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Intranasal Salmon Calcitonin for the Prevention and Treatment of Postmenopausal Osteoporosis

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Abstract. In a randomized, double-blind, placebo-controlled trial, we have studied the effects of intranasal salmon calcitonin (SCT) on bone mineral density (BMD) and biochemical markers of bone turnover over a period of 2 years. Our study comprised 117 Caucasian postmenopausal women, otherwise healthy apart from reduced bone density. They received either intranasal synthetic SCT (200 IU either three times weekly or daily) or placebo. Compared with placebo, daily intranasal calcitonin resulted in no significant bone loss in the lumbar spine, as assessed by dual photon absorptiometry, over the 2-year study period ($P < 0.02$). In this group, women more than 5 years postmenopause, with the lowest baseline bone mass, showed the greatest response to this treatment, with a total increase placebo in lumbar spine BMD of 3.1%. Significant spinal bone loss ($P < 0.005$) occurred in women receiving either placebo or thrice-weekly calcitonin. Although the rates of bone loss in the proximal femur were not significantly different in the three groups, there were differences over time. Whereas bone loss in the daily calcitonin group was insignificant, women who received placebo or thrice-weekly calcitonin experienced significant bone loss ($P < 0.001$). No significant changes in biochemical markers were observed in any group. Therapy was well tolerated and there were no significant treatment-related adverse events. We conclude that intranasal SCT 200 IU daily is effective and safe for the prevention of bone loss in postmenopausal women with reduced bone mass.

Key words: Calcitonin — Intranasal administration — Bone mineral density — Postmenopausal osteoporosis.

Postmenopausal osteoporosis is the most common metabolic bone disease in the western world and is a cause of considerable morbidity and mortality. Osteoporosis can be prevented by various forms of hormone replacement therapy (HRT) [1–3]. However, there are some women who, for a variety of reasons, either cannot or do not wish to take HRT, and therefore alternative antiresorptive agents are needed.

Calcitonin has been shown to be effective in the treatment and prevention of postmenopausal osteoporosis [4] and appears as effective as HRT in arresting postmenopausal bone loss [5]. However, the necessity of intramuscular or subcutaneous injection results in reduced patient compliance [5]. To circumvent this problem, intranasal calcitonin sprays have been developed. Early studies have suggested that this route of administration is effective in both the prevention [6] and treatment [7] of postmenopausal osteoporosis. We have now evaluated the effects of an intranasal preparation of salmon calcitonin (SCT) on bone mass in a group of postmenopausal women studied over 2 years.

Patients and Methods

Patients

One hundred and seventeen Caucasian women between 48 and 64 years of age were recruited. All had ceased menstruating or, in women who had undergone prior hysterectomy, had experienced the onset of menopausal symptoms at least 6 months prior to study entry. Postmenopausal status was always confirmed by measurement of follicle-stimulating hormone (FSH) levels. All patients had reduced bone mineral density (BMD) (at least 10% less than the average for a woman 20–30 years of age, $T < -1.2$) in either the spine or hip. All were apparently healthy, none had undergone bilateral oophorectomy, and none had taken HRT in the previous 3 months; none had received estradiol implants during the previous 12 months or had taken any other treatment known to affect bone metabolism. All gave written informed consent and the study was approved by the Ethics Committees of the Wynn Division of Metabolic Medicine and of King's College Hospital.

In this placebo-controlled study, patients randomized to receive active treatment were provided with 2.0 ml spray bottles containing synthetic SCT [Miacalcic (calcitonin-salmon) Nasal Spray: Sandoz Pharmaceuticals, UK] in a carrier solution. Each activation of the spray delivered 200 IU of synthetic SCT. Patients randomized to receive placebo were given identical bottles containing only the carrier solution.

Patients were randomized to one of four treatment groups: group 1—200 IU SCT daily; group 2—200 IU SCT thrice weekly on Monday, Wednesday, and Friday (MWF); group 3—placebo daily; group 4—placebo thrice weekly (MWF) (Results from groups 3 and 4 were amalgamated at the end of the study.)

