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Calcitonin Therapy in Osteoporosis

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Abstract

Osteoporosis is the most prevalent metabolic bone disease and is characterized by diminished bone strength predisposing to an increased risk of fracture. Its incidence is particularly high in postmenopausal women but it can also affect other groups, such as men and patients receiving corticosteroid therapy.

Calcitonin is a naturally occurring peptide which acts via specific receptors to strongly inhibit osteoclast function. It has been used in the treatment of osteoporosis for many years. Historically, calcitonin was administered as a parenteral injection, but the intranasal formulation is now the most widely used because of its improved tolerability. New approaches are currently being investigated to enhance the bioavailability and effects of calcitonin, including oral, pulmonary, and transdermal routes of administration, and novel allosteric activators of the calcitonin receptor.

Several controlled trials have reported that calcitonin stabilizes and in some cases produces a short-term increase in bone density at the lumbar spine level. The most relevant clinical trial to evaluate the effect of calcitonin in the prevention of fractures was the Prevent Recurrence of Osteoporotic Fractures (PROOF) study, a 5-year double-blind, randomized, placebo-controlled trial showing that salmon calcitonin nasal spray at a dosage of 200 IU/day can reduce the risk of vertebral osteoporotic fractures by 33% (relative risk [RR] = 0.67; 95% CI 0.47, 0.97; p = 0.03). However, the 100 and 400 IU/day dosages did not significantly reduce vertebral fracture risk. Effects on nonvertebral fractures were not significant (RR = 0.80; 95% CI 0.59, 1.09; p = 0.16).

There is mounting evidence to show that calcitonin diminishes bone pain in osteoporotic vertebral fractures, which may have clinical utility in vertebral crush fracture syndrome. A recent study suggests that nasal salmon calcitonin appears to be a promising therapeutic approach for the treatment of men with idiopathic osteoporosis, although long-term trials are necessary to confirm these results and evaluate fracture rate as an endpoint in men.

The role of calcitonin in corticosteroid-induced osteoporosis remains controversial, hence it can only be considered a second-line agent for the treatment of patients with low bone mineral density who are receiving long-term corticosteroid therapy.

Osteoporosis is the most frequently occurring metabolic bone disease and is characterized by diminished bone strength predisposing to an increased risk of fracture; its prevalence is particularly high in postmenopausal women, although this disease can also affect males and patients receiving corticosteroid therapy.[1] Osteoporotic fractures and their associated complications constitute the most significant clinical consequence of this highly prevalent condition and represent a major international health problem in both men and women.[2] Many studies indicate that prior fracture is the most significant risk factor for further fractures,[3] and a recent study indicates that the subsequent risk is nonlinear, being extremely high in the few months after a vertebral fracture and decreasing thereafter.[4]

Bone strength reflects the integration of two main features: bone density and bone quality.[1,5] Bone quality refers to architecture, turnover, damage accumulation (e.g. microfractures) and mineralization. There is currently no accurate measure of overall bone strength. Prior analyses of data from randomized placebo-controlled clinical trials conducted in postmenopausal women suggest that the increase in bone mineral density during antiresorptive therapy accounts for much of the reduction in the risk of radiographic vertebral fractures.[6,7] Despite these analyses, the debate continues regarding the extent to which reductions in fracture risk during antiresorptive therapy may be related to changes in bone mineral density.[8] For example, it has been proposed that some antiresorptive agents might reduce vertebral fracture risk substantially by reducing rates of bone resorption, while having little or no effect on bone mineral density.[9]

Calcitonin is a naturally occurring peptide that acts through specific receptors to powerfully inhibit osteoclast function. The existence of this hypocalcemic hormone was discovered in the 1950s. In 1967, Raisz et al.[10] and Friedman and Raisz[11] published accounts of its effects on bone resorption in their studies employing tissue cultures. Later, in 1982, Chambers and Magnus[12] demonstrated a direct effect of femtomolar calcitonin concentrations on osteoclast function. The antiresorptive action of calcitonin has led to its use in treating metabolic bone diseases characterized by excessive bone resorption, such as Paget's disease of the bone and hypercalcemia of malignancy. In particular, calcitonin has been used for many years in the management of osteoporosis. A possible effect of calcitonin with respect to enhancing bone quality, which cannot be assessed by routinely available methods, is currently being investigated in a prospective trial.[13]

This review analyzes the key pharmacological properties of calcitonin as well as the current state of scientific evidence regarding its therapeutic efficacy and tolerability in the management of osteoporosis.

1. Biological and Pharmacological Properties

1.1 Chemistry

Calcitonin is a polypeptide hormone secreted by the parafollicular cells (C cells) of the thyroid gland in mammals and by the ultimobranchial gland in birds and fish. Calcitonin, from any source, is a 32-amino acid peptide chain, the amino acid sequence of which may differ considerably from that of human calcitonin, depending on the species (figure 1). Structural relationships to potency and duration of effect are complex and may depend more on spatial relationships than on the amino acid sequence. Calcitonin is commercially available as salmon calcitonin. Salmon calcitonin and human calcitonin differ structurally at amino acids 2, 8, 11–13, 15–17, 19, 20, 22, 24, 26, 27, 29, and 31.[14] The pharmacological properties of these calcitonins are the same, but salmon calcitonin is substantially more potent on a weight-by-weight basis (approximately 40–50 times that of human calcitonin) and has a longer duration of action.[15] Salmon calcitonin is prepared synthetically and contains the 32 amino

