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VI. Meta-Analysis of Calcitonin for the Treatment of Postmenopausal Osteoporosis

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A. Abstract

Objective: To review the effect of calcitonin on bone density and fractures in postmenopausal women.

Data Source: We searched MEDLINE and EMBASE from 1966 to 2000 and examined citations of relevant articles and the proceedings of international osteoporosis meetings. We contacted osteoporosis investigators to identify additional studies and primary authors for unpublished data.

Study Selection: We included 30 studies that randomized women to calcitonin or an alternative (placebo or calcium and/or vitamin D) and measured bone density or fracture incidence for at least 1 yr.

Data Extraction: For each trial, three independent reviewers assessed the methodological quality and abstracted data.

Data Synthesis: Calcitonin reduced the incidence of vertebral fractures, with a pooled relative risk (RR) of 0.46 [95% confidence interval (CI) 0.25–0.87, $P = 0.02$, n = 1404, 4 trials]. However, the RR from the one relatively large randomized controlled trial (RCT) was 0.79 (95% CI 0.62–1.00, $P = 0.05$, n = 1108). For nonvertebral fractures, the pooled RR was 0.52 (95% CI 0.22–1.23, $P = 0.14$, n = 1481, 3 trials). Once again, the single large trial showed a less impressive effect than the smaller trials (RR 0.80, 95% CI 0.59–1.09, $P = 0.16$, n = 1245). For bone density of the lumbar spine, the pooled weekly dose of 250 to 2800 IU per week resulted in significant increase in the weighted mean difference (WMD) of 3.74 (2.04–5.43, $P < 0.01$, n = 2260, 24 trials). The combined forearm showed a similar effect, with a WMD of 3.02 (95% CI 0.98–5.07, $P < 0.01$, n = 468, 9 trials). At the femoral neck, the pooled weighted mean difference showed a nonsignificant trend toward benefit, WMD 3.80 (95% CI −0.32–7.91, $P = 0.07$, 9 trials, n = 513). Methodologically weaker studies tended to show greater effects on bone density, and the lumbar spine results suggested the possibility of publication bias.

Conclusions: Calcitonin likely increases bone density in postmenopausal women predominantly at the lumbar spine and forearm for weekly doses of greater than 250 IU, although the true effect may be smaller than the pooled estimate would suggest. Calcitonin likely reduces the risk of vertebral fracture; its effect on nonvertebral fracture remains uncertain.

B. Background

CALCITONIN IS AN endogenous polypeptide hormone that inhibits bone resorption by osteoclasts (1). A number of randomized trials have suggested that sc or intranasal calcitonin is effective in prevention of trabecular bone loss in late menopause (2–5). An observational study by Kanis *et al*. (6) demonstrated a 30% reduction in hip fractures in patients treated with injectable calcitonin. In addition, calcitonin may have an analgesic effect in women with acute vertebral fractures, which appears to be independent of its effect on osteolastic resorption (4, 7).

Salmon calcitonin is approximately 40–50 times more potent than human calcitonin. and the majority of the randomized trials have used salmon calcitonin(7). Calcitonin was initially administered by injection but is now available in an intranasal formulation, which provides 25–50% of the biological activity of the parenterally administered dose (200 IU of nasal calcitonin would be equivalent to 50 IU of injectable). The nasal formulation is widely available in the United States, Canada, and Europe. Although the development of antibodies to calcitonin presents a potential problem, the biological or clinical significance of antibody development remains speculative (5, 8). There is also concern that prolonged exposure to calcitonin may down-regulate the calcitonin receptors on osteoclasts, which could allow the osteoclasts to recover from the suppressive action of calcitonin (9). Intermittent administration of calcitonin has been recommended as a strategy to avoid clinical resistance.

National Osteoporosis Foundation-published guidelines have recommended calcitonin as an alternative to hormone replacement therapy or alendronate for patients who have found other treatments unsuccessful or difficult to tolerate (10).

Two previous meta-analyses of calcitonin demonstrated the efficacy of calcitonin in increasing bone density and decreasing vertebral fractures, but suffered from a number of limitations (11, 12). The authors of one meta-analysis (11) used the number of fractures as opposed to number of individuals with fractures. Neither group of investigators contacted authors or industry sources to confirm data accuracy and obtain important information omitted in the original reports. The authors noted the heterogeneity in treatment

Abbreviations: BMD, Bone mineral density; CI, confidence interval; PROOF, Prevent Recurrence of Osteoporotic Fractures; RCT, randomized controlled trial; RR, relative risk; QCT, quantitative computed tomography; WMD, weighted mean difference.

effect, but failed to fully explore sources of heterogeneity. The Kanis and McCloskey (12) meta-analyses included pre- and postmenopausal as well as steroid-induced postmenopausal women. Finally, and most important, these reviews failed to include all trials, and in particular were completed prior the recent fracture trial, the Prevent Recurrence of Osteoporotic Fractures trial (PROOF) (13, 14).

We therefore conducted a systematic review and meta-analysis of the efficacy of calcitonin on bone mineral density (BMD) and fractures. Our goals included considering all published and unpublished RCTs, estimating effects on vertebral and nonvertebral fractures, and determining the consistency of calcitonin effect on postmenopausal women across different treatment groups.

C. Methods

We followed the procedure defined by the Cochrane Collaboration (15) for conducting systematic reviews as outlined in *Section I*.

1. Inclusion criteria. Trials satisfied the following inclusion criteria: 1) RCTs of at least 1-yr duration, comparing calcitonin therapy *vs.* placebo or calcium and/or vitamin D; 2) outcomes included BMD (sites included outlined in the *Section I*) or fracture incidence; and 3) participants were postmenopausal women.

2. Study search and selection. Using the strategy presented in *Section I*, we searched for relevant studies published from 1966 to October 2000 and hand-searched conference abstract books from international meetings and the proceedings of the Food and Drug Administration. Our search included the following key and text terms: calcitonin, nasal calcitonin, Miacalcin, postmenopausal, fractures, and bone mineral density.

Two reviewers (A.C., V.R.) examined all potentially relevant trials. For abstracts consistent with study eligibility, we obtained the full text. Reviewers resolved disagreements in study selection by consensus.

3. Methodological quality. Three reviewers (A.C., V.R., N.Z.) independently extracted all data, which included evaluation of each trial for four characteristics related to methodological quality: concealment, intention-to-treat analysis, blinding, and the completeness of follow-up.

4. Data collection. The reviewers also abstracted data related to study population, treatment duration, dosage, and patient status with respect to outcomes at baseline and end of study. When the article presented inadequate or unclear data, we contacted the authors for additional information.

5. A priori hypotheses regarding heterogeneity. We developed *a priori* hypotheses that might explain the heterogeneity of study results. Specifically, we compared groups according to: 1) population—prevention *vs.* treatment; 2) duration of treatment; 3) route of administration—sc, ip, and rectal *vs.* nasal; 4) dose of calcitonin; 5) concurrent treatments including total calcium intake or vitamin D; 6) administration—daily *vs.* intermittent; 7) SD provided or estimated; and 8) individual components of the quality assessment—including concealed randomization, blinding, and loss to follow-up (less than 20% *vs.* greater).

If the T-score was available, we divided studies into those that restricted their population to women whose bone density was at least two SD values below peak bone mass (treatment) and those that included women in which the bone density was within 2 SD values of the mean (prevention) mass. The precision of quantitative computed tomography (QCT) is not as good as dual x-ray absorptiometry of the posterior/anterior spine (16). QCT provides a measure of volumetric density, and higher rates of bone change have been reported with QCT. Thus, we decided to pool all bone density measures but QCT.

Given that there are different types of osteoporotic fractures and that treatments may impact more on certain types of fractures, we conducted analyses on the following endpoints: all vertebral fractures and nonvertebral fractures.

6. Statistical analysis. We used a random-effects model, which includes differences between studies in calculating the variance estimate, for all final analyses of all treatment effects (17).

As outlined in detail in *Section I*, we conducted separate analyses for each bone density site (lumbar spine, femoral neck, total body, and combined forearm; one third distal radius and then one third distal radius and ulna). We constructed regression models, which included parameters for each year, and for nasal *vs.* other routes of administration. Thus, independent variables were year and route of administration, and the dependent variable the size of the treatment effect. We sought the most parsimonious model for our final analysis.