Prior to use, the pump attached to each bottle was primed (six activations of the pump) until a uniform cloud of solution was

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Table 1. Demographic data

Treatment group (n)	Mean age years (SD)	Mean weight kg (SD)	Mean height cm (SD)	Mean daily Ca intake g (SD)
200 IU daily				
All patients (36)	55.4 (3.9)	63.0 (7.0)	161.2 (5.5)	627 (244)
Early (18)	52.9 (2.9)	64.0 (7.2)	161.9 (5.3)	643 (218)
Late (18)	57.9 (3.0)	61.9 (6.9)	160.5 (5.8)	610 (277)
200 IU MWF				
All patients (35)	55.9 (3.8)	63.2 (7.8)	162.1 (6.2)	565 (235)
Early (17)	53.5 (2.9)	62.5 (8.7)	161.3 (7.4)	636 (224)
Late (18)	58.2 (3.1)	63.9 (7.0)	162.9 (5.0)	499 (233)
Placebo				
All patients (46)	56.1 (4.3)	62.1 (7.5)	161.0 (5.6)	582 (218)
Early (24)	53.8 (3.7)	61.1 (8.0)	159.5 (6.0)	615 (227)
Late (22)	58.6 (3.6)	63.1 (6.8)	162.7 (4.9)	547 (208)

delivered. Once primed, each bottle provided 14 administrations without the need for further priming. Prior to every administration, each patient was required to blow her nose to ensure the nasal passages were clear, and then insert the pump nozzle deeply into the chosen nostril and activate the spray once. Study medication was administered as one activation in one nostril in the morning.

Study Design

At a screening visit, a complete physical examination, including pelvic and nasal examinations, was performed. Levels of serum gonadal hormones (estrone and estradiol) and gonadotropins were also measured. At the baseline visit, blood was taken for complete hematological and biochemical analyses to exclude patients with any significant abnormalities. Serum thyroid-stimulating hormone (TSH), parathyroid hormone (PTH), and 25-hydroxyvitamin D levels were measured to exclude any women with significant thyroid or parathyroid disease and osteomalacia. Fasting serum glucose levels, serum lipid levels, and biochemical tests of liver function were checked at 12-month intervals during the study.

Biochemical markers of bone metabolism were measured at 6-month intervals. These included serum alkaline phosphatase (total and bone-specific isoenzyme) and the fasting urinary calcium: creatinine and hydroxyproline:creatinine ratios. Serum albumin, calcium (adjusted for albumin levels), and phosphate were also measured.

BMD of the lumbar spine (L1–L4) and hip (femoral neck, greater trochanter, and Ward's triangle) was measured at 6-month intervals by dual photon absorptiometry (DPA) on a Lunar DP3 (Lunar Corporation, Madison, Wisconsin, USA), using software version 2.2. This system utilized a ^{153}Gd source which was replaced four times during the study period. The precision of these measurements and effect of source changes were monitored throughout the study by serial measurements of the BMD of young healthy normals, phantoms, and cadaveric samples. Values from vertebrae with structural deformities, significant osteophyte formation, or other osteoarthritic changes were excluded from the analyses. Likewise, values from any vertebrae that were overlaid with soft tissue calcifications were also excluded. Where possible, the average value of L2–L4 was used, but when this was not possible the same vertebral combination measurement was used throughout in each individual patient.

Quantitative computed tomography (QCT) measurements of the lumbar trabecular BMD (L2–L4) were also performed at yearly intervals using a Siemens Somatom 2 CT scanner [8]. Lateral radiographs of the thoracic and lumbar spine (T4–T12, L1–L5) were obtained at baseline and again 24 months later at the end of the study. These radiographs were examined both qualitatively and quantitatively for evidence of fractures. A height reduction threshold of at least 20% was used to determine fracture deformity. From digitized radiographs, and using specially designed computer software [9], measurements of anterior, mid, and posterior vertebral heights were made to determine fracture occurrence by Kleerekoper's method [9], Melton's method [10], and a height-reduction-from-baseline method.

Compliance was assessed at every visit by comparing the amount of unused medication returned with the amount of medication dispensed at the previous visit. A patient was considered compliant if she took at least 75% of the prescribed nasal spray in any 1-year period.

Dietary calcium intake was assessed at baseline and at 12 and 24 months by means of detailed questionnaires completed by each patient. No patient received any calcium supplement during the study.