	10							20										30			
C	S	N	L	S	T	C	V	L	G	K	L	S	Q	E	L	H	K	L	Q	T	Y	P	R	T	N	T	G	S	G	T	P	**CTs**
C	S	N	L	S	T	C	V	L	G	K	L	S	Q	E	L	H	K	L	Q	T	Y	P	R	T	D	V	G	A	G	T	P	**CTa**
C	S	S	L	S	T	C	V	L	G	K	L	S	Q	E	L	H	K	L	Q	T	Y	P	R	T	N	V	G	A	G	T	P	**CTg**
C	T	S	L	S	T	C	V	V	G	K	L	S	Q	Q	L	H	K	L	Q	N	I	Q	R	T	D	V	G	A	A	T	P	**CTst**
C	A	S	L	S	T	C	V	L	G	K	L	S	Q	E	L	H	K	L	Q	T	Y	P	R	T	D	V	G	A	G	T	P	**CTp**
C	S	N	L	S	T	C	V	L	S	A	Y	W	R	N	L	N	N	F	H	R	F	S	G	M	G	F	G	P	E	T	P	**CTpr**
C	S	N	L	S	T	C	V	L	S	A	Y	W	K	D	L	N	N	Y	H	R	Y	S	G	M	G	F	G	P	E	T	P	**CTo**
C	S	N	L	S	T	C	V	L	S	A	Y	W	K	D	L	N	N	Y	H	R	F	S	G	M	G	F	G	P	E	T	P	**CTb**
C	S	N	L	S	T	C	V	L	G	T	Y	S	K	D	L	N	N	F	H	T	F	S	G	M	G	F	G	A	E	T	P	**CTp**
C	G	N	L	S	T	C	M	L	G	T	Y	T	Q	D	F	N	K	F	H	T	F	P	Q	T	A	I	G	V	G	A	P	**CTh**
C	G	N	L	S	T	C	M	L	G	T	Y	T	Q	D	L	N	K	F	H	T	F	P	Q	T	S	I	G	V	G	A	P	**CTr**
C	G	N	L	S	T	C	M	L	G	T	Y	T	Q	D	L	N	K	F	H	T	F	P	Q	T	A	I	G	V	V	A	P	**CTc**

Fig. 1. Peptide structure of the calcitonins from several species. They all have cysteine in position 1 and 7 joined by a disulfide bridge, glycine in position 28 and terminal proline residues. The marked amino acids are those that coincide with the salmon calcitonin sequence (CTs). The following species are represented: eel (CTa), goldfish (CTg), stingray (CTst), chicken (CTp), porcine (CTpr), ovine (CTo), bovine (CTb), dog (CTp), human (CTh), rat (CTr), and rabbit (CTc).

acids in the same linear sequence as they occur in natural calcitonin of salmon origin. The potency of salmon calcitonin is expressed in International Units (IU) based on a bioassay in comparison with the International Reference Preparation of Salmon Calcitonin for Bioassay, distributed by the National Institute for Biological Standards and Control, Holly Hill, London, UK.

1.2 Calcitonin Receptors

There are approximately one million calcitonin receptors per rat osteoclast.[16] Several calcitonin receptor subtypes have been cloned and sequenced.[17] All are membrane receptors with seven transmembrane domains and a long extracellular domain, which binds calcitonin with high affinity[18] (figure 2).

Several calcitonin receptor isoforms have been identified on a pharmacological basis, even prior to their molecular cloning.[19] Human calcitonin receptor subtypes arise from alternative splicing of the primary mRNA transcript of the human calcitonin receptor gene, which consists of multiple exons separated by lengthy introns that allow for splicing.[20]

Little is known, however, about the regulation of calcitonin receptor expression. Recent findings have reported that calcitonin can inhibit calcitonin receptor expression through a transcriptional mechanism,[21] that glucocorticoids stimulate calcitonin receptor expression,[22] and that calcitonin receptor expression in osteoclasts is down regulated during osteoclastogenesis.[23] A further interesting finding, albeit not unexpected, is that calcitonin receptors can be induced to appear in mammary tissue during pregnancy.[24] The physiological significance of this observation is unclear. Finally, the transgenic expression of the calcitonin receptor in mice indicates its role in morphogenesis in general, and skeletal development in particular.[25] Several investigators have cloned calcitonin receptor-like receptors that bind primarily to calcitonin gene-related peptide and amylin.[26-28]

There was an initial suggestion that identified the osteoclast calcitonin receptor with the Ca^{2+}-sensing receptor, but it was later shown that this simply reflected the cation-sensitive nature of calcitonin binding.[29-31] It is now becoming clear that osteoclast Ca^{2+}-sensing is a function of a uniquely expressed surface ryanodine receptor.[32-34] There is thus the possibility that cellular mechanisms related to the calcitonin and Ca^{2+} receptor systems in the osteoclast interact at several levels of cellular organization.

The recent use of chimeric receptor constructs and site-directed mutagenesis has further advanced our understanding of calcitonin receptor biology.[35]

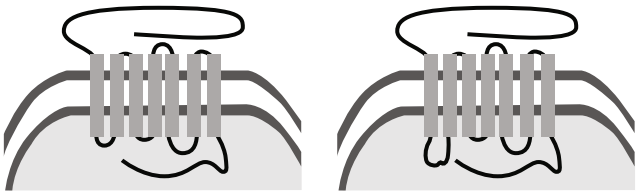

Fig. 2. Isoforms of the human calcitonin receptor with the extra and intracellular domains (left side: cloned from cells T47D; right side: cloned from cells BIN-67). The gray zone (inferior) represents the cellular cytoplasm.

