Calcitonin in the prevention and treatment of glucocorticoid-induced osteoporosis

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ABSTRACT

Calcitonin inhibits bone resorption by its direct inhibition of osteoclasts. Its efficacy in the prevention and treatment of glucocorticoid-induced osteoporosis has been tested in only a small number of studies. The two randomised, placebo-controlled trials published do not show any significant increase in bone mass. The unblinded trials have shown more positive effects on spinal bone density, but there are substantial differences in the outcome of these trials which are difficult to explain. Injectable calcitonin may have a greater effect than the nasal spray preparation, but its use is limited by a high incidence of side effects and low patient acceptability. There is no evidence that calcitonin reduces the fracture rates in these patients as there have been no studies of sufficient size to address this question. Given the availability of other therapeutic options of proven efficacy for bone protection in patients receiving long-term glucocorticoids, calcitonin should be regarded as a second-line agent.

Introduction

The principal effect of calcitonin on bone is its inhibition of bone resorption by means of the direct suppression of osteoclast function (1) and number (2). Earlier studies of osteoporosis used porcine calcitonin (3, 4), but in the last two decades salmon calcitonin has been used. The development of salmon calcitonin administered by nasal spray has significant advantages over the injectable preparations in terms of patient compliance and acceptability. Most studies of calcitonin treatment in postmenopausal osteoporosis show only small increases in bone mass: up to 2% in the spine and usually no significant increases at the hip and other sites (5-8). Its efficacy in reducing osteoporotic fractures has not yet been definitively established in randomised controlled trials (9).

Primary prevention

The efficacy of calcitonin in the prevention and treatment of glucocorticoid-induced osteoporosis has been studied in a small number of trials over the last decade (Table I). Of these, three were randomised, double-blind, placebo-controlled studies of the primary prevention of glucocorticoid-induced osteoporosis (10-12). Healey *et al.* (11) assessed the efficacy of subcutaneous calcitonin in preventing osteoporosis in a two-year study of 48 patients with newly diagnosed polymyalgia rheumatica and/or temporal arteritis starting steroid therapy. Patients were randomised to receive either subcutaneous calcitonin or placebo. In addition, all patients also received calcium and vitamin D3 (calciferol) supplementation. Unlike other studies which have generally found parenteral administration of calcitonin to have low patient acceptability, the study medications were well tolerated and compliance with injections and oral medications was good (> 80% and 90%, respectively). Eight patients withdrew from the study, none because of adverse events related to the study medication. There were no differences in the changes in bone density over the 2-year study between the two groups: in the lumbar spine they were -0.1 ± 3.3% and -0.2 ± 8.3% (mean ± SD) in the calcitonin and placebo groups respectively, and in the femoral neck they were -3.6 ± 6.6% and -6.8 ± 10.9%. The rates of new fractures were not different between the calcitonin (2/19, 11%) and placebo (3/21, 14%) groups. The cumulative dose of prednisone over the two years was the only significant correlate of change in bone density. Adjusting for prednisone dose did not change the outcome of the analysis.

Adachi *et al.* (12) investigated the use of intranasal calcitonin in the prevention of steroid-induced bone loss. A group of 31 patients with newly diagnosed polymyalgia rheumatica were studied within

Table I. Summary of randomised controlled trials of salmon calcitonin in the prevention and treatment of glucocorticoid-induced osteoporosis.

Author	Design	1° or 2° prevention	Duration (months)	Patients (mean age & gender)	Underlying diagnosis	Prednisone dose (mean)	Number entered; completed	Treatment sCT dose	Route	Comparator
Healey (1995)	RDPC	1°	24	72 yrs (45-87) 12m, 36f	Temporal arteritis, polymyalgia rheumatic; other vasculitides	9.4 mg/d during 1st year, 4.4mg/d during 2nd year	48; 42	100 IU thrice weekly	sc	Placebo
Adachi (1997)	RDPC	1°	12	70 yrs 13m, 18f	Polymyalgia rheumatica	18 mg/d at baseline	31; 27	200 IU/d	in	Placebo
Ringe (1987)	RC	2°	6	50 yrs (25-67) 7m, 29f	Chronic steroid dependent lung diseases	16.5 mg/d during study	38; 36	100 IU/alternate day	sc	None
Luengo (1990)	RC	2°	12	60 yrs 16m, 24f	Asthma	10.7 mg/d at baseline	62; 40	100 IU/thrice weekly	sc	None
Rizzato (1988)	RC	2°	15	38 yrs 23m, 30f	Sarcoidosis	12.1 mg/d during study	53; 53	100 IU/d	im	None
Luengo (1994)	RC	2°	24	59 yrs 6m, 38f	Asthma	10.3 mg/d at baseline, 7.8 mg/d at 2nd year	44; 30	200 IU/d	in	None
Kotaniemi (1996)	RC	2°	12	51 yrs 63f	Rheumatoid arthritis	8.5 mg/d at baseline and 1 yr	63; 49	100 IU/d	in	None