Statistics

Between-group comparisons of efficacy were made with a two-sample, two-tailed t test using the pooled error term from a one-way analysis of variance (ANOVA). A P value of 0.025 was taken as indicating a significant result for between-group comparisons by applying the Bonferroni criterion for multiple-comparison adjustments. Within-group comparisons for changes from baseline were performed using a one-sample, two-tailed t test. A P value of 0.05 was used to indicate a significant change from baseline.

Results

Demographic data for the 117 women who entered the study are shown in Table 1. There were no significant baseline differences in any parameter among the treatment groups. Dietary calcium intake did not change significantly during the study (data not shown). To assess the effect of time since loss of ovarian function on skeletal response to calcitonin, all patients were subdivided according to menopausal age.

Early postmenopausal: patients whose last menses occurred less than 5 years ago or, for hysterectomized patients, whose onset of menopausal symptoms was less than 5 years ago.

Late postmenopausal: patients whose last menses occurred more than 5 years ago or, for hysterectomized patients, whose onset of menopausal symptoms was more than 5 years ago.

Hysterectomized women who had no reported menopausal symptoms, or women in whom menses data were missing, were classified by their age: those under age 55 were classified as early postmenopausal and those over age 55 were classified as late postmenopausal. The mean time

Table 2. Patients discontinuing trial, with reasons

Reason	No. of patients
Adverse reaction	
Rhinitis	2
Taste perversion	1
Epistaxis	1
Illness unrelated to study medication	
Breast cancer	1
Back pain	1
Pneumonia	1
Primary hyperparathyroidism	1
Protocol violation	
Use of corticosteroids to treat unrelated illness	4
Hormone replacement	2
High bone density	1
Nonmedical reasons	4
Treatment ineffective	1
Total	20

since menopause in the early postmenopausal group was 35.0 months (range 5–60) and in the late postmenopausal group 93.4 months (range 61–122). There was no significant difference in age at menopause in any of the three treatment groups of the two population subgroups.

Twenty patients withdrew voluntarily or were excluded by the investigators, leaving 97 who were compliant with the study medication and completed the 2-year study. Reasons for withdrawal are given in Table 2. Results presented below are for these 97 patients who are considered valid completers.

Lumbar Spine BMD

DPA Results (Table 3). The long-term, *in vivo* precision for lumbar spine BMD during the study was 1.25%. The system response to replacement of the ^{153}Gd source was predictable and well within specifications. At baseline, there were no significant differences in BMD among the three treatment groups. Results were analyzed by treatment group for all women, and a separate analysis was conducted for the early and late postmenopausal women. For all women, significant bone loss occurred by 12 months in those receiving placebo or thrice-weekly calcitonin [−1.5% ($P < 0.005$) and −1.8% ($P < 0.005$), respectively]. This loss continued to the end of the study [−2.4% ($P < 0.001$] and −2.1% ($P < 0.005$), respectively]. However, daily intranasal calcitonin therapy resulted in no significant bone loss over the 2-year study period (Fig. 1).

Overall, the late postmenopausal subgroup had a slightly lower bone density than the early subgroup at baseline but showed the greatest response to active daily treatment, with an increase in bone density of 1.4% over 2 years. This change was 3.1% greater than in the placebo group by the end of the study. This difference first became apparent after 6 months and increased throughout the study.

In contrast, in the early postmenopausal patients, bone loss continued in all treatment groups. Between-group comparisons for these women showed no significant differences in the rates of bone loss among any of the three treatment groups, although the trend of the daily calcitonin group showing the best response persisted.

QCT Results (Table 4). The precision for this measurement was 2.2% [8]. Mean percentage changes from baseline were negative in all subgroups regardless of treatment after 2 years, but again the trend of the daily calcitonin group showing the best effect persisted, although between-group comparisons showed no significant differences.

Proximal Femur BMD

Femoral Neck (Table 5). The long-term *in vivo* precision of measurement at the femoral neck during the study was 1.9%. BMD fell significantly from baseline in all women receiving placebo (−2.2%, $P < 0.001$). In the late postmenopausal subgroup there was no significant change in BMD over the 2 years in those who took daily calcitonin. In the early postmenopausal subgroup, rates of bone loss in those who received placebo and those receiving daily calcitonin were similar (−2.6% and −2.0%, respectively; $P < 0.05$). There was a small, nonsignificant bone loss in those who received thrice-weekly calcitonin.