1.3 Cellular and Molecular Actions of Calcitonin

Calcitonin inhibits both basal and stimulated resorption of organ-cultured intact bone.[36] It directly and rapidly causes a loss of the ruffled border of osteoclasts in bone sections and reduces osteoclast numbers in bone over the longer term.[37-39] The application of near-physiological femtomolar calcitonin concentrations stops cytoplasm motility and produces a gradual pseudopodial retraction in isolated osteoclasts *in vitro*, which would decrease the area of cell contact with bony substrate, and possibly thereby reduce resorption.[40,41]

Calcitonin also inhibits osteoclast secretory activity, particularly of tartrate-resistant acid phosphatase (TRAP) in terms of both synthesis and release.[42] By altering Na^+-K^+-ATPase activity, and carbonic anhydrase localization, as well as direct H^+-ATPase inhibition, it reduces osteoclast acid secretion.[43-45]

Such cellular effects of calcitonin correlate with a reproducible inhibition of bone resorption in every osteoclast resorption assay studied, including the classical pit-forming assay.[46-48] The calcitonins display different inhibitory potency, with salmon calcitonin being the most potent and human calcitonin the least potent. The therapeutically used calcitonins follow a rank order of potency in exerting their osteoclast-inhibitory effects on the skeleton. Fish calcitonins, notably salmon and eel, are about 40–50 times more potent,[15] weight-by-weight, compared with mammalian (human or porcine) calcitonins in lowering plasma calcium or reducing markers of bone turnover.

Recent studies have reported surprising additional actions. Calcitonin, even at femtomolar concentrations, releases osteoclasts from the inhibitory effects of high extracellular Ca^{2+}.[33] This apparently paradoxical effect may explain the lack of bone loss when circulating calcitonin is absent, such as after thyroidectomy, or the absence of osteopetrosis under conditions of high circulating calcitonin in medullar thyroid carcinoma. Second, calcitonin interacts with osteoblasts in some systems, despite no convincing evidence for calcitonin receptors on any osteoblast-like cells. Thus, eel calcitonin exerts an anabolic effect on osteoblasts that enhances osteoinduction by bone morphogenic protein-2.[49,50] It also increases the concentration of insulin-like

growth factors in serum-free cultures of human osteoblast-like cells.[51] Calcitonin may also prevent osteoblast and osteocyte apoptosis, but this action is again controversial.[52] Despite these reports, any effect of calcitonin on osteoblasts remains unclear. Furthermore, calcitonin inhibits the osteoclastogenic effects of the osteoprotegerin ligand, an effect that may be therapeutically relevant.[53]

Moreover, pharmacological calcitonin concentrations increase renal calcium and phosphate excretion and 1,25-dihydroxycholecalciferol production.[54,55] More recently, calcitonin has been shown to regulate the expression of the renal 25-hydroxyvitamin D3 hydroxylase gene in normocalcemic rats.[56] Calcitonin may also affect other tissues indirectly related to mineral metabolism; for example, it increases mRNA expression of the 25-hydroxyvitamin D3 1-hydroxylase (CYP27B1) enzyme, which catalyzes the biosynthesis of 1,25-dihydroxyvitamin D3 from 25-hydroxyvitamin D3 in renal proximal tubules.[57] In addition, calcitonin alters the localization of critical ion exchangers in renal tubular cells.[58]

Calcitonin was introduced for the treatment of disorders of bone and mineral metabolism, principally because of its inhibitory effect on osteoclastic bone resorption. Plasma calcium is reduced, and this is accompanied by an equally transient increase in plasma parathyroid hormone.[59] The latter effect is partially reinforced by the short calciuric effect of the drug. A decrease in urinary markers of bone resorption occurs within a few hours of administration of pharmacological doses.[42] The response to medication at supraoptimal doses is more pronounced in disorders characterized by high bone turnover, such as Paget's disease of the bone and hypercalcemia of malignancy, whereas lower doses have less complete effects. However, osteoclastic activity is inhibited for less than 24 hours, with alterations in basal markers for bone metabolism relatively less effectively altered as rapid reversal occurs after treatment ceases.[60]

1.4 Calcitonin Resistance and the 'Escape' Phenomenon

Resistance to calcitonin action can develop for the acute hypocalcemic effects or can lead to a lack of efficacy of long-term treatment. It has been best described in the context of Paget's disease;[61-64] however, there is no clear evidence that it can also occur in the case of osteoporosis treatment. In fact, in the Prevent Recurrence of Osteoporotic Fractures (PROOF) study, the presence of high titers of calcitonin antibodies did not seem to have an effect on the therapeutic response.[65] The resistance may be on either an immune or a nonimmune basis. The formation of antibodies against heterologous calcitonins such as salmon calcitonin is common and occurs in 40–70% of the patients treated for more than 4 months[66] and in some cases of human calcitonin administration.[67] Not all of these patients, however, develop a secondary resistance to salmon calcitonin; therefore, the clinical significance of such antibodies is controversial. For most authors, however, the clinical importance of this phenomenon in osteoporosis therapy remains unproven and serum antibodies are more frequently found rather than true resistance.[66,68-70] *In vivo* and *in vitro* approaches demonstrate a neutralizing effect in 35–60% of the patient sera with antibodies against salmon calcitonin.[71,72] These neutralizing antibodies appear to explain some cases of clinically relevant secondary resistance to salmon calcitonin treatment in Paget's disease, which can occur in a subgroup of patients after treatment periods of 6 months and longer.[66] Few cases develop secondary resistance in the absence of salmon calcitonin binding antibodies, and the mechanism of this phenomenon is unclear.

Although calcitonin inhibits bone resorption, it has been found, *in vitro* and *in vivo*, that calcitonin inhibition is followed by an 'escape', which is defined as an increase in resorption in bones stimulated by a resorptive agent. This phenomenon develops despite the continued presence of calcitonin concentrations that are maximally inhibitory.[73,74] Studies of osteoclasts in culture have shown that calcitonin treatment results in downregulation of the calcitonin receptor.[73,75] Both short and continuous treatment of osteoclasts with calcitonin results in a rapid and prolonged downregulation of calcitonin receptor mRNA.[76,77] Significantly, calcitonin-treated osteoclasts regained the ability to resorb bone, suggesting that functional, calcitonin-resistant osteoclasts result from exposure to pharmacological doses of calcitonin.[73] However, there is no convincing evidence that desensitization of osteoclasts can occur in the context of osteoporosis treatment.