In considering the impact of dose, we dealt with the great variability in individual calcitonin dose and in frequency of administration by calculating a weekly dose of calcitonin based on the daily dose and the number of times the patients received that dose in the course of a week.

After using the regression results to decide on the extent of pooling across groups with different routes of administration or length of follow-up, we calculated the impact of treatment on bone density for each stratum that remained separate. We decided that in addition to using the regression analyses to inform our pooling decisions, we would pool any two doses if the random-effects CI for one was completely contained within the CI for the other.

We calculated heterogeneity between studies using the χ^2 distribution with N-1 degrees of freedom, where N is the number of studies (17). Irrespective of the results of the tests of heterogeneity, for each of the *a priori* hypotheses, we divided the studies into two groups based upon the heterogeneity analyses. For each *a priori* hypothesis, we then tested whether we could reject chance as the explanation of the variability in WMDs between the two groups (18).

For fractures, a weighted average of the relative risk was calculated. We constructed two-by-two tables for vertebral and nonvertebral fractures in each study for which the data were available and calculated the associated RR.

D. Results

1. Trial characteristics. We identified 770 articles from our electronic search strategy and 6 from hand searching the reference lists, and we retrieved 75 for closer examination. Eleven of the trials had no placebo or control group to compare (19–29). Thirteen trials included control groups, but treatment allocation was determined by a mechanism other than randomization (30–42). Six of the trials were duplicate populations described in other trials (43–48). One trial examined only premenopausal women (49). Seven trials presented BMD for less than 1 yr, or treatment duration was less than 1 yr (50–56). One trial (57) reported only metacarpal index. Three trials measured only the ultra-distal radius site, which was excluded from analyses *a priori* (58–60), and three trials measured BMD using QCT measurements (61–63). For the PROOF trial (13), originally identified in abstract form, we used the most recent data from the 2000 PROOF publication by Chesnut *et al*. (14).

In total, 30 trials (14, 64–92) were RCTs (n = 3993, treatment n = 2569) (Fig. 1 and Table 1). All of the trials except two (79, 81) used salmon calcitonin. Sixteen trials were classified as treatment trials, thirteen were classified as prevention trials, and one trial was a combination prevention and treatment trial (68). Fifteen trials used some blinding, and 16 concealed allocation to treatment. Twenty-eight trials provided a description of dropouts and withdrawals; 4 trials had a loss to follow-up of less than 1%, 2 trials from 2–4%, 13 trials from 5 to 20%, and of the remaining 9 trials over 20% were lost to follow-up (Table 1). Large loss to follow-up is a threat to trial validity and can result in biased estimates of the treatment effect, spuriously increasing or decreasing the magnitude of treatment effect. For example, if individuals at greater risk of fracture are lost preferentially from the control arm, the results may bias against the treatment.

2. Vertebral and nonvertebral fractures. Pooling the four trials (n = 1404) that reported results for vertebral fracture (14, 69, 84, 92) using a random-effects model reveals a RR of 0.46 (95% CI 0.25–0.87, $P = 0.02$). However, these results come from three very small trials that provided point estimates suggesting large treatment effects (RR of 0.52, 0.23, and 0.27), two of which showed statistically significant reduction in vertebral fractures (Fig. 2). A fourth larger study examining clinical vertebral fractures, PROOF, demonstrated borderline significance with a RR of 0.79 (95% CI 0.62–1.00, n = 1108, $P = 0.05$). The large variability in results between the three small trials and the fourth larger trial is reflected in a significant test of heterogeneity ($P = 0.01$). Losses to follow-up in the four trials were 18.7, 21%, 45%, and 59.3%, respectively, with the greatest loss to follow-up in the PROOF trial. A fifth trial reported incident vertebral fractures in patient-years (74). We contacted both the author and the pharmaceutical company to establish the number of actual fractures but were unsuccessful in obtaining the results. Therefore, we excluded the trial from these analyses.

The results of the three trials reporting nonvertebral fractures demonstrate the same issues (14, 76, 84). The pooled estimate from the three trials shows a nonsignificant RR of 0.52 (95% CI 0.22–1.23, n = 1481, heterogeneity $P = 0.087$, $P = 0.14$). There are two small trials, one of which suggests a very large statistically significant effect (RR 0.25, 95% CI 0.10–0.65), and the other provides a point estimate suggesting a large effect but was not statistically significant (RR 0.60, 95% CI 0.08–4.31) (Fig. 3 and Table 2). However, the largest trial, PROOF (14), shows a much more modest treatment effect that did not reach statistical significance (RR 0.80, 95% CI 0.59–1.09, n = 1245, $P = 0.16$).

3. Bone density. The timing of outcome measurements (after 1, 2, and 3–5 yr of treatment) had no apparent influence on the magnitude of the treatment effect. Therefore, we present final-year results for each bone density site. Dose also had relatively little apparent impact on the magnitude of the treatment effect. For the lumbar spine, the dominant parsimonious model combined 8 doses from 250 to 2800 IU/wk and separated only the 80 IU/wk dose. For the femoral neck and combined forearm, dose had no apparent impact on the magnitude of effect, and so we pooled doses pooled from 350

Potentially relevant studies identified and screened for retrieval [n=75]

Studies excluded, with reasons [n=45]

Reason for exclusion: Lack of control group [n = 11], not randomized [n = 13], duplicate report or earlier report of another study [n = 6], premenopausal women examined [n = 1], duration of follow-up less than one year [n = 7], meta-carpal index measured as outcome [n = 1], ultra-distal radial site measured [n = 3], and QCT bone density measurements only [n = 3].

Potentially appropriate RCTs to be included in the meta-analysis [n=30]

Authors contacted for additional data [n = 17]

RCTs included in meta-analysis [n=30]

FIG. 1. Search results for the calcitonin review.

TABLE 1. Subject characteristics from calcitonin-included trials

Trial (first author/ year/Ref.) (prevention/ treatment)	No. of patients (Tx/Control)	Mean age (SD) Years postmenopausal (SD) Baseline LS-BMD (SD) g/cm^2 T-score	Intervention [type route] (Calcium or vitamin D supplementation)	Duration (years)	Outcomes measured	Overall lost to follow-up (%)
Chesnut PROOF trial, 2000 (14) (treatment)	1255 (944/311)	68.3 (7.6) 22.2 (3.8) 0.85 (0.12) −1.8	Placebo *vs.* 100 IU, 200 IU or 400 IU calcitonin daily [Intranasal salmon calcitonin] (1 g calcium and 400 IU vitamin D - all groups)	5	BMD: Lumbar spine and femoral neck. Vertebral and Hip Fractures	744/1255 (59.3%)
Flicker, 1997 (64) (treatment)	62 (32/30)	70.4 (6.5) 22.4 (9) 0.83 (0.17) g/cm2 T-score −2.0	Placebo *vs.* 400 IU calcitonin daily [Intranasal salmon calcitonin] (1 g calcium/d to all groups)	2	BMD: Lumbar spine and femoral neck	9/62 (14.5%)
Grigoriou, 1997 (65) (prevention)	45 (23/22)	45 7 days post bilateral oophorectomy–	Placebo *vs.* 100 IU calcitonin daily [Intranasal salmon calcitonin] (1 g calcium/d all groups)	2	BMD: Lumbar spine	7/45 (15.6%)
Gurlek, 1997 (66) (treatment)	20 (10/10) (etidronate group excluded)	55.3 (2.0) 9.3 (6.0) 0.85 (0.03) g/cm^2 −2.0	Control *vs.* 100 IU calcitonin [Intranasal salmon calcitonin] (500 mg calcium and 125 IU vitamin D daily - to all groups)	1	BMD: Lumbar spine	0/20 (0%)
Kapetanos, 1997 (67) (treatment)	46 (23/23)	58.5 (2.0) 3.5 (0.6) 0.76 g/cm^2 −2.5	Placebo *vs.* 200 IU calcitonin [Intranasal salmon calcitonin daily] (1 g calcium/d - all groups)	1	BMD: Lumbar spine, femoral neck, interotrochanteric, and ward's triangle	0/46 (0%)
Ellerington, 1996 (68) (prevention/ treatment)	117 (71/46)	55.8 (4) 5.3 yr postmenopausal 1.11 (0.13) g/cm^2 −1.0	Placebo *vs.* 200 IU calcitonin [Intranasal salmon calcitonin administered daily or Monday, Wednesday, and Friday]	2	BMD: Lumbar spine, femoral neck, trochanter, and ward's triangle	20/117 (17.1%)
Hizmetli, 1996 (69) (treatment)	107 (76/31)	58.0 (9.5) 14.3 (9.7) 0.73 (0.07) −2.9	Placebo *vs.* 50 IU and 100 IU calcitonin daily [Intranasal salmon calcitonin] (1 g calcium/d all groups)	2	BMD: Lumbar spine and femoral neck. Vertebral fractures	20/107 (18.7%)
Melis, 1996 (70) (prevention)	102 (52/50) (HRT groups excluded)	53.2 (1.1) 1.5 (0.5) – –	Control *vs.* 100 IU calcitonin [Intranasal salmon calcitonin] (500 mg calcium - all groups)	1	BMD: Distal radius	4/102 (3.9%)
Perez-Jaraiz, 1996 (71) (prevention)	52 (26/26)	50 (4.5) 1–5 yr postmenopausal	Placebo *vs.* 40 IU eel calcitonin [Eel calcitonin] (500 mg calcium/d - all groups)	1	BMC: Total body	2/52 (3.8%)
Thamsborg, 1996 (72) (treatment)	62 (31/31)	65.4 (6.7) 15.1 (6.9) 0.83 (0.15) g/cm^2 −2.0	Placebo *vs.* 200 IU calcitonin [Intranasal salmon calcitonin daily] (500 mg calcium/ d - all groups)	2	BMD: Lumbar spine, femoral neck, and distal forearm	0/62 (0%)
Perez, 1995 (73) (treatment)	88 (43/45)	62.4 15.5 – –	Control *vs.* 100 IU calcitonin daily [Intranasal salmon calcitonin] (500 mg calcium/d - all groups)	1	Vertebral and nonvertebral fractures	–/88
Reginster, 1995 (74) (prevention)	251 (168/83)	53.1 (1.5) 3 (0.4) 0.80 (0.14) g/cm^2 −2.2	Placebo *vs.* 50 IU or 200 IU Calcitonin 5 d/wk [Intranasal salmon calcitonin] (500 mg calcium/d - all groups)	2	BMD: Lumbar spine	50/251 (20%)