RC = randomised controlled; RDPC = randomised, double-blind, placebo-controlled,; sCT = salmon calcitonin; sc=subcutaneus; im = intramuscular; in =

4 weeks of starting steroid therapy. The patients were randomised to either calcitonin nasal spray or placebo. Calcium supplementation was given to those whose dietary calcium was less than 800 mg/d (2 patients). Calcitonin nasal spray was well tolerated.

Calcitonin was slightly more effective than placebo in reducing the rate of bone loss from the lumbar spine. Mean spinal density changed from 1.06 g/cm^2 to 1.04 g/cm^2 (-1.29 ± 6.76%) in the calcitonin group and from 1.11 g/cm^2 to 1.08 g/cm^2 (-4.95 ± 3.5%) in the placebo group over 12 months. The discrepancy between the percentage changes reported and the absolute bone density values is presumably attributable to the use of different subgroups of patients for each parameter, i.e. intention-to-treat-analysis versus patients completing the study. This difference was statistically significant using a one-tailed test, but the clinical significance of such a small difference must be marginal. In the proximal femur, the between-group trends were of similar magnitude but in the opposite direction, and in the total body scans the two groups responded identically. At neither of these sites was there a significant difference.

The study of Sambrook *et al.* (10) was complicated in its design, and there was no direct comparison of calcitonin treatment alone with placebo. 103 patients with underlying rheumatic, immunologic and respiratory diseases were randomised into 3 groups within 4 weeks of starting steroid therapy: (1) calcitonin nasal spray with calcitriol and calcium; (2) calcitriol and calcium with placebo nasal spray; or (3) calcium with double placebo. The treatment period was 1 year with follow-up to 2 years; the patients received no calcitonin, calcitriol or calcium in the second year. The group consisted of both young and old subjects (age range 18-77 yrs.) of both sexes, Of the 103 patients enrolled, 69 completed one year and 60 completed the two years of the study. Cessation of steroid therapy (21 patients) was the main cause of dropout from the study, while non-compliance, side effects and protocol violation accounted for the remainder.

In the first year, bone loss from the lumbar spine but not the femoral neck or radius was reduced by treatment with calcium and calcitriol. The addition of calcitonin did not have a significant added benefit. The changes in lumbar bone density in the first year were: -0.2 ± 6.5, -1.3 ± 5.6, and -4.3 ± 5.5 percent per year for groups 1, 2, and 3 respectively (P = 0.0035). The difference between groups 1 and 2 was not statistically significant. The rate of bone loss in the femoral neck was similar in all three groups in the first year (-2.8 ± 13.1, -2.8 ± 10.3, and -2.9 ± 6.8 percent per year for groups 1, 2, and 3 respectively). The changes in the radius were more variable, with small increases in groups 1 and 2, and a decrease in the calcium-only patients (group 3), but the differences were not statistically significant.

During the second year, when these steroid-treated patients received no bone protection medication, no bone loss was observed in group 1 (who originally received calcitonin, calcitriol and calcium) though the other groups did lose bone (changes in spine bone density: +0.7 ± 7.8, -3.6 ± 5.4, and -2.3% ± 6.9 percent per year in groups 1, 2, and 3 respectively; P = 0.044). The authors suggested that calcitonin might have had a persistent benefit to explain this trend, but offered no plausible biological mechanism for this.