1.5 Routes of Delivery

For many years, it was necessary to administer calcitonin parenterally, by either intramuscular or subcutaneous injection. With respect to the prevention and treatment of postmenopausal osteoporosis, the chronic nature of the disease and the subsequent long duration of the pharmacological intervention required uncomfortable, repetitive, long-term administration. New routes of administration have therefore been developed.

The interest in calcitonin for the long-term prevention and treatment of osteoporosis has considerably increased since the introduction of the nasal calcitonin spray, which has pharmacological bioequivalence of up to 40% compared with parenteral delivery[78] in the clinical setting of osteoporosis treatment, but not in other disorders. A wide range of values has been reported for the bioavailability of nasal calcitonin because of unsatisfactory assay methodology. One study performed in healthy volunteers reported

that the intranasal formulation (200IU) shows an average bioavailability of 1.6%.[79] In a review,[80] it was concluded from comparative studies evaluating the effects of intranasal and parenteral salmon calcitonin in the context of postmenopausal osteoporosis treatment that equivalent biochemical effects are obtained when the intranasal dosage is approximately two to four times that of the parenteral dosage, although full dose-response curves are not concurrently available for the two routes of administration. Intranasal calcitonin is currently the most widely used formulation of calcitonin.

Oral administration of polypeptide hormones such as calcitonin in their natural state is precluded because of gastrointestinal absorption, and therefore two main pathways have been explored for the pharmaceutical development of an oral formulation. Protection of salmon calcitonin against proteolytic degradation in the intestinal lumen has been attempted using acid additives, protease inhibitors, water/oil emulsions, slow-release and mucoadhesive microparticle formulations, polymer-based hydrogels, or direct conjugation to fatty acids or short polymers.[81-83] Alternatively, improvement of the mucosal penetration of salmon calcitonin has been sought using permeation enhancers such as bile acids derivatives, acylcarnitine, detergents, phospholipids, fatty acids, or oil emulsions.[81,84-87] Various formulations associating salmon calcitonin with such additives have been patented and tested in animals over the past years. A new family of low molecular weight carriers, derived from N-acylated amino acids, have been recently developed. They are thought to selectively increase the mucosal uptake by inducing conformational changes in the peptide molecules.[88]

Recently, Buclin et al.[89] tested a new oral formulation of salmon calcitonin associated with a caprylic acid derivative as carrier. Healthy volunteers received single doses of salmon calcitonin 400, 800, and 1200μg orally, a placebo, and salmon calcitonin 50IU by intravenous infusion. Salmon calcitonin was reliably absorbed from the oral formulation, with an absolute bioavailability of 0.5–1.4%, depending on the dose. The authors concluded that oral delivery of salmon calcitonin was well tolerated with reproducible absorption and systemic biological efficacy.

Given rectally, salmon calcitonin is well absorbed, and few mild local adverse effects have been reported.[90] Data regarding its efficacy are controversial; some authors have described beneficial effects on bone metabolism,[91] while others have not.[92] Lyritis et al.[93] reported that salmon calcitonin suppositories (200IU daily) caused a dramatic decrease in spinal pain in patients with recent osteoporotic vertebral fractures and influenced the early mobilization and the gradual restoration of their locomotor functions.

Electrically enhanced transdermal delivery of salmon calcitonin is under development and may allow delivery of therapeutic levels of calcitonin.[94-96]

Deftos et al.[97] have evaluated the intrapulmonary route in healthy subjects for the delivery of salmon calcitonin administered with a dry powder delivery inhaler; each subject also received intramuscular salmon calcitonin. When compared by dose, intrapulmonary salmon calcitonin had 66% of the bioactivity and 28% of the bioavailability of intramuscular calcitonin.

1.6 Tolerability and Safety

The injectable formulation of calcitonin can produce unpleasant local and systemic reactions that result in the cessation of long-term treatment in approximately 45% of patients.[98]

The adverse effects associated with the clinical use of parenteral formulations of human or salmon calcitonin have usually been infrequent and mild, although they may occasionally be severe enough to require discontinuation of the drug.[99,100] Adverse effects of parenteral salmon calcitonin most frequently involve the gastrointestinal tract. Transient nausea, with or without vomiting, is the most common adverse effect and is usually mild and diminishes or disappears with continued therapy. Nausea and vomiting may occur within 30 minutes of injection of calcitonin and may be minimized by the use of an anti-emetic.[98,101] Other adverse effects of calcitonin include anorexia/poor appetite, diarrhea, epigastric discomfort, and abdominal pain.[100] Flushing of the face, ears, hands, and feet also commonly occurs within minutes of injection of salmon calcitonin.[101]

Because salmon calcitonin is a protein, the possibility of systemic allergic reaction should be considered. Serious, potentially fatal hypersensitivity reactions have been reported in patients receiving salmon calcitonin after parenteral delivery. Hypersensitivity reactions should be differentiated from generalized flushing and hypotension associated with administration of the drug.[101]

In contrast, administration by nasal spray is usually well tolerated, an increase in the rate of transient rhinitis being the most frequent adverse effect.[98,102] In the PROOF study[65] the only significant adverse effect related to intranasal calcitonin that was reported was rhinitis, generally of mild or moderate severity.