TABLE 1. Continued

Trial (first author/ year/Ref.) (prevention/ treatment)	No. of patients (Tx/Control)	Mean age (SD) Years postmenopausal (SD) Baseline LS-BMD (SD) g/cm^2 T-score	Intervention [type route] (Calcium or vitamin D supplementation)	Duration (years)	Outcomes measured	Overall lost to follow-up (%)
Reginster, 1995 (75) [rectal] (prevention)	150 (100/50)	60 (0.6) 4.9 (0.5) 0.94 (0.02) g/cm^2 −1.0	Placebo *vs.* 100 IU calcitonin 5 times/wk or 200 IU calcitonin 3 times/wk [Salmon calcitonin suppository] (500 mg calcium - all groups)	1	BMD: Lumbar spine and femoral neck	71/150 (47%)
Rico, 1995 (76) (treatment)	72 (36/36)	69.2 (1.3) 18.5 (3.5) –	Control *vs.* 100 IU calcitonin [Salmon calcitonin im 10 d/month] (500 mg calcium 10 d/month - all groups)	2	BMC: Total body	4/72 (5.6%)
Campodarve[a], 1994 (77) (prevention)	236 (116/66) (Completing)	– 1–6 yr postmenopausal – –	Placebo *vs.* 50 IU, 100 IU, or 200 IU/d [Intranasal salmon calcitonin]	2	BMD: Lumbar spine	54/236 (22.9%)
Kollerup, 1994 (78) (treatment)	54 (37/17)	70.8 (7.5) 25.3 (13.7) 0.77 (0.03) g/cm^2 −2.5	Placebo vs. 100 IU or 200 IU calcitonin 3 or 6 times/wk [Salmon calcitonin suppository] (500 mg calcium/d - all groups)	1	BMD: Lumbar spine and femoral neck	15/54 (28%)
Overgaard, 1994 (79) (prevention)	134 (101/33)	52.2 (2) 2.2 (1.5) 0.98 (0.15) g/cm^2 −0.6	Placebo *vs.* 100 IU, 200 IU, or 400 IU calcitonin daily [Intranasal salmon calcitonin] (500 mg calcium/d - all groups)	2	BMD: Lumbar spine BMC: Distal forearm	21/134 (16%)
Reginster, 1994 (80) (prevention)	287 (142/145)	– 1.8 (0.1) 0.88 (0.01) g/cm^2 −1.5	Control vs. 50 IU calcitonin 5 d/wk [Intranasal salmon calcitonin] (500 mg calcium - all groups)	3	BMD: Lumbar spine	101/287 (35%)
Meschia, 1993 (81) (treatment)	46 (26/20) (HRT groups excluded)	54.2 (4.1) 4.0 (2.7) 0.82 (0.07) g/cm^2 −2.1	Control *vs.* 40 IU 2 times/ wk im [Elcatonin eel]	2	BMD: Lumbar spine	12/46 (26%)
Fioretti, 1992 (82) (prevention)	60 (40/20)	47.3 (3.4) 10–30 d post bilateral oophrectomy – –	Control vs. 200 IU calcitonin [Intranasal salmon calcitonin daily or cyclically 3 months on, 1 off] (500 mg calcium/d all groups)	2	BMD: Distal radius	12/60 (20%)
Gennari, 1992 (83) (prevention)	21 (11/10)	50.4 (2.5) – 0.78 (0.07) g/cm^2 −2.4	Placebo *vs.* 200 IU calcitonin/d [Intranasal salmon calsitonin]	1	BMC: Lumbar spine	0/21 (0%)
Overgaard, 1992 (84) (treatment)	208 (156/52)	70 (1) 22.3 (5.3) 35.8 (7.2) BMC –	Placebo vs. 50 IU, 100 IU, or 200 IU calcitonin daily [Intranasal salmon calcitonin] (500 mg calcium/d - all groups)	2	BMC: Lumbar spine and distal forearm	44/208 (21%)
Perrone, 1992 (85) (treatment)	60 (45/15)	55.0 (3.0) 4.3 (1.3) 0.76 (0.73) −2.6	Control *vs.* 100 IU calctonin daily, alternate cycles 2 months on 1 month off, or 3 months on 3 months off [Intranasal salmon calcitonin] (500 mg calcium/d–all groups)	1	BMD: Lumbar spine and distal radius	4/60 (6.67%)

TABLE 1. Continued

Trial (first author/ year/Ref.) (prevention/ treatment)	No. of patients (Tx/Control)	Mean age (SD) Years postmenopausal (SD) Baseline LS-BMD (SD) g/cm^2 T-score	Intervention [type route] (Calcium or vitamin D supplementation)	Duration (years)	Outcomes measured	Overall lost to follow-up (%)
Stevenson, 1992 (86) (treatment)	97 (58/39)	– – – –	Control vs. 100 IU daily or 200 IU 3 times/wk calcitonin [Intranasal salmon calcitonin]	2	BMD Lumbar spine	–/97 (–%)
Thamsborg, 1991 (87) (treatment)	40 (30/10)	66.5 (12) – 30.7 (5.2) g BMC –	Placebo *vs.* 50 IU, 100 IU, or 200 IU calcitonin [Intranasal salmon calcitonin] (500 mg calcium/d - all groups)	1	BMC: Lumbar spine	7/40 (17%)
Meunier[a], 1990 (88) (prevention)	109 (53/56)	52.3 (3.2) 2 (1.3) – –	Placebo *vs.* 100 IU calcitonin [Intranasal salmon calcitonin]	1 (2nd year data not included in analysis due to dose increase)	BMD: Lumbar spine BMC: Distal and midshaft forearm	11/109 (10.1%)
Tremollieres[a], 1990 (89) (prevention)	38 (19/19)	40.4 (4.5) 1.0 (0.75) – –	Placebo *vs.* 50 IU or 100 IU calcitonin daily [Intranasal salmon calcitonin]	1	BMD: Lumbar spine and femoral neck	6/38 (16%)
Overgaard, 1989 (90) (prevention)	52 (26/26)	52.6 (2.1) 2.5–5 yr 35.3 (1.7) g BMC –	Placebo *vs.* 100 IU calcitonin daily [Intranasal salmon calcitonin] (500 mg calcium/d to all groups)	2	BMC: Lumbar spine, total skeleton, proximal and distal forearm	13/52 (25%)
Overgaard, 1989 (91) (treatment)	40 (20/20)	64.6 17.1 40 (5.8) g BMC –	Placebo *vs.* 200 IU calcitonin daily [Intranasal salmon calcitonin] (500 mg calcium/d - all groups)	1	BMD: Lumbar spine and distal forearm	3/40 (7.5%)
Gennari, 1985 (92) (treatment)	82 (54/28)	58.7 (1.5) 10.7 (1.2) – –	Control *vs.* 100 IU calcitonin im or sc daily or every other day [Salmon calcitonin] (1 g calcium/d - all groups)	1	BMC: Lumbar spine and femoral neck. Vertebral fractures	45/82 (45%)

–, Not available, BMC, Bone mineral content (grams).
[a] Abstract publication.

