 postmenopausal women with established osteoporosis [24]. The authors intranasally administered the calcitonin for 12 months and measured the pain intensity at baseline and at the end of the treatment using a Visual Analogue Scale. They found a 42% pain reduction in the calcitonin group, and 23% in the control group ($P < 0.05$). This finding was reflected by early restoration of sitting, walking and standing in the calcitonin group. The data from our study contradicts this observation. We examined the effect of 3 months treatment with intranasal salmon calcitonin plus calcium on chronic back pain and daily activities in osteoporotic postmenopausal women. We did not find that calcitonin combined with calcium had any beneficial effect on chronic back pain in osteoporotic women with concomitant degenerative disorders or non-specific back pain. Similarly, we did not find any statistical difference in chronic back pain intensity or disability score in osteoporotic patients with vertebral fractures. This finding could be attributable to the short course of administration of calcitonin in this study being 3 months compared to 12 months in the study by Peichl et al. However, the beneficial effect of administration of calcitonin in patients with acute pain previously reported by several authors could be related to the different pathophysiological mechanisms governing the two entities of acute and chronic low back pain (19). Further studies are indicated to investigate the role of calcitonin in patients with chronic back pain.

Conclusions

Intranasal calcitonin does not appear to have any beneficial effect on chronic back pain and functional capacity in women with osteoporosis regardless of the presence of fractures, degenerative disorders or chronic back pain of non-specific origin.

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