A further study in the primary prevention of glucocorticoid-induced osteoporosis was a case series of 29 consecutive patients with previously untreated sar-

Calcium or vit. D supplement	Endpoint	Results		Comment
		Inter-group differences in change in bone density at end of study	Within group change in bone density from baseline to end of study	
Calcium 1.5 g/d & calciferol 400 IU/d all patients	DXA spine, femoral neck	Lumbar 0.1% (ns) Femur: 3.2% (ns)	sCT: -0.1%, -3.6% (lumbar, femur) Control: -0.2%, -6.8% (lumbar femur) (P values not stated)	
Supplementary calcium if dietary intake < 800 mg/d	DXA spine hip, total body	Lumbar: 3.7%*	sCT: -1.3% Control: -5.0% (P values not stated)	
	SPA forearm	Mid-radius: 4.0%* Distal radius: 6.2%*	sCT: +2.6%*, +2.7%* (mid-, distal radius) Control: -1.4%*, -3.5%* (mid-, distal radius)	40% sCT group reported side effects
Calcium 1 g/d all patients	DPA spine	Lumbar: 6.5%*	sCT: +4.0%* Control: -2.5%*	100% sCT group reported side effects of varying degrees; 35% dropped out due to intolerance
	QCT spine	Lumbar: 12.0%*	sCT: -2.2% Control: -1.4% (P values not stated)	20% dropped out from sCT due to low compliance with i.m. injections
Calcium 1 g/d all patients	DPA spine	Lumbar: 5.5% (12 months)* 10.6% (24 months)*	sCT: +2.7% (ns), +2.8% (ns) (12, 24 mths) Control: -2.8% (ns), -7.8%* (12, 24 mths)	
Calcium 500 mg/d all patients	DXA spine	Lumbar: 1.1% (ns) Femoral neck 3.0%*	sCT: +0.5% (ns), +0.3% (ns) (lumbar, femur) Control: -0.6% (ns), -2.7%* (lumbar, femur)	

intranasal; SPA = single-photon absorptometry; DPA = dual-photon absorptometry; DXA = dual energy x-ray absorptometry; * = P < 0.05; NS = not significant.

coidosis who were simultaneously starting prednisone and calcitonin (13). The first 18 patients received intramuscular salmon calcitonin (i.m. sCT) for 2 years, and the other 11 patients received intramuscular injections for the first 4 months and continued with intranasal calcitonin spray (i.n. sCT) for a further 20 months. Thirty-five historical cases were selected as the control group for comparison. Bone densities were measured by quantitative computed tomography. The decrease in spinal bone densities over the 2 years was significantly greater in the historical control group than in the 2 calcitonin groups: control, -15.35 ± 2.6%; i.m. sCT, -4.05 ± 4.6%; i.n. sCT, -3.68 ± 3.4%, P < 0.03. Most of the bone loss occurred in the first year. The reduction in bone density over time was significant in the control and not in the calcitonin groups. Bone loss was not different in the two calcitonin groups, but side effects were much more common in the i.m. sCT group.

Secondary prevention

Secondary prevention with intramuscular, subcutaneous, or intranasal calcitonin has been studied in patients on established steroid therapy. All of these studies lacked a placebo control group (14-18). Most only measured bone density changes at a single site, either radial (14) or vertebral (15-17). The studies where calcitonin was administered parenterally (either intramuscular or subcutaneous) were characterised by high incidences of side effects and low patient compliance (14-16).

Ringe *et al.* (14) investigated the effect of treatment with subcutaneous calcitonin in a group of patients with steroid-dependent lung diseases. They found a 4-6% difference in changes in forearm bone density between the treated and the control groups at six months, corresponding to a small gain in bone density of ~2-3% in the treatment group and a loss of ~1-3% in the untreated group. Nearly 40% of the calcitonin treated patients experienced side effects of flushing or nausea, and one dropped out of the study because of intolerance of calcitonin injections.

Another secondary prevention study in steroid-dependent asthmatic patients had a high dropout rate of 35% from the subcutaneous calcitonin group because of non-compliance and side effects (16). All 20 patients who completed the 12 months of calcitonin treatment experienced side effects of mild to moderate degree. The final analysis included only these 20 patients with 20 sex-matched controls. In those who were able to continue with calcitonin there was an increase of 4% ($P \leq 0.001$) in the lumbar spine bone density at one year as compared with a decrease of 2.5% ($P \leq 0.05$) in the control patients.