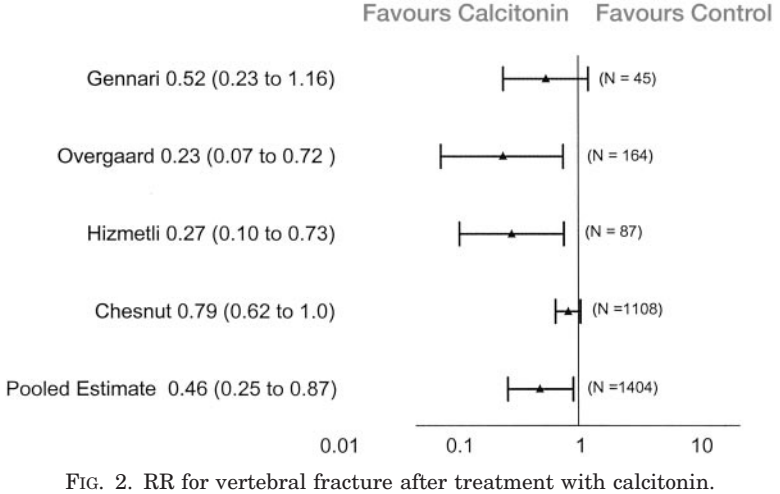

FIG. 2. RR for vertebral fracture after treatment with calcitonin.

to 2800 IU. Dose had an apparent impact on the magnitude of calcitonin effect on total body bone density in three small trials, but the result was anomalous (Table 3, and below).

Table 3 demonstrates statistically significant increases in bone density with calcitonin therapy in the lumbar spine for the 250-2800 IU dose/wk, 3.74 (95% CI 2.04–5.43, $P < 0.01$; Fig. 4). For femoral neck, we found a large but nonsignificant treatment effect (3.80, 95% CI −0.32–7.91, $P < 0.07$). For

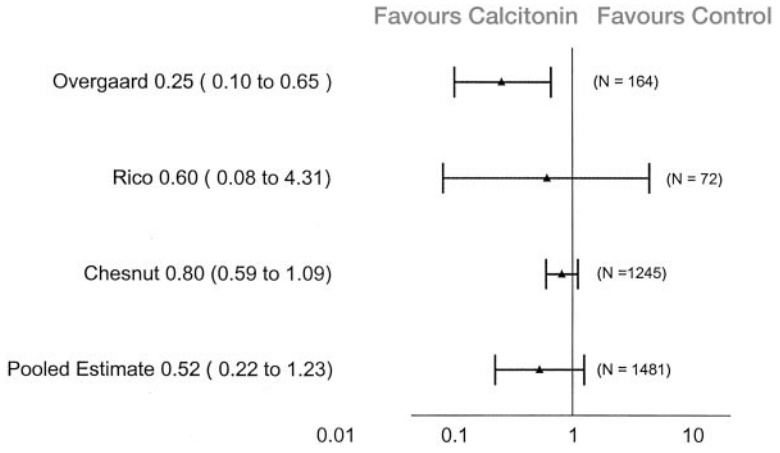

FIG. 3. RR for nonvertebral fracture after treatment with calcitonin.

TABLE 2. Weighted RR with 95% CI after treatment with calcitonin

Fracture sites	Year	Dose	No. of trials	No. of patients	RR (95% CI)	RR *P* value	Heterogeneity *P* value
Vertebral	All	All	4	1404	0.46 (0.25, 0.87)	0.02	0.01
Nonvertebral	All	All	3	1481	0.52 (0.22, 1.23)	0.14	0.08

We interpreted $P \leq 0.10$ as indicating important between-study differences in results.

TABLE 3. WMD of bone density after treatment with calcitonin

Bone density site	Dose	No. of trials	Sample size (n)	WMD (95% CI)	*P* value	Test of heterogeneity *P* value
Total body	94 IU/wk	1	52	0.12 (−2.14, 2.38)	0.92	–
	233 IU/wk	1	68	8.00 (6.89, 9.11)	<0.01	–
	700 IU/wk	1	39	−0.10 (−2.87, 2.67)	0.94	–
Lumbar spine	80 IU/wk	1	22	−4.80 (−7.99, −1.61)	<0.01	–
	250–2800 IU/wk	24	2260	3.74 (2.04, 5.43)	<0.01	<0.01
Femoral neck	350–2800 IU/wk	9	513	3.80 (−0.32, 7.91)	0.07	<0.01
Combined forearm	350–2800 IU/wk	8	468	3.02 (0.98, 5.07)	<0.01	<0.01

We interpreted the heterogeneity $P \leq 0.10$ as indicating important between-study differences in results.

combined forearm, at the pooled weekly dose of 350-2800 IU, the increase at final year was significant with a WMD of 3.02 (95% CI 0.98–5.07). The results of three trials that examined the impact of calcitonin on total body bone density were discordant. The 94-IU/wk and 700-IU/wk doses showed no effect, whereas the 233-IU/wk dose showed a large WMD of 8.00 (95% CI 6.89–9.11, n = 68, $P < 0.01$).

Trial-to-trial results differed considerably for each of lumbar spine, femoral neck, and combined forearm sites, reflected in the statistically significant tests of heterogeneity for all three sites (Table 3). Table 4 presents the results of our search for explanations of the study-to-study variability in results. For the lumbar spine, trials that did not conceal allocation demonstrated significantly larger effects (difference 11.88, 95% CI 4.17–19.58, $P < 0.01$). Trials that used nasal calcitonin as the route of administration resulted in a significantly smaller effect size for lumbar spine than trials that used im or sc administration (difference 7.09, 95% CI 2.91–11.28, $P < 0.01$).

For femoral neck, statistically larger effects were noted for trials including vitamin D supplementation (difference 13.07; 95% CI 9.37, 16.76; $P < 0.01$) and trials that did not conceal allocation (difference 10.79, 95% CI 0.14–21.45, $P = 0.05$). Daily administration of calcitonin resulted in a significantly larger effect size at the femoral neck in comparison to intermittent administration (difference 5.85, 95% CI 0.69–10.97, $P = 0.03$), and im or sc administration resulted in a larger effect size than rectal (difference 5.33, 95% CI 3.52–7.14, $P < 0.01$).

4. Publication bias. The funnel plots suggested the possibility of publication bias for the lumbar spine BMD outcome (Fig. 5). Although the single large RCT showed a very small effect on lumbar spine bone density, a number of small trials showed a much larger effect. The femoral neck funnel plot did not suggest publication bias. Although the small number of trials available for fracture incidence prevents a strong inference, the observation that the single large trial yielded a much smaller effect than the smaller trials raises the concern of publication bias (Figs. 2 and 3).