Trochanter (Table 6). Changes in BMD at the trochanter mirrored the results in the lumbar spine, probably because the trochanter is composed largely of trabecular bone. Thus, BMD tended to fall in all early postmenopausal patients but increased in the late postmenopausal patients treated with either calcitonin regimen. BMD fell significantly in the placebo group.

Ward's Triangle (Table 7). The overall trend at the Ward's triangle was for BMD to fall in all patients, irrespective of subgroup or treatment group. The fall in BMD (−4.3% by 24 months) was statistically significant ($P < 0.01$) in all those who received placebo and in the early postmenopausal subgroup who received thrice-weekly calcitonin (−4.6% and −5.0% at 12 and 24 months, respectively; $P < 0.05$).

Biochemical Markers of Bone Turnover

Results of measurement of biochemical markers of bone turnover were variable over the 2-year study period in all groups. No significant changes, compared with placebo, were observed (data not shown).

Vertebral Deformities

Too few events occurred in any group during the study to permit analyses of fracture rate (data not shown).

Safety and Acceptability

During the study, patients experienced a variety of minor adverse events and demonstrated sporadic laboratory abnormalities. However, their distribution throughout the study population was random and none could be related to the study medication.

Thirty-four percent of patients receiving calcitonin and 24% of those receiving placebo complained of minor local nasal or respiratory disorders. Rhinitis was more common in

Table 3. Changes in lumbar vertebral DPA BMD*

Treatment group	0 mos.	6 mos.	12 mos.	18 mos.	24 mos.
All patients					
200 IU daily	1.13 ± 0.13	0.3	0.2[a]	−0.4	−0.4[a]
200 IU MWF	1.11 ± 0.10	−0.9	−1.8	−1.2	−2.1[c]
Placebo	1.09 ± 0.14	−0.7	−1.5	−1.5	−2.4[d]
Late postmenopause					
200 IU daily	1.10 ± 0.12	1.2[a]	1.0[a]	1.1	1.4[b]
200 IU MWF	1.09 ± 0.10	−0.4	−1.0	−0.5	−1.1
Placebo	1.11 ± 0.11	−1.2	−1.2	−1.1	−1.7[c]
Early postmenopause					
200 IU daily	1.17 ± 0.13	−0.6	−0.6	−1.7	−2.6
200 IU MWF	1.13 ± 0.11	−1.5	−2.5	−2.0	−3.2[d]
Placebo	1.08 ± 0.17	−0.3	−1.8	−1.9	−3.1[c]

* Baseline mean ± SD g/cm^2 and mean % change
[a] $P < 0.025$, [b] $P < 0.01$ between-group comparison
[c] $P < 0.01$, [d] $P \leq 0.001$ within-group comparison

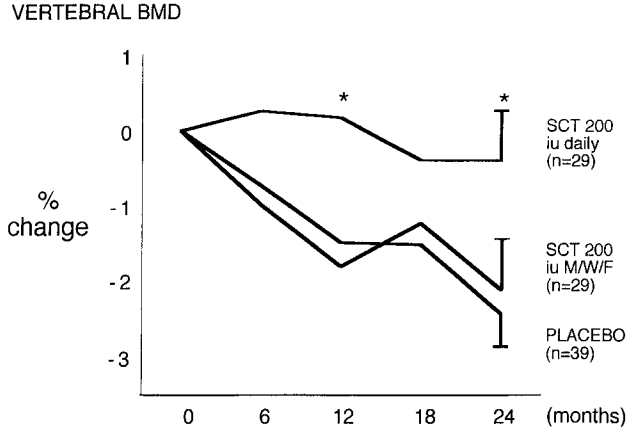

Fig. 1. Percentage change in vertebral BMD in all patients treated with either intranasal salmon calcitonin (SCT) 200 IU daily, SCT 200 IU thrice weekly (MWF), or placebo. Vertical bars represent SEM (*$P \leq 0.02$).