In one study of treatment with intramuscular calcitonin in prednisone-treated sarcoidosis patients, 20% of the original patients in the calcitonin group stopped calcitonin after a few injections due to low compliance (15). They were subsequently included in the control group. A difference of 12% ($P < 0.001$) in change in spinal bone density was found between the groups at 15 months. Both groups lost bone: ~2% in the calcitonin group and 14% in the control group. The control group on average received a 24% higher dose of prednisone than the calcitonin group, although the difference was not statistically significant. Spinal bone density was measured using quantitative computed tomography, which assesses the density of the vertebral body trabecular bone, which has a higher turnover. This would account for the greater changes in bone density than are seen in

other studies using dual energy x-ray or dual-photon absorptometry, which measure a mixture of cortical and trabecular bone.

Compared with its injectable forms, calcitonin given by nasal spray is better tolerated by patients. Although a dose of 200 IU calcitonin administered by the nasal route is considered to be equivalent to 80-100 IU given parenterally (19), the bioavailability of the nasal preparation is probably less. Doses of intranasal calcitonin tested in glucocorticoid-induced osteoporosis range from 100-400 IU/d (10, 12, 17, 18). Luengo *et al*. (17) compared the efficacy of intranasal calcitonin plus calcium versus calcium alone in preventing bone loss in steroid-dependent asthmatics. All 44 patients completed the first year, and 34 completed two years of the study. Nine patients ceased to be steroid-dependent while one calcitonin-treated patient dropped out of the study because of side effects. Analysis was performed at one and two years on the results of the patients who remained on the study medications. In the calcitonin-treated group there were non-significant increases of 2.7% and 2.8% in the lumbar bone density at one and two years, respectively, while in the control group there were decreases of 2.8% (not significant) and 7.8% ($P = 0.007$) at one and two years. The differences in change in bone density from baseline between the groups were statistically significant at both time points. There was no difference in fracture rates, with 3 new fractures in each group. The side effects of intranasal calcitonin were mild: rhinorrhoea, nausea, facial redness, and headaches were reported.

Kotaniemi *et al*. (18) tested the efficacy of intranasal calcitonin in rheumatoid patients on steroids. Intranasal calcitonin plus calcium was compared with calcium alone over a 12-month period. This is the only study to show any statistically significant beneficial effect of calcitonin in preventing bone loss from the proximal femur – in those patients who completed the study a 3% difference between groups at the femoral neck ($P < 0.05$) was seen. The calcium-only group showed a reduction in bone density of 2.7% at 12 months ($P < 0.05$) versus a non-significant minor increase of 0.3% in the calcitonin plus calcium group. There was no significant difference in the changes at the lumbar spine. Twenty percent of the 63 enrolled patients experienced side effects. These were generally mild and none of the patients withdrew from the study because of side effects.

In summary, the evidence that calcitonin is efficacious in preventing steroid-induced bone loss is unconvincing. The two placebo-controlled studies do not really show any significant effect when analysed using conventional statistical methods. Only one study has shown effects at the hip. In the spine, where positive results have been more common, there are substantial differences in outcome between trials which are difficult to explain. Injected calcitonin may have a greater effect than the nasal spray preparation, but its use is limited by a high incidence of side effects and resulting low patient acceptability. There is no evidence that any formulation of calcitonin reduces the fracture rates in these patients because studies of sufficient size have not been undertaken. In contrast, there are now a large number of studies on bisphosphonates which generally show greater beneficial effects on bone density than the calcitonin studies, are consistent between studies, and which have also shown fracture prevention in some cases. Therefore, calcitonin can only be regarded as a second-line agent for use when other therapeutic options are not available.