5. Adverse effects. In general, the trials were poor in their reporting of adverse events. The pooled RR for headache from one trial (PROOF) was 0.57 (95% CI 0.34–0.93, $P = 0.02$). The pooled RR for rhinitis from 4 trials (n = 1663) was 1.72 (95% CI 0.92–3.23, $P = 0.09$), and the pooled RR for climac-

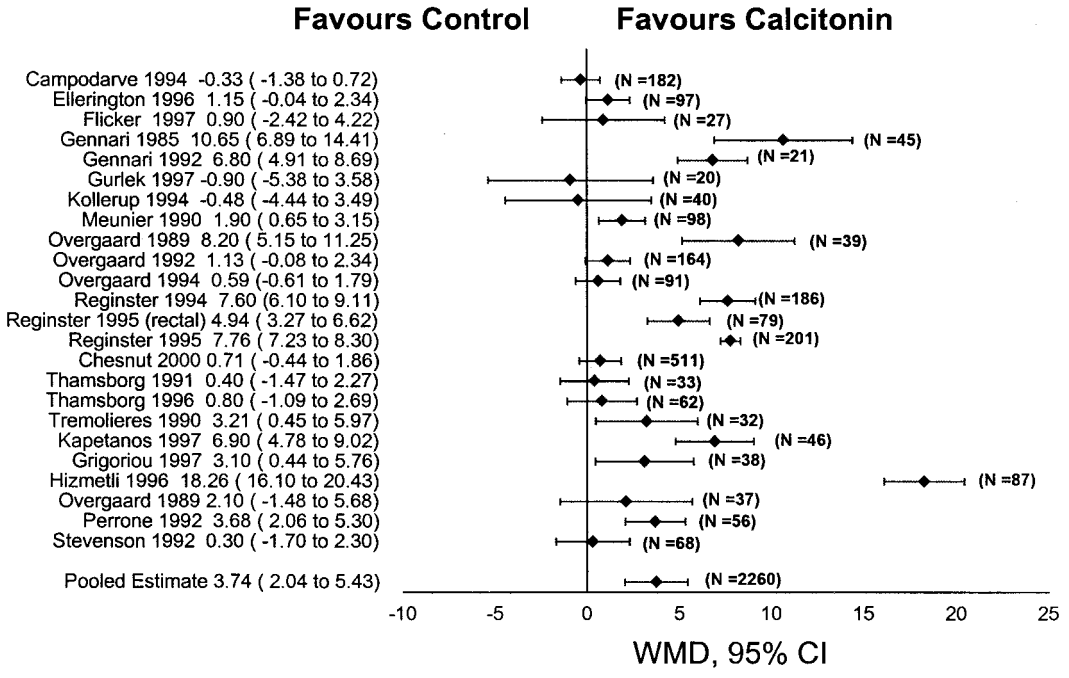

FIG. 4. WMD for lumbar spine after treatment with calcitonin (final year, doses >80 IU/wk).

teric symptoms from one trial (n = 60) was 0.20 (95% CI 0.05–0.77, $P = 0.02$). Loss to follow-up was similar in treatment and control groups, and to the extent that loss to follow-up reflects adverse effects, does not support a high incidence of problems with adverse effects of calcitonin.

E. Discussion

In this meta-analysis, we conducted a comprehensive literature search, specified inclusion and exclusion criteria, and conducted a rigorous data analysis. We made a systematic effort to obtain complete data from all published trials.

Our pooled analysis suggests that calcitonin reduces the incidence of vertebral fractures by over 50% (Table 2). In this case, however, there are a number of reasons for skepticism regarding this pooled estimate. The large effect size is driven by the results of 3 small trials with a sample size of 45–164 (Fig. 3). This raises two concerns. Most serious is the possibility of publication bias. Large studies are more likely to provide precise estimates of treatment effect, and one would anticipate the results of smaller studies to be more or less uniformly distributed around the results of larger studies. In this case, the larger PROOF trial demonstrated a point estimate in fracture RR reduction, 21%, appreciably lower than did the small studies. It is possible that other small studies that failed to show a benefit remain unreported.

A second concern relates to the random-effects model we have chosen for our analyses. In general, the random-effects model estimates yield wider CIs than fixed-effect models, and are thus more conservative. However, random-effects models give relatively larger weight to small studies in comparison to fixed-effect models. In this case, in which smaller studies have yielded larger effects, this drives the point estimate of RR downward, potentially inflating the treatment effect.

A final concern relates to the large loss to follow-up, particularly in the PROOF trial. Particularly given the possibility of publication bias we raised above, one would like to look to the PROOF trial to provide the most robust estimate of the treatment effect. The PROOF trial's loss to follow-up of over 50% (Table 1) makes relying on this study's results appreciably less secure. Although we failed to find a systematic effect of loss to follow-up in this meta-analysis, or any other of our osteoporosis meta-analyses, loss to follow-up of this magnitude must reduce the strength of any inferences.

All these considerations suggest that the magnitude of the impact of calcitonin on vertebral fracture remains uncertain. One approach to interpretation would suggest that the magnitude of the relative risk reduction is closer to the 21% suggested by the PROOF trial than the 54% suggested by the pooled estimate. Alternatively, it is possible that the large loss to follow-up has biased the PROOF trial against the active treatment. This would occur if those at greater risk of fracture were preferentially lost to follow-up from the control arm. Unfortunately, we find it difficult to escape the conclusion that inferences regarding the magnitude of calcitonin's effect on vertebral fracture remain weak.

Exactly the same issues apply to our estimate of the effect of calcitonin on nonvertebral fractures. Two of the small trials show large effects (RR reductions of 75% and 40%), whereas the PROOF trial provides a point estimate of the RR reduction of 20%. In this case, the random-effects CI overlaps no effect, giving a nonsignificant point estimate. Whether calcitonin reduces nonvertebral fractures remains unestablished.

Our meta-analysis confirms that calcitonin increases bone density of the lumbar spine and combined forearm, but again a number of issues suggest that the point estimates of the magnitude of effect may be inflated. First, the pattern of results in the lumbar spine analysis, in which the single larger

TABLE 4. Heterogeneity of difference of bone mineral density after treatment with calcitonin

Bone density site Study year Dose	Study population Prevention *vs.* treatment Difference (95% CI) *P* value	Administration Daily *vs.* intermittent Difference (95% CI) *P* value	Route of administration Nasal *vs.* im or sc Difference (95% CI) *P* value	Route of administration Rectal *vs.* im or sc Difference (95% CI) *P* value	Calcium supplementation ≤500 mg *vs.* >500 mg Difference (95% CI) *P* value	Vitamin D supplementation No *vs.* yes Difference (95% CI) *P* value	Concealment Yes *vs.* no Difference (95% CI) *P* value	Lost to follow-up <20% *vs.* >20% Difference (95% CI) *P* value	SD Provided or estimated Difference (95% CI) *P* value
Lumbar Spine	3.24; 3.99	3.61; 2.47	3.56; 10.65	2.54; 10.65	2.07; 4.29	3.37; 6.08	2.74; 14.62	3.85; 3.90	3.78; 3.43
Final Year	0.76 (−2.31, 3.82)	1.14 (−2.42, 4.70)	7.09 (2.91, 11.28)	8.11 (1.63, 14.59)	2.21 (0.57, 4.99)	2.72 (−10.24, 15.67)	11.88 (4.17, 19.58)	0.05 (−3.30, 3.41)	0.35 (−4.12, 4.82)
250–2800 IU/wk	*P* = 0.63	*P* = 0.53	*P* <0.01	*P* = 0.01	*P* = 0.12	*P* = 0.68	*P* < 0.01	*P* = 0.97	*P* = 0.88
Femoral Neck	1.20; 6.03	5.10; −0.73	5.15; 4.60	−0.73; 4.60	1.98; 4.26	2.31; 15.37	−0.84; 9.96	5.15; 1.15	2.64; 7.90
Final Year	4.84 (−2.26, 11.93)	5.83 (0.69, 10.97)	0.55 (−6.53, 7.63)	5.33 (3.52, 7.14)	2.28 (−3.61, 8.16)	13.07 (9.37, 16.76)	10.79 (0.14, 21.45)	4.00 (−4.15, 12.15)	5.26 (−9.71, 20.22)
All doses	*P* = 0.18	*P* = 0.03	*P* = 0.88	*P* < 0.01	*P* = 0.45	*P* < 0.01	*P* = 0.05	*P* = 0.34	*P* = 0.49
Combined Forearm	4.05; 0.60	One subgroup	One subgroup	One subgroup	One subgroup	One subgroup	3.60; 0.60	2.46; 4.90	One subgroup
Final Year	3.45 (−0.46, 7.35)						3.01 (0.18, 5.85)	2.44 (−5.02, 9.90)	
350–2800 IU/wk	*P* = 0.08						*P* = 0.04	*P* = 0.52	

We interpreted the heterogeneity $P \leq 0.05$ as indicating important between-study differences in results. We also compared nasal *vs.* rectal and nasal *vs.* other where applicable, and the results were not statistically significant ($P = 0.11–0.72$).