Table 4. Changes in lumbar vertebral QCT BMD*

Treatment group	0 mos.	12 mos.	24 mos.
All patients			
200 IU daily	102.5 ± 20.3	−1.0	−4.7[b]
200 IU MWF	101.7 ± 20.6	−2.7[a]	−5.4[b]
Placebo	101.0 ± 25.5	−2.7[a]	−6.3[b]
Late postmenopause			
200 IU daily	94.4 ± 15.0	−0.1	−2.7
200 IU MWF	97.1 ± 21.1	−2.0	−4.4[a]
Placebo	96.4 ± 18.2	−1.4	−4.1[a]
Early postmenopause			
200 IU daily	113.8 ± 22.0	−2.2	−7.1[b]
200 IU MWF	107.3 ± 19.5	−3.5[b]	−6.5[b]
Placebo	107.3 ± 32.8	−4.5[b]	−9.2[b]

* Baseline mean ± SD mg/cm^3 and mean % change
[a] $P < 0.05$ within-group comparison
[b] $P \leq 0.01$ within-group comparison

the calcitonin-treated patients (23%) than in those given placebo (7%). No nasal ulcers were reported in any patient.

There was an 11% dropout rate in women who received calcitonin compared with 13% in those who received placebo. Overall acceptability at the end of the study was excellent, with greater than 89% of all patients describing calcitonin therapy as either good or very good.

Discussion

Our data from this study indicate that daily calcitonin administered intranasally is effective in preventing postmenopausal bone loss, and hence osteoporosis, in the spine although this effect was largely confined to those women more than 5 years postmenopause.

Although mean vertebral bone mass (as measured by DPA) was conserved in the group who received daily calcitonin and who completed the study, those who were 5 or more years postmenopausal showed the best response, with a small increase in BMD. Furthermore, a positive response was detected as early as 6 months after the start of therapy which continued for up to 24 months. Whether bone mass would continue to increase with further duration of therapy is unknown.

The BMD results obtained in the spine by QCT and in the proximal femur by DPA confirmed the trend shown in the spine by DPA, but did not achieve statistical significance. This may have been due to greater variability in the measurements.

The results of measuring the biochemical indices of bone turnover were highly variable and of little value. This variability may be because the specificity, precision, and accuracy of the measurements are poor [11], and perhaps because the biological variability of such parameters is high.

Several other studies support our findings. Overgaard et al. [7] reported conservation of bone mineral content in the forearm and lumbar spine of women with established postmenopausal osteoporosis using 200 IU intranasal SCT daily. In contrast with our study, they also showed highly significant biochemical changes indicating decreased bone turnover in their study population. Reginster et al. [12] showed that 200 IU of intranasal SCT produced a similar

Table 5. Changes in femoral neck BMD*

Treatment group	0 mos.	12 mos.	24 mos.
All patients			
200 IU daily	0.86 ± 0.10	−0.7	−1.5
200 IU MWF	0.82 ± 0.08	−1.1	−1.5
Placebo	0.82 ± 0.09	−0.9	−2.2[b]
Late postmenopause			
200 IU daily	0.84 ± 0.08	0.1	−0.1
200 IU MWF	0.81 ± 0.07	−0.0	−2.2[a]
Placebo	0.83 ± 0.09	−0.4	−1.8[a]
Early postmenopause			
200 IU daily	0.88 ± 0.12	−1.4	−2.0
200 IU MWF	0.83 ± 0.08	−2.4	−0.8
Placebo	0.81 ± 0.10	−1.4[b]	−2.6[a]

* Baseline mean ± SD g/cm^2 and mean % change
[a] $P < 0.05$ within-group comparison
[b] $P \leq 0.01$ within-group comparison

Table 6. Changes in trochanteric BMD*

Treatment group	0 mos.	12 mos.	24 mos.
All patients			
200 IU daily	0.73 ± 0.10	0.4	−1.9
200 IU MWF	0.73 ± 0.08	0.8	−0.2
Placebo	0.72 ± 0.10	−1.7[a]	−2.8[a]
Late postmenopause			
200 IU daily	0.71 ± 0.10	2.5	0.7
200 IU MWF	0.72 ± 0.09	2.6[a]	1.0[a]
Placebo	0.72 ± 0.10	−1.1	−2.4[a]
Early postmenopause			
200 IU daily	0.74 ± 0.10	−1.7	−4.2[a]
200 IU MWF	0.74 ± 0.07	−1.3	−1.7
Placebo	0.71 ± 0.11	−2.3[a]	−3.2[a]