References

1. SINGER FR, MELVIN KEW, MILLS BG: Acute effects of clacitonin on the number of osteoclasts in man. *Clin Endocrinol* 1976; 5: 333-40.
2. HEDLUND T, HULTH A, JOHNELL O: Early effects of parathyroid hormone and calcitonin on the number of osteoclasts and on serum calcium in rats. *Acta Orthop Scand* 1983; 54: 802-4.
3. BROWN P, THIN CG, MALONE DNS, ROSCOE P, STRONG J: Metabolic studies with porcine calcitonin in osteoporosis. *Scott Med J* 1970; 15: 207-12.
4. JOWSEY J, RIGGS BL, GOLDSMITH RS, KELLY PJ, ARNAUD CD: Effects of prolonged administration of porcine calcitonin in postmenopausal osteoporosis. *J Clin Endocrinol Metab* 1971; 33: 752-8.
5. GRUBER HE, IVEY JL, BAYLINK DJ *et al.*: Long-term calcitonin therapy in postmenopausal osteoporosis. *Metabolism* 1984; 33: 295-03.
6. REGINSTER J, DENIS D, ALBERT A *et al.*: One-year controlled randomised trial of prevention of early postmenopausal bone loss by intranasal calcitonin. *Lancet* 1987; Dec 26:1481-3.
7. OVERGAARD K, RIIS BJ, CHRISTIANSEN C, PØDENPHANT J, JOHANSEN JS: Nasal Calcitonin for the treatment of established osteoporosis. *Clin Endocrinol* 1989; 30: 435-42.
8. ELLERINGTON MC, HILLARD TC, WHITECROFT SI *et al*.: Intranasal salmon calcitonin for the prevention and treatment of postmenopausal osteoporosis. *Calcif Tiss Int* 1996; 59: 6-11.
9. SILVERMAN SL, CHESTNUT C, ANDRIANO K: Salmon calcitonin nasal spray (NS-CT) reduces risk of vertebral fracture(s) (VF) in established osteoporosis and has continuous efficacy with prolonged treatment: Accrued 5 year worldwide data of the PROOF study. *Bone* 1998; 23 (Suppl.): S174.
10. SAMBROOK P, BIRMINGHAM J, KELLY P *et al.*: Prevention of corticosteroid osteoporosis. *N Engl J Med* 1993;328:1747-52.
11. HEALEY JH, PAGET SA, WILLIAM-RUSSO P *et al.*: A randomized controlled trial of salmon calcitonin to prevent bone loss in corticosteroid-treated temporal arteritis and polymyalgia rheumatica. *Calcif Tiss Int* 1996; 58: 73-80.
12. ADACHI JD, BENSEN WG, BELL MJ *et al.*: Salmon calcitonin nasal spray in the prevention of corticosteroid-induced osteoporosis. *Br J Rheumatol* 1997; 36: 255-9.
13. MONTEMURRO L, SCHIRALDI G, FRAIOLI P, TOSI G, RIBOLDI A, RIZZATO G: Prevention of corticosteroid-induced osteoporosis with salmon calcitonin in sarcoid patients. *Calcif Tiss Int* 1991; 49: 71-6.
14. RINGE JD, WEZEL D: Salmon calcitonin in the therapy of corticosteroid-induced osteoporosis. *Eur J Clin Pharmacol* 1987; 33: 35-9.
15. RIZZATO G, TOSI G, SCHIRALDI G, MONTEMURRO L, ZANNI D, SISTI S: Bone protection with salmon calcitonin (sCT) in the long-term steroid therapy of chronic sarcoidosis. *Sarcoidosis* 1988; 5: 99-103.
16. LUENGO M, PICADO C, DEL RIO L, GUANABENS N, MONTSERRAT JM, SETOAIN J: Treatment of steroid-induced osteopenia with calcitonin in corticosteroid-dependent asthma. A one-year follow-up study. *Am Rev Respir Dis* 1990; 142: 104-7.
17. LUENGO M, PONS F, MARTINEZ DE OSABA MJ, PICADO C: Prevention of further bone mass loss by nasal calcitonin in patients on long term glucocorticoid therapy for asthma: A two-year follow up study. *Thorax* 1994; 49: 1099-102.
18. KOTANIEMI A, PIIRAINEN H, PAIMELA L *et al.*: Is continuous intranasal salmon calcitonin effective in treating axial bone loss in patients with active rheumatoid arthritis receiving low dose glucocorticoid therapy. *J Rheumatol* 1996; 23: 75-9.
19. REGINSTER JY, DENIS D, ALBERT A, FRANCHIMONT P: Assessment of the biological effectiveness of nasal synthetic salmon calcitonin (SSCT) by comparison with intramuscular (i.m.) or placebo injection in normal subjects. *Bone Min* 1987; 2: 133-40.