FIG. 5. Heterogeneity of difference in BMD after treatment with calcitonin (final year, doses >80 IU/wk).

trial reveals a substantially smaller point estimate than many of the smaller trials, suggests the possibility of publication bias. Indeed, Fig. 5 resembles the classic pattern of a funnel plot suggesting publication bias, with studies missing in the *left lower quadrant*. Several larger studies with point estimates approximating those of the PROOF trial would strengthen this hypothesis.

Second, in the lumbar spine meta-analysis, the methodologically stronger studies demonstrated smaller treatment effects than the weaker studies (Table 4). In particular, concealed trials showed an appreciably smaller effect than unconcealed trials.

Given that nasal calcitonin is the most widely used commercial preparation, further concern about the lumbar spine estimate arises from the fact that effect sizes for lumbar spine proved substantially smaller in studies using nasal calcitonin than in studies of parenteral calcitonin (Table 4). This observation is consistent with the fact that nasal calcitonin has a variable bioavailability and may therefore be less effective. On the other hand, nasal and parenteral calcitonin demonstrated similar effects on femoral bone density (Table 4).

The pooled estimates of calcitonin's effect on bone density are somewhat lower than those of the bisphosphonates. Reflections on the relation between bone density and fracture reduction in calcitonin *vs.* other agents would, in our view, be completely speculative. The reasons include the considerable remaining uncertainty about calcitonin's effect on both bone density and fracture reduction, and the many mechanisms that may impact on antiresorptive drugs' impact on fracture reduction.

We did not detect any difference in the pooled estimates for lumbar spine BMD when comparing daily with intermittent administration, suggesting that the issue of down-regulation of calcitonin receptors may not be of clinical significance. However, we were not able to adequately determine whether an extended break/holiday from calcitonin, which would theoretically allow for the up-regulation of the receptors, and would result in a larger treatment effect.

It was difficult to confidently estimate pooled RRs for adverse effects due to inadequate reporting in all the trials.

Our results will be useful to clinicians and policy-makers involved in the development and implementation of guidelines for the treatment of osteoporosis. Our results highlight the considerably uncertainty that remains concerning the effects of calcitonin on bone density, and in particular on vertebral and nonvertebral fractures.

F. Bibliography

1. **Reginster JY** 1991 Effect of calcitonin on bone mass and fracture rates. Am J Med 91(Suppl 5B):19S–22S
2. **Reginster JY** 1993 Calcitonin for prevention and treatment of osteoporosis. Am J Med 93(Suppl 5A):44S–47S
3. **Wallach S** 1993 Effects of calcitonin on bone quality and osteoblastic function. Calcif Tissue Int 52:335–339
4. **Carstens JH** 1991 Future horizons for calcitonin: a US perspective. Calcif Tissue Int 49(Suppl 2):S2–S6
5. **Silverman S** 2001 Calcitonin. Rheum Dis Clin North Am 27: 187–196
6. **Kanis JA, Johnell O, Gulberg BO, Allander E, Dilsen G, Gennari C** 1992 Evidence for efficacy of drugs affecting bone metabolism in preventing hip fracture. BMJ 305:1124–1128
7. **Plosker GL, McTavish D** 1996 Intranasal salcatonin: a review of its pharmacological properties and role in the management of postmenopausal osteoporosis. Drugs Aging 8:378–400
8. **Grauer A, Reinel HH, Ziegler R, Raue F** 1993 Neutralizing antibodies against calcitonin. Horm Metab Res 25:486–488
9. **Takahashi S, Goldring S, Katz M** 1995 Downregulation of calcitonin receptor mRNA expression by calcitonin during human osteoclast-like cell differentiation. J Clin Invest 1995;95:167–171
10. **Eddy DM** 1998 Osteoporosis: review of the evidence for prevention, diagnosis and treatment and cost-effectiveness analysis. Osteoporosis Int 8:S1–S88
11. **Cardona JM, Pastor E** 1997 Calcitonin *vs.* etidronate for the treatment of postmenopausal osteoporosis: a meta-analysis of published clinical trials. Osteoporosis Int 7:165–174
12. **Kanis JA, McCloskey EV** 1999 Effect of calcitonin on vertebral and other fractures. Q J Med 92:143–149
13. **Stock JL, Avioli LV, Baylink DJ, Chestnut C, Genant HK, Maricic MJ, Silverman SL, Schaffer AV, Feinblatt J** 1997 Calcitonin-Salmon nasal spray reduces the incidence of new vertebral fractures in post-menopausal women: three year interim results of the PROOF Study. J Bone Miner Res 12(Suppl 1):S149 (Abstract)
14. **Chesnut III CH, Silverman S, Andriano K, Genant H, Giomona A, Harris S, Kiel D, LeBoff, M, Maricic M, Miller P, Moniz C, Peacock M, Richardson P, Watts N, Baylink D** 2000 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 109:267–276
15. **Mulrow CD, Oxman AD, eds.** 1997 Cochrane Collaboration Handbook. Oxford: Cochrane Collaboration.
16. **Genant HJ, Block JE, Steiger P, Gluer C** 1987 Quantitative computed tomography in the assessment of osteoporosis. In: Genant HK, ed. Osteoporosis update. San Francisco: University of California Printing Services; 49–72
17. **Fleiss JL** 1993 The statistical basis of meta-analysis. Stat Methods Med Res 2:121–145
18. **Hedges LV, Olkin I** 1985 Statistical methods for meta-analysis. San Diego: Academic Press; 159–165
19. **Tolino A, Romano l, Ronsini S, Riccio S, Montemagno U** 1993 Treatment of postmenopausal osteoporosis with salmon calcitonin nasal spray: evaluation by bone mineral content and biochemical patterns. Int J Clin Pharm Ther Tox 31:358–360
20. **Szucs J, Horvath C, Kollin E, Szathmari M, Hollo I** 1992 Three year calcitonin combination therapy for postmenopausal osteoporosis with crush fractures of the spine. Calcif Tissue Int 50:7–10
21. **Adami S, Baroni MC, Broggini M, Carratelli L, Caruso I, Gnessi L, Laurenzi M, Lombardi A, Norbiato G, Ortolani S, Ricerca E, Romanini L, Subrizi S, Weinberg J, Yates AJ** 1993 Treatment of postmenopausal osteoporosis with continuous daily oral alendronate in comparison with either placebo or intranasal salmon calcitonin. Osteoporosis Int 3:S21–S27
22. **Genaro M, Palmieri A, Pitcock JA, Brown P, Karas JG, Roen LJ** 1989 Effect of calcitonin and vitamin D on osteoporosis. Calcif Tissue Int 45:137–141
23. **Kapuscinski P, Talalaj M, Borowicz J, Marcinowska-Suchowierska E, Brzozowski R** 1996 An analgesic effect of synthetic human calcitonin in patients with primary osteoporosis. Mater Med Pol 28:83–86
24. **Granata Q, Amato A, Salvati R, Barberis F** 1991 Activity of salmon calcitonin in senile osteoporosis. Cur Ther Res 49:784–791
25. **Hodsman AB, Fraher LJ, Watson PH, Ostbye T, Stitt LW, Adachi JD, Taves DH, Drost D** 1997 A randomized controlled trial to compare the efficacy of cyclical parathyroid hormone versus cyclical parathyroid hormone and sequential calcitonin to improve bone mass in postmenopausal women with osteoporosis. J Clin Endocrinol Metab 82:620–628
26. **Stepan J, Formankova J, Masatova A, Michalsky M, Rosenova Z** 1997 [Comparison of the effectiveness of 17-beta-estradiol and calcitonin in women with postmenopausal bone loss]. Casopis Lekaru Ceskych 136:242–248
27. **Dottori L, D'Ottavio D, Brundisini B** 1982 [Calcifediol and calcitonin in the therapy of rheumatoid arthritis. A short-term controlled study.] Minerva Med 73:3033–3040
28. **Gonnelli S, Cepollaro C, Montomoli M, Gennari L, Montagnani A, Palmieri R, Gennari C** 1997 Treatment of postmenopausal osteoporosis with recombinant human growth hormone and salmon calcitonin: a placebo controlled study. Clin Endocrinol (Oxf) 46: 55–61
29. **Overgaard K, Hansen MA, Dirksen KL, Christiansen C** 1992 Rectal salmon calcitonin for the treatment of postmenopausal osteoporosis. Calcif Tissue Int 51:184–188
30. **Jimenez FE, Albizuri JMA, Soto JJM, Canales AG** 1995 Effectiveness and safety of medium and long-term elcatonin use in the prevention and treatment of bone mass loss. Curr Ther Res 56: 385–399
31. **Civitelli R, Gonnelli S, Zacchei F, Bigazzi S, Vattimo A, Avioli LV, Gennari C** 1988 Bone turnover in osteoporosis, effect of calcitonin treatment. J Clin Invest 82:1268–1274
32. **Gruber HE, Ivey JL, Baylink DJ, Matthews M, Nelp WB, Sisom K, Chesnut III CH** 1984 Long-term calcitonin therapy in postmenopausal osteoporosis. Metab Clin Exp1:295–303
33. **Pontiroli AE, Pajetta E, Caldera A, Alberetto M, Pozza G, Manganelli V, Resmini G, Tessari L, Maresca V** 1991 Intranasal and intramuscular human calcitonin in female osteoporosis in Paget's disease of bones: a pilot study. J Endocrinol Invest 14:47–51
34. **Wimalawansa SJ** 1993 Long and short term side effects and safety of calcitonin in man: a prospective study. Calcif Tissue Int 53:90–93
35. **Mazzuoli GF, Gennari C, Passeri M, Acca M, Camporeale A, Pioli G** 1993 Hip fracture in Italy: epidemiology and preventive efficacy of bone-active drugs. Bone 14:81–84
36. **Chesnut CH III, Campodarve I, Rencken M, DeBrock J, Pitzel P, Rogers M** 1993 Lack of efficacy of nasal spray calcitonin in early postmenopausal women. J Bone Mineral Res 8(Suppl 1): (Abstract 530)
37. **Meschia M, Brincat M, Barbacini P, Carena Maini M, Marri R, Crosignani PG** 1992 Effect of hormone replacement therapy and calcitonin on bone mass in postmenopausal women. Eur J Obstet Reprod Biol 47:53–57
38. **Ringe JD** 1990 Treatment of primary osteoporosis with calcium and salmon calcitonin. DMW 115:176–82
39. **Passeri M, Palummeri E, Barbagallo M, Butturini L, Pedrazzoni M, Davoli L, Pioli G, Benassi L, Girasole G, Ciotti G, Bergonzani M, Cervellin G, Prisco M, Costi D** 1987 Lasequenza calcitriolo-calcitonina nella terapia dellósteoporosi. Minerva Endocr 14:57–62
40. **Reginster JY, Meurmans L, Deroisy R, Jupsin I, Biquet I, Albert A, Franchmont P** 1994 A 5-year controlled randomized study of prevention of postmenopausal trabecular bone loss with nasal salmon calcitonin and calcium. Eur J Clin Invest 24:565–569
41. **Agnusdei D, Gonnelli S, Camporeale A, Batignani T, Nardi P, Ianes A, Gennari C** 1989 Efficacia clinica di un trattamento con calcitonia di salmone, somministrata per via endonasale per un anno nell'osteoporosi postmenopausale stabilizzata. Minerva Endocrinol 14:169–176
42. **Rico H, Hernandez ER, Revilla M, Gomez-Castresana F** 1992 Salmon calcitonin reduces vertebral fracture in postmenopausal crush fracture syndrome. Bone Miner 16:131–138
43. **Reginster JY, Meurmans L, Deroisy R, Jupsin I, Biquet I, Albert A, Franchimont P** 1994 A 5-year controlled randomized study of prevention of postmenopausal trabecular bone loss with nasal salmon calcitonin and calcium. Eur J Clin Invest 24:565–569
44. **Reginster JY, Albert A, Lecart MP, Lambelin P, Denis D, Deroisy**