1.7 Dosage and Administration

The optimal frequency and dosage of calcitonin for the prevention as well as treatment of osteoporosis are still under investigation. In established osteoporosis, there appears to be a dose-dependent effect on the trabecular and cortical bone mass.[103,104] In the prevention of osteoporosis, there is some inconclusive evidence relating to the minimal effective dosage of salmon

calcitonin needed to prevent bone loss, although the optimum dose is not clearly defined. Reginster et al.[105] performed a double-blind, placebo-controlled, randomized study of three parallel groups who received intranasal salmon calcitonin 50 or 200IU, or placebo, on 5 days per week. Salmon calcitonin 50 IU/day prevented lumbar bone loss, and 200 IU/day resulted in a significant increase in lumbar bone mineral density. In the treatment of established osteoporosis, Rico et al.[106] reported that intramuscular salmon calcitonin 100 IU/day plus elemental calcium 500mg for 10 days each month is effective, with a specific action on both cortical and trabecular bone. The PROOF study suggests that the combination of daily doses of nasal salmon calcitonin 200IU, calcium 1000mg and vitamin D 400IU can significantly reduce the relative risk (RR) of new vertebral fractures compared with placebo.[65,107] In this study, there was an early increase in bone mineral density, which thereafter remained stable.

Studies with sensitive biochemical markers of bone resorption have shown that intranasal salmon calcitonin 200IU has a significant effect 3–6 hours after administration, with a rebound effect approximately 12 hours later, independently of the timing of administration, whether in the morning or in the evening.[108]

2. Therapeutic Aspects

2.1 Postmenopausal Osteoporosis

There are many reports of randomized controlled trials evaluating the effect of calcitonin in postmenopausal women with osteoporosis. Most used salmon calcitonin delivered by nasal spray. Results based on surrogate endpoint parameters of bone biochemical markers or bone densitometry were generally consistent across studies: calcitonin treatment produced modest, but reproducible, reductions in bone resorption and increases in bone mineral density over 1–5 years. However, calcitonin is only approved by the US FDA for the treatment of established osteoporosis, not for the prevention of postmenopausal osteoporosis. In most of the countries of the European Union, calcitonin is approved for the treatment of osteoporosis, with or without prevalent fractures.

Only one trial, the PROOF study, had sufficient power and was designed to detect a change in fracture rates.[65] The reduction in fracture risk can be dissociated from the long-term effects on bone mineral density. Moreover, a benefit in fracture risk precedes changes in bone mineral density. This may reflect trabecular microarchitecture, constituting an important causal factor in the pathogenesis of vertebral fractures.[109] Recent clinical trials with calcium plus vitamin D and raloxifene indicate significant protection from fracture despite only modest increases in bone mineral density, possibly through an effect on conserving bone quality.[110] The larger increase in bone mineral density with bisphosphonates is mainly due to an increase in mineralization and not in the amount of bone tissue.[111,112] Such a phenomenon does not seem to occur with the use of calcitonin.

2.1.1 Effects on Bone Mass

In a 2-year placebo-controlled study of nasal calcitonin 200IU daily in 33 postmenopausal osteoporotic women, the increase in bone mass was only minor (+2.5%, 95% CI 0.9, 4.2% versus +1.7%; 95% CI 0.3, 3.1 in the placebo group), but a decrease in resorption depth was seen at histomorphometry.[113] In another randomized but open study including 79 women within 3 years of menopause, Reginster et al.[114] demonstrated that calcitonin at low dosages administered intranasally (50 IU/day, 5 days/week) for 1 year prevented early postmenopausal bone loss at the lumbar level (gain of 1.38 ± 0.38%), whereas the control group lost an average of 3.16 ± 0.6% of bone mass. The trial was extended for 3 and 5 years and the prevention of postmenopausal bone loss at the lumbar level was confirmed (gain of 1.1% ± 1.1 compared with a loss of 6.6% ± 1.0 in the control group; $p < 0.01$).[115]

Similar results have been observed in two randomized, double-blind, placebo-controlled studies in early postmenopausal women; however, they included fewer patients. Overgaard et al.[116] studied 52 patients for 2 years who received nasal calcitonin 100 IU/day, and observed an increase in lumbar spine bone mass in the treated group compared with a placebo group; after 1 year the difference was 3.8% (95% CI 0.0, 7.6) and after 2 years it was 8.2% (95% CI 3.8, 12.6). In the study of Gennari et al.,[117] which included only 21 patients with signs of increased bone turnover, treatment with nasal salmon calcitonin at dosages of 200 IU/day significantly increased bone mass at the lumbar spine by 2.7 ± 0.9% at 6 months, and 3.3 ± 0.8% at 1 year, whereas a progressive decline was observed in the placebo group (−2.6 ± 0.5% and −3.5 ± 0.5% after 6 and 12 months, respectively). In these studies a protective effect on cortical bone was not investigated or was absent.

However, other studies in early postmenopausal women showed that daily doses of nasal calcitonin 100 IU/day were insufficient to increase bone mass,[118] in contrast with positive results obtained in older women whose bone turnover was increased to a lesser degree.[119] Surprisingly, after treating 14 early postmenopausal women selected on the basis of a high bone turnover for 1 year with nasal calcitonin 100 IU/day, an impressive increase of 8.5% in spinal bone mass was obtained, whereas the placebo group ($n = 14$) showed a decrease of 8%.[120]

The results are more consistent in women with established osteoporosis. In a small series of 37 patients with a history of an osteoporotic fracture of the wrist who were treated with nasal calcitonin 200 IU/day and calcium supplements for 1 year, a

significant increase in lumbar bone mass was reported (+1.4% versus −0.7% compared with a placebo group; $p < 0.01$), together with a slight protective effect at the level of cortical bone.[121] The gain in bone mass was, however, not maintained when the drug was discontinued, although there was no accelerated bone loss. Overgaard et al.[103] carried out a dose-response study (0, 50, 100, or 200 IU/day of nasal calcitonin for 2 years) in 208 women presenting with established osteoporosis, and they suggested that trabecular bone mass at the lumbar spine level increases by about 1% for each 100IU daily dose of calcitonin (0.2–1.7%, $p = 0.008$). Reginster et al.[105] reported that daily administration of nasal calcitonin 50IU prevents postmenopausal bone loss at the lumbar spine (+0.82%; 95% CI −0.26, 1.89), whereas bone mass increases slightly with a dosage of 200 IU/day for 2 years (+2.03%; 95% CI 0.92, 3.15; $p = 0.001$). Other authors have also shown a significant increase in bone mass at the lumbar spine with a similar daily dose[122] (table I).