* Baseline mean ± SD g/cm^2 and mean % change
[a] $P < 0.05$ within-group comparison

Table 7. Changes in Ward's Triangle BMD*

Treatment group	0 mos.	12 mos.	24 mos.
All patients			
200 IU daily	0.76 ± 0.12	−0.8	−2.2[a]
200 IU MWF	0.69 ± 0.08	−1.6	−3.0[a]
Placebo	0.69 ± 0.12	−2.4[b]	−4.3[b]
Late postmenopause			
200 IU daily	0.74 ± 0.11	−0.6	−2.2
200 IU MWF	0.68 ± 0.08	1.0	−1.3
Placebo	0.69 ± 0.12	−1.7	−3.1[b]
Early postmenopause			
200 IU daily	0.77 ± 0.13	−1.0	−2.3
200 IU MWF	0.71 ± 0.07	−4.6[b]	−5.0[b]
Placebo	0.70 ± 0.13	−3.1[a]	−5.5[b]

* Baseline mean ± SD g/cm^2 and mean % change
[a] $P < 0.05$ within-group comparison
[b] $P \leq 0.01$ within-group comparison

hypocalcemic response to 80 IU administered intramuscularly. Rizzato et al. [13] showed that 200 IU daily via a nasal spray could also protect against glucocorticoid-induced osteoporosis. One recent study of intranasal calcitonin administration in women with postmenopausal osteoporosis demonstrated a significant reduction in new vertebral fractures compared with results in women receiving placebo over a 2-year period [14]. Although this result is encouraging, suggesting that maintenance of bone density by calcitonin translates into prevention of fracture, it should be noted that the number of fracture events in this study was very low. Longer studies of larger numbers of patients are needed to confirm these findings.

We were unable to demonstrate significant prevention of bone loss in the proximal femur by calcitonin compared with placebo. However, no significant loss from baseline was found with daily calcitonin treatment, and it may be that a greater number of patients or a longer study period is required to demonstrate a significant effect. It is encouraging to note that calcitonin has been shown to reduce the incidence of hip fractures in elderly women [15], suggesting that this apparent effect of calcitonin on femoral neck bone density is real.

HRT remains the first-line therapy for the prevention and treatment of osteoporosis. Other potential antiresorptive therapies include bisphosphonates. Studies have shown that various bisphosphonates may be useful in both the prevention and treatment of osteoporosis [16–18]. Bisphosphonates have the advantage of being active when administered orally. However, they have a very long skeletal half-life and their long-term side effects remain unknown. Furthermore, etidronate has been shown to produce focal osteomalacia in some patients with Paget's disease even when given at very low doses [19]. In contrast, the long-term safety of calcitonin is well established.

Conclusions

Calcitonin is a therapeutic option and this study has clearly demonstrated that intranasal SCT, 200 IU daily, prevents postmenopausal bone loss and hence osteoporosis, particularly in women beyond 5 years postmenopause. Less-frequent doses appear ineffective. Acceptability of the nasal spray appears to be excellent, with none of the side effects associated with either subcutaneous or intramuscular injection of calcitonin. Thus, intranasal calcitonin should prove a major addition to the armamentarium for the prevention and treatment of osteoporosis. Intranasal calcitonin could be particularly appropriate for use in women with established osteoporosis who do not wish to take HRT and in whom there are no other indications to take estrogens, such as the persistence of menopausal symptoms or increased risk of arterial disease. Older women in their late 60s and beyond are often reluctant to take therapy that may result in uterine bleeding; alternative therapies such as calcitonin may be of particular value in such patients.