R, Fontaine MA, Franchimont P 1987 One year controlled randomized trial of prevention of early postmenopausal bone loss by intranasal calcitonin. Lancet 2:1481–1483
45. **Overgaard K, Christiansen C** 1991 Long-term treatment of established osteoporosis with intranasal calcitonin. Calcif Tissue Int 49:S60–S6
46. **Overgaard K, Hansen MA, Nielsen VH, Juel B** 1990 Discontinuous calcitonin treatment of established osteoporosis-effects of withdrawal of treatment. Am J Med 89:1–6
47. **Ribot C, Tremollieres F, Pouilles JM, Ruffaud C** 1992 Long term effect of nasal calcitonin on vertebral and femoral bone mass in early menopause; results of a controlled prospective 3-yr study. J Bone Miner Res 7:S196 (Abstract)
48. **Maricic MJ, Silverman SL, Chesnut C, Baylink DJ, Altman R, Genant HK, Giomona A, Andriano K, Richardson P** 1998 Salmon-calcitonin nasal spray prevents vertebral fractures in established osteoporosis. Further interim results of the "PROOF" study. ACR Concurrent Session: Osteoporosis, November 9, 1998. Arthritis Rheum 41 (Abstract 578)
49. **Arnala I, Saastamoinen J, Alhava E** 1996 Salmon calcitonin in the prevention of bone loss at peri-menopause. Bone 18:629–632
50. **Mango D, Ricci S, Natili G, Dell'Acqua S** 1993 Preventive treatment of cortical bone loss with salmon nasal calcitonin in early postmenopausal women. Minerva Endocrinol 18:115–121
51. **Mazzuoli GF, Passeri M, Gennari C, Minisola S, Antonelli R, Valtorta C, Palummeri E, Cervellin GF, Gonnelli S, Francini G** 1986 Effects of salmon calcitonin in postmenopausal osteoporosis: a controlled double-blind study. Calcif Tissue Int 39:3–8
52. **Ljunhall S, Gardsell P, Johnell O, Larsson K, Lindh E, Obrant K, Sernbo I** 1991 Synthetic human calcitonin in postmenopausal osteoporosis: a placebo-controlled, double-blind study. Calcif Tissue Int 49:17–19
53. **Resch H, Pietschmann P, Willvonseder R** 1989 Estimated long-term effect of calcitonin treatment in acute osteoporotic spine fractures. Calcif Tissue Int 45:209–213
54. **Vega E, Gonalaez D, Ghiringhelli G, Maualen C** 1989 Acute effect of the intranasal administration of salmon calcitonin in osteoporotic women. Bone Miner 7:267–273
55. **Lobianco R, Merola B, Lupoli G, Cocca A, Guarino M, Pia M, Guerriero S, Lombardi G** 1992 Studio comparativo randomizzato con carbocalcitonina IM *vs.* carbocalcitonina spray nasale vs ipriflavone x os nel trattamento dell'osteoporosi post-menopausale. Minerva Endocrinol 17:79–84
56. **Yoshikawa S, Shiba M, Hoshino T, Igarashi M, Orimo H, Sakuma A, Tsuyama N** 1983 Effect of eel calcitonin derivative (elcatonin) in osteoporosis. J Jpn Orthop Assoc 57:1717–1728
57. **Crespo R, Revilla M, Crespo E, Villa LF, Rico H** 1997 Complementary medical treatment for Colles' fracture: a comparative, randomized, longitudinal study. Calif Tissue Int 60:567–570
58. **Santi I, Monti M, Verde G, Sensalari G, Cuniette E** 1992 Nasal spray salmon calcitonin in the treatment of senile osteoporosis. Bone Miner 17(Suppl 1):181 (Abstract)
59. **Mazzuoli GF, Passeri M, Gennari C, Minisola S, Antonelli R, Valtora C, Palummeri E, Cervellin GF, Gonelli S, Francini G** 1986 Effects of salmon calcitonin in postmenopausal osteoporosis: a controlled double-blind clinical study. Calcif Tissue Int 38:3–8
60. **Diez A, Puig J, Nogues X, Cucurull J, Martinez MT, Aubia J, Bosh J, Knobel H** 1992 Prevention of postmenopausal bone loss with intranasal calcitonin. Calcif Tissue Int 51:244 (Abstract)
61. **Dambacher MA, Ruegsegger P, Goldmann AR, Schmid K, Welzel D** 1987 Treatment of postmenopausal osteoporosis with calcitonin nasal spray evaluated with quantitative computed tomography. In: Christiansen C, Johansen JS, Riis BJ, eds. Osteoporosis. Copenhagen: Osteopress; 1271–1272
62. **Macintyre I, Whitehead MI, Banks LM, Stevenson JC, Wimalawansa SJ, Healy MJR** 1988 Calcitonin for the prevention of postmenopausal bone loss. Lancet 1:900–901
63. **Villareal DT, Rupich RC, Pacifici R, Griffin MG, Maggio D, Avioli LV, Civitelli R** 1992 Effect of estrogen and calcitonin on vertebral bone density and vertebral height in osteoporotic women. Osteoporosis Int 2:70–73
64. **Flicker L, Hopper JL, Larkins RG, Lichtenstein M, Buirski G, Wark JD** 1997 Nandrolone decanoate and intranasal calcitonin as therapy in established osteoporosis. Osteoporosis Int 7:29–35
65. **Grigoriou O, Papoulias I, Vitoratos N, Papadias C, Konidaris S, Antoniou G, Chryssikopoulous A** 1997 Effects of nasal administration of calcitonin in oophorectomized women: 2-year controlled double-blind study. Maturitas 28:147–151
66. **Gurlek A, Bayraktar M, Gedik O** 1997 Comparison of calcitriol treatment with etidronate-calcitriol and calcitonin-calcitriol combinations in Turkish women with postmenopausal osteoporosis: a prospective study. Calif Tissue Int 61:39–43
67. **Kapetanos G, Symeonides PP, Dimitriou C, Karakatsanis K, Potoupnis M** 1997 A double blind study of intranasal calcitonin for established postmenopausal osteoporosis. Acta Orthop Scand Suppl 275:108–111
68. **Ellerington MC, Hillard TC, Whitcroft SIJ, Marsh MS, Lees B, Banks LM, Whitehead MI, Stevenson JC** 1996 Intranasal salmon calcitonin for the prevention and treatment of postmenopausal osteoporosis. Calcif Tissue Int 59:6–11
69. **Hizmetli S, Elden H, Kaptanoglu E, Nacitarhan V, Kocagil S** 1996 The effect of different doses of calcitonin on bone mineral density and fracture risk in postmenopausal osteoporosis. Int J Clin Pract 52:453–455
70. **Melis GB, Cagnacci A, Bruni V, Falsetti L, Jasonni AM, Nappi C, Polatti F, Volpe A** 1996 Salmon calcitonin plus intravaginal estriol: an effective treatment for the menopause. Maturitas 24:83–90
71. **Perez-Jaraiz M, Revilla M, Alvarez de los Heros J, Villa L, Rico H** 1996 Prophylaxis of osteoporosis with calcium, estrogens and/or eelcatonin: comparative longitudinal study of bone mass. Maturitas 23:327–332
72. **Thamsborg G, Jensen J, Kollerup G, Hauge E, Melsen F, Sorensen O** 1996 Effect of nasal salmon calcitonin on bone remodeling and bone mass in postmenopausal osteoporosis. Bone 18:207–212
73. **Abellan Perez M, Bayina Garcia FJ, Calabozo M, Carpintero Benitez P, Figueroa Pedrosa M, Fernandez Crisostomo C, Garcia Lopez A, Garcia Perez S, Mesa Ramos M, Paulino Tevar J, Perez MR, Vallina SJM, Castaon AV, Gomez JP, Trenado AS** 1995 [Multicenter comparative study of synthetic salmon calcitonin administered nasally in the treatment of established postmenopausal osteoporosis]. An Med Interna 12:12–16
74. **Reginster JY, Deroisy R, Lecart MP, Sarlet N, Zegels B, Jupsin I, Longueville M, Franchimont P** 1995 A double-blind placebo-controlled, dose finding trial of intermittent nasal salmon calcitonin for prevention of postmenopausal lumbar spine loss. Am J Med 98:452–458
75. **Reginster JY, Jupsin I, Deroisy R, Biquet I, Frachimont N, Franchimont P** 1995 Prevention of postmenopausal bone loss by rectal calcitonin. Calcif Tissue Int 56:539–542
76. **Rico H, Revilla M, Hernandez ER, Villa LF, Alverex de Buergo M** 1995 Total and regional bone mineral content and fracture rate in postmenopausal osteoporosis treated with salmon calcitonin: a prospective study. Calcif Tissue Int 56:181–185
77. **Campodarve I, Drinkwater BL, Insogna KL, Johnston C, Lane R, Lindsay R, Neer R, Slovik DM, Gaich G, Procaccini R, Chesnut III CH** 1994 Intranasal calcitonin 50–200 IU does not prevent bone loss in early postmenopausal women. J Bone Miner Res 9:S391 (Abstract)
78. **Kollerup G, Hermann AP, Brixen K, Lindnlad BE, Mosekilde L, Sorenson OH** 1994 Effects of salmon calcitonin suppositories on bone mass and turnover in established osteoporosis. Calcif Tissue Int 54:12–15
79. **Overgaard K** 1994 Effect of intranasal calcitonin therapy on bone and bone turnover in early postmenopausal women; a dose response study. Calcif Tissue Int 55:82–86
80. **Reginster JY, Denis D, Deroisy R, Lecart MP, de Longueville M, Zegels B, Sarlet N, Noirfalisse P, Franchmont P** 1994 Long term (3 years) prevention of trabecular bone loss with low-dose intermittent nasal salmon calcitonin. J Bone Miner Res 9:69–73
81. **Meschia M, Brincat M, Barbacini P, Crossignani PG, Albisetti W** 1993 A clinical trial of the effects of a combination of elcatonin and conjugated estrogens on vertebral bone mass in early postmenopausal women. Calcif Tissue Int 53:17–20
82. **Fioretti P, Gambacciani M, Taponeco F, Melis GB, Capelli N,**