2.1.2 Antifracture Outcomes

Compared with other anti-osteoporotic therapies, the effect of calcitonin on reduction in fracture risk has not been well examined. To date, no prospective, placebo-controlled study with a sufficient number of patients has demonstrated that long-term parenteral calcitonin administration reduces the risk of osteoporotic fractures.

Nevertheless, Rico et al.[123] performed a retrospective review of 32 osteoporotic women with two or more crush fractures treated with calcitonin at a dosage of 100 IU/day by intramuscular injection, 10 days/month for 2 years. At 24 months, the new vertebral fracture rate per 100 patient-years decreased by 60% (20%, 14%, and 8% at 6, 12, and 24 months, respectively) in the calcitonin group and increased by 35% (31%, 33%, and 42%, at 6, 12, and 24 months, respectively) in the calcium group ($p < 0.025$). The same investigators later conducted a prospective randomized trial in 72 women with a similar degree of osteoporosis receiving salmon calcitonin 100 IU/day by intramuscular injection for 10 days each month versus calcium alone.[106] During 2 years of follow-up, there were five new vertebral fractures in the treated patients compared with 31 in the control group; thus, at 24 months, the calcitonin group showed a 60% reduction in the number of new fractures and the group receiving only calcium had a 45% increase ($p < 0.001$). The incidence of vertebral fractures was 0.07 per patient-year in the group treated with calcitonin and 0.45 per patient-year in the group treated with calcium ($p < 0.001$). Furthermore, the calcitonin regimen led to an increase of 12% in cortical bone mass on metacarpal radiogrammetry.

Hizmetli et al.[124] investigated nasal calcitonin 50 and 100 IU/day in 107 postmenopausal women, and found that both of the calcitonin groups were superior to the placebo group regarding effects on bone mineral density and incidence of fracture.

The effects of nasal calcitonin on the incidence of vertebral fracture was best examined in the PROOF study[65] (table II and table III). This was a prospective 5-year, placebo-controlled, dose-response study of nasal calcitonin (100, 200, or 400IU daily) that included 1255 postmenopausal women who also received elemental calcium 1000mg and vitamin D 400IU daily. A total of 783 women completed 3 years of treatment (37% discontinuation rate) and 511 completed the 5 years (59% discontinuation rate). The increase in lumbar spine bone mineral density and the reduction in bone turnover were modest but significant, however the response was not clearly dose dependent. The RR of developing new vertebral fractures was reduced by 33% at the end of the study in the 200IU dose group (RR = 0.67, 95% CI 0.47–0.97, $p = 0.03$). When all active treatment groups were combined (calcitonin 100, 200 and 400 IU/day), the risk was reduced by 21% (RR = 0.79; 95% CI 0.62–1.00; $p = 0.05$). In the 817 women with one to five prevalent vertebral fractures at enrollment, the risk was reduced by 36% (RR = 0.64, 95% CI 0.43–0.96, $p = 0.03$).

A recent post-hoc stratification analysis reported that women aged ≥75 years taking nasal calcitonin 200IU (n = 58) had a 62% RR reduction for new vertebral fracture compared with those in placebo group (n = 47) [RR = 0.38; 95% CI 0.10–0.84; $p = 0.03$].[125] The 100 and 400IU doses of calcitonin also reduced vertebral fracture risk, but the difference did not reach the classical level of statistical significance. The absence of a significant effect on fracture outcomes in the highest dosage group (400 IU/day) was unexpected, and the reason for these results remains unclear. The rate of adverse events was similar in the four groups except for a significant increase in rhinitis among calcitonin-treated patients. The fact that there was a significant reduction in fracture risk without substantial effects on bone mineral density or on markers of bone turnover is difficult to explain. One answer may be a possible effect of calcitonin on bone quality.[126]

A review based on pooled data from 14 randomized trials (parenteral or nasal calcitonin versus placebo, calcium or no therapy) concluded that calcitonin treatment results in a significant reduction in the rate of vertebral fractures (RR = 0.43, 95% CI 0.38–0.50) and of nonvertebral fractures (RR = 0.34, 95% CI 0.17–0.68).[127]

A recent meta-analysis[128] including 30 randomized, controlled trials (of a least 1 year in duration) in postmenopausal women showed that calcitonin administered by nasal, parenteral, and rectal routes reduced the incidence of vertebral fractures, with a pooled RR of 0.46 (95% CI 0.25–0.87; $p = 0.02$) and an increase in bone density of the lumbar spine of 3.74 (weighted mean differ-

ence [WMD] 2.04–5.43; $p < 0.01$) [table IV]. No significant effect was demonstrated on the nonvertebral fracture rate.