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References

1. Lindsay R, Hart DM, Aitken JM, MacDonald EB, Anderson JB, Clarke AC (1976) Long-term prevention of postmenopausal osteoporosis by oestrogen. Lancet i:1038–1041
2. Christiansen C, Christensen MS, McNair P, Hagen C, Stocklund K, Transbøl IB (1980) Prevention of early postmenopausal bone loss: a controlled 2-year study in 315 normal females. Eur J Clin Invest 10:273–279
3. Hillard TC, Whitcroft SJ, Marsh MS, Ellerington MC, Lees B, Whitehead MI, Stevenson JC (1994) Long-term effects of transdermal and oral hormone replacement therapy on postmenopausal bone loss. Osteoporos Int 4:341–348
4. Gruber HE, Ivey JL, Baylink DJ, Matthews M, Nelp WB, Sisom K, Chesnut CH III (1984) Long-term calcitonin therapy in postmenopausal osteoporosis. Metabolism 33:295–303
5. MacIntyre I, Stevenson JC, Whitehead MI, Wimalawansa SJ, Banks LM, Lealy MJR (1988) Calcitonin for prevention of postmenopausal bone loss. Lancet i:900–902
6. Reginster JY, Denis D, Albert A, Deroisy R, Lecart MP, Fontaine MA, Lambelin P, Franchimont P (1987) 1-year controlled randomised trial of prevention of early postmenopausal bone loss by intranasal calcitonin. Lancet ii:1481–1483
7. Overgaard K, Riis BJ, Christiansen C, Pdenphant J, Johansen JS (1989) Nasal calcitonin for treatment of established osteoporosis. Clin Endocrinol 30:435–442
8. Banks LM, Stevenson JC (1986) Modified method of spinal computed tomography for trabecular bone mineral measurements. J Comput Assist Tomogr 10:463–467
9. Kleerekoper M, Parfitt AM, Elliss BI (1984) Measurement of vertebral fracture rate in osteoporosis. In: Christiansen C, Arnaud CD, Nordin BEC, Parfitt AM, Peck WA, Riggs BL (eds) Osteoporosis. Proc Copenhagen Int Symp on Osteoporosis, vol 1. Stiftsbogtrykkeri, Aalborg, pp 103–109
10. Melton LJ III, Kan SH, Frye MA, Wahner HW, OFallon WM, Riggs BL (1989) Epidemiology of vertebral fractures in women. Am J Epidemiol 129:1000–1011
11. Kanis JA (1991) Pathophysiology and treatment of Paget's disease of bone. Martin Dunitz Ltd, London, p 298
12. Reginster JY, Deroisy R, Denis D, Lecart MP, Sarlet N, Franchimont P (1988) Is there any place for salmon calcitonin in prevention of postmenopausal bone loss? Gynaecol Endocrinol 2:195–204
13. Rizzato G, Schiraldi G, Tosi G, Locicero S, Montemurro L, Zanni D, Sisti S (1989) Administration of salmon calcitonin nasal spray for long-term treatment of corticosteroid-induced osteoporosis. A preliminary report. Curr Ther Res 45:761–766
14. Overgaard K, Hansen MA, Jensen SB, Christiansen C (1992) Effect of calcitonin given intranasally on bone mass and fracture rates in established osteoporosis: a dose-response study. Br Med J 305:556–561
15. Kanis JA, Johnell O, Gullberg B, Allander E, Dilsen G, Gennari C, Vas AAL, Lyritis GP, Mazzuoli G, Miravet L, Passeri M, Cano RP, Rapado A, Ribot C (1992) Evidence for efficacy of drugs affecting bone metabolism in preventing hip fracture. Br Med J 305:1124–1128
16. Storm T, Thamsborg G, Steiniche T, Genant HK, Srensen OH (1990) Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in women with postmenopausal osteoporosis. N Engl J Med 322:1265–1271
17. Harris ST, Watts NB, Jackson RD, Genant HK, Wasnich RD, Ross P, Miller PD, Licata AA, Chesnut CH III (1993) Four-year study of intermittent cyclic etidronate treatment of postmenopausal osteoporosis: three years of blinded therapy followed by one year of open therapy. Am J Med 95:557–567
18. Liberman UA, Weiss SR, Broll J, Minne HW, Quan H, Bell NH, Rodriguez-Portales J, Downes RW, Dequeker J, Favus M, Seeman E, Recker RR, Capizzi T, Santora AC, Lombardi A, Shah RV, Hirsch LJ, Karpf DB (1995) Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. N Engl J Med 333:1437–1443
19. Boyce BF, Smith L, Fogelman I, Johnston E, Ralston S, Boyle IT (1984) Focal osteomalacia due to low-dose diphosphonate therapy in Paget's disease. Lancet i:821–824