Spinette A 1992 Effects of continuous and cyclic nasal calcitonin administration in ovariectomized women. Maturitas 15:225–232
83. **Gennari C, Agnusdei D, Montagnami M, Gonneli S, Civitelli R** 1992 An effective regimen of intranasal salmon calcitonin given in early postmenopausal bone loss. Calcif Tissue Int 50:381–383
84. **Overgaard K, Hansen MA, Jensen SB, Christiansen C** 1992 Effect of salcalcitonin given intranasally on bone mass and fracture rated in established osteoporosis: a dose-response study. BMJ 305:556–561
85. **Perrone G, Galoppi P, Valente M, Capri O, D'Ubaldo C, Anelli G, Zichella L** 1992 Intranasal salmon calcitonin in postmenopausal osteoporosis: effect of different therapeutic regimens on vertebral and peripheral bone density. Gynecol Obstet Invest 33:168–171
86. **Stevenson JC, Lees B, Ellerington MC, Whitcroft SIJ, Marsh MS, Whitehead MI** 1992 Postmenopausal osteoporosis: a double-blind placebo-controlled study. J Bone Miner Res 7S:325 (Abstract)
87. **Thamsborg G, Storm TL, Sykulski R, Brinch E, Kaspersen H, Sorenson OH** 1991 Effect of different doses of nasal calcitonin on bone mass. Calcif Tissue Int 48:302–307
88. **Meunier PJ, Gozzo I, Chaumet-Riffaud, Guignard DM, Chapuy MC, Duboeuf F** 1992 Dose-effect on bone density and parathyroid function of intranasal salmon calcitonin when administered without calcium in postmenopausal women. J Bone Miner Res 7:S330 (Abstract)
89. **Tremollieres F, Pouilles JM, Horlait S, Giugnard M, Ribot C,** The role of intranasal salmon calcitonin in the prevention of vertebral and femoral neck bone loss after early menopause. Third International Symposium on Osteoporosis 455 Copenhagen, Denmark, 1990 (Abstract)
90. **Overgaard K, Riis BJ, Chrisitansen C, Hansen MA** 1989 Effect of salcatonin given intranasally on early postmenopausal bone loss. Br Med J 299:477–479
91. **Overgaard K, Riis BJ, Christiansen C, Podenphant J, Johansen JS** 1989 Nasal calcitonin for treatment of established osteoporosis. Clin Endocrinol (Oxf) 30:435–442
92. **Gennari C, Chierichetti SM, Bigazzi S, Fusi L, Gonnelli S, Ferrara R, Zacchei F** 1985 Comparative effects on bone mineral content of calcium plus salmon calcitonin given in two different regimens in postmenopausal osteoporosis. Curr Ther Res 38:455–462