The effects on hip fracture are less consistent. Kanis et al.[130] examined the effects of bone metabolism-altering drugs on the risk of hip fracture among more than 5600 women in a retrospective,

Table I. Characteristics of clinical studies focusing on the changes in bone mineral density or content of the lumbar spine with intranasal salmon calcitonin plus oral calcium versus calcium only

Study	Study population	Study design[a]	No. of patients	Dose regimen[b]	BMD or BMC change[c]
Reginster et al.[114]	Early postmenopausal nonosteoporotic women	nb	30	S 50IU 5/7 × 1y	+1.4 (BMD)
			30	Ca 500mg 5/7 × 1y	−3.2 (BMD)
Overgaard et al.[116]	Early postmenopausal nonosteoporotic women	db, pc	19	S 100 IU/day × 2y	+2.5 (BMC)
			20	Ca 500mg 5/7 × 2y	−5.7 (BMC)
Overgaard et al.[119]	Postmenopausal women with established osteoporosis	db, pc	17	S 200 IU/day × 1y	+1.4 (BMC)
			20	Ca 500mg × 1y	−0.7 (BMC)
Thamsborg et al.[104]	Postmenopausal women with established osteoporosis	db, pc	9	S 50 IU/day × 1y	Unchanged (BMC)
			7	S 100 IU/day × 1y	+3.1 (BMC)
			9	S 200 IU/day × 1y	+7.6 (BMC)
			8	Ca 500mg × 1y	+1.9 (BMC)
Overgaard et al.[103]	Postmenopausal women with established osteoporosis	db, pc	40	S 50 IU/day × 2y	+1.7 (BMC)
			43	S 100 IU/day × 2y	+1.7 (BMC)
			41	S 200 IU/day × 2y	+3.0 (BMC)
			40	Ca 500mg × 2y	+1.0 (BMC)
Gennari et al.[117]	Early postmenopausal nonosteoporotic women	nb, pc	11	S 200IU every other day × 1y	+3.3 (BMC)
			10	Ca 500–1000mg × 1y	−3.5 (BMC)
Reginster et al.[115]	Early postmenopausal nonosteoporotic women	nb	42	S 50IU 5/7 × 5y	+1.1 (BMD)
			45	Ca 500mg 5/7 × 5y	−6.7 (BMD)
Reginster et al.[105]	Early postmenopausal nonosteoporotic women	db, pc	61	S 50 IU/day × 2y	+0.8 (BMD)
			74	S 200 IU/day × 2y	+2.0 (BMD)
			66	Ca 500mg × 2y	−6.3 (BMD)
Lyritis et al.[120]	Early postmenopausal nonosteoporotic women	db, pc	14	S 100 IU/day × 1y	+8.5 (BMC)
			14	Ca 1000mg × 1y	−8.0 (BMC)
Thamsborg et al.[113]	Postmenopausal women with established osteoporosis	db, pc	33	S 200 IU/day × 2y	+2.5 (BMD)
			29	Ca 500mg × 2y	+1.7 (BMD)

a All studies were randomized with parallel groups.

b All patients in the treated groups also received oral calcium 500–1000mg daily.

c Mean percentage change from baseline to the end of the treatment period at lumbar spine level.

BMC = bone mineral content; **BMD** = bone mineral density; **Ca** = oral calcium; **db** = double-blind; **nb** = nonblind; **pc** = placebo-controlled; **S** = intranasal salmon calcitonin; **5/7** = 5 days per week.

Table II. Summary of the main characteristics of the Prevent Recurrence of Osteoporotic Fractures (PROOF) study

Study design	5-year, double-blind, randomized, placebo-controlled, multicenter clinical trial
Investigators	42 centers in the US and five in the UK
Purpose	To determine the long-term efficacy and safety of salmon calcitonin nasal spray in the prevention of vertebral fractures in postmenopausal women with osteoporosis
Subjects	Osteoporotic women at least 1 year postmenopausal and with one to five prevalent thoracic or lumbar vertebral compression fractures
Participants	1255 women were initially enrolled
	783 completed 3 years
	511 completed 5 years
Primary efficacy endpoint	Risk of new vertebral fractures in the salmon calcitonin nasal spray 200IU daily group compared with the placebo group

population-based, case-control study by questionnaire, and reported that the RR was reduced to 0.69 (95% CI 0.51–0.92) among women who had ever received calcitonin. In the PROOF study, participants in the nasal calcitonin 100 IU/day group had a lower incidence of hip fractures (RR = 0.1; 95% CI 0.01–0.90; p = 0.04) and all nonvertebral fractures (RR = 0.64; 95% CI 0.41–0.99; p < 0.05) but those in the 200 IU/day and 400 IU/day groups did not.[65] However, the small number of hip and femoral fractures precluded a meaningful statistical analysis. The meta-analysis by Cranney et al.[128] assessed three trials reporting nonvertebral fractures. It showed a nonsignificant RR of 0.52 (95% CI 0.22–1.23; p = 0.14).

Thus, the effect of calcitonin on hip and nonvertebral fractures remains uncertain and needs to be further investigated in prospective trials.

2.1.3 Analgesic Properties

Acute bone pain is a disabling symptom in osteoporotic patients. There is mounting evidence that calcitonin can reduce bone pain in osteoporotic vertebral fractures,[131,132] and analgesic effects are documented in other disorders such as reflex sympathetic dystrophy syndrome and bone metastases.[133] To date, several controlled studies have demonstrated the analgesic activity of calcitonin given by nasal spray, intramuscular injection or by suppositories in patients with vertebral crush fractures and bone pain.[93,134-137]

A placebo-controlled clinical trial evaluating the analgesic efficacy of calcitonin suppositories (200IU) included 40 patients (8 men and 32 postmenopausal women) who had recently (within the last 5 days) experienced a nontraumatic osteoporotic vertebral fracture and received either one calcitonin or placebo suppository once daily for 28 days.[93] All calcitonin-treated patients experienced an overall statistically significant (all p values < 0.001) decrease in spinal pain, as assessed by the Huskinsson's visual analog scale and a pain-meter device. Other trials have shown that salmon calcitonin at a daily dose of 100IU subcutaneously or 200IU intranasally dramatically reduces back pain after a recent osteoporotic vertebral fracture, and promotes the early mobility of patients.[131]

The mechanism for the analgesic effect of calcitonin is yet to be clarified. In humans, similarities between calcitonin and morphine-induced analgesia, and reports of calcitonin-induced elevation of plasma β-endorphin concentrations, suggest the possible involvement of the endogenous opiate system in mediating the analgesic action of calcitonin.[138-140] However, the demonstration of calcitonin binding sites in areas of the brain involved in pain

Table III. Incidence and relative risk of fracture in the Prevent Recurrence of Osteoporotic Fractures (PROOF) study

Intent-to-treat analysis	Placebo	Calcitonin[a]		
	(n = 311)[a]	100 IU/day (n = 316)	200 IU/day (n = 316)	400 IU/day (n = 312)
New vertebral fracture				
Incidence (no. of patients)	70	59	51	61
Relative risk vs placebo (95% CI)		0.85 (0.60, 1.21)	0.67 (0.47, 0.97)	0.84 (0.59, 1.18)
New nonvertebral fracture				
Incidence (no. of patients)	48	32	46	41
Relative risk vs placebo (95% CI)		0.64 (0.41, 0.99)	0.88 (0.59, 1.32)	0.81 (0.53, 1.23)

a All participants received elemental calcium 1000mg and vitamin D 400IU daily.

Table IV. Comparison of effects of different pharmacological therapies for postmenopausal osteoporosis according to a recent meta-analysis[129]

	No. of RCTs (no. of patients)	Outcome (95% CI)	p-Value
Alendronate (2–3 years' therapy; 5–40 mg/day)			
% change in BMD (WMD)	8 (8219)	5.81 (5.33, 6.29)	<0.01
RR of vertebral fracture	8 (9360)	0.52 (0.43, 0.65)	<0.01
RR of nonvertebral fracture	8 (8603)	0.87 (0.73, 1.02)	0.09
Risedronate (1.5–3 years' therapy; 5 mg/day)			
% change in BMD (WMD)	6 (2138)	4.54 (4.12, 4.97)	<0.01
RR of vertebral fracture	5 (2604)	0.64 (0.54, 0.77)	0.01
RR of nonvertebral fracture	7 (12 958)	0.73 (0.61, 0.87)	<0.01
Calcitonin (1–5 years' therapy; 100–400 IU/day)			
% change in BMD (WMD)	24 (2260)	3.74 (2.04, 5.43)	<0.01
RR of vertebral fracture	1 (1108)[a]	0.79 (0.62, 1.00)	0.05
RR of nonvertebral fracture	1 (1245)[a]	0.80 (0.59, 1.09)	0.16
Raloxifene (2–3 years' therapy; 60 mg/day)			
% change in BMD (WMD)	4 (6053)	2.51 (2.21, 2.82)	<0.01
RR of vertebral fracture	1 (6828)	0.60 (0.50, 0.70)	0.01
RR of nonvertebral fracture	2 (6961)	0.91 (0.79, 1.06)	0.24
HRT (2 years' therapy)			
% change in BMD (WMD)	21 (1658)	6.76 (5.63, 7.89)	<0.01
RR of vertebral fracture	5 (3117)	0.66 (0.41, 1.07)	0.12
RR of nonvertebral fracture	6 (3986)	0.87 (0.71, 1.08)	0.10

a In their analysis of fracture outcomes after treatment with calcitonin Cranney et al. chose to present the results of the largest study (PROOF), rather than the pooled results including three small trials with very large RR reductions, to prevent possible publication bias.

BMD = bone mineral density; **HRT** = hormone replacement therapy; **RCTs** = randomized controlled trials; **RR** = relative risk; **WMD** = weighted mean difference calculated using a random-effect model.

perception and a series of animal studies have raised the possibility that calcitonin may directly modulate nociception in the central nervous system. In support of this hypothesis are some observations of an analgesic effect obtained by direct epidural or subarachnoidal injection of calcitonin in humans.[131] Another explanation is that changes in descending serotonergic modification on the sensory transmission mediated by C afferents contribute to the analgesic effects of calcitonin on pain in osteoporotic patients.[131,132]

The finding that injectable or intranasally administered salmon calcitonin effectively controls severe pain in osteoporotic patients with a recent vertebral fracture, allowing them earlier mobility and reducing the considerable bone loss that may occur during prolonged bed rest, makes this drug an attractive therapeutic proposition for patients with fracture.[132]

2.2 Male Osteoporosis

Osteoporosis is a disease predominantly affecting postmenopausal women, but conditions associated with low bone mass and osteoporotic fractures are not uncommon in men.[141] Up to 20% of symptomatic vertebral fractures and 30% of hip fractures can occur in men, causing substantial morbidity, increased mortality, and health service expenditure.[142]

Unlike women, men frequently have an underlying secondary cause of osteoporosis and some authors have found such a cause in >50% of men with osteoporosis.[143,144] There is a subgroup of patients (40–50% of men in most series) without associated risk factors who are believed to have primary osteoporosis.[145,146] Few clinical trials have been performed solely in male populations with idiopathic osteoporosis to examine the effects of treatment on bone density and fracture incidence, and therefore there is no well established treatment for this type of osteoporosis in men.

Little information is available on the efficacy of calcitonin in men with osteoporosis. In a small, randomized study of men with idiopathic osteoporosis, parenteral calcitonin treatment for 2 years produced a decrease in vertebral fracture incidence compared with calcium or multivitamin treatment.[147] More recently, Trovas et al.[148] conducted a 12-month randomized, double-blind, placebo-

controlled trial of the effects of intranasal salmon calcitonin on bone mineral density and biochemical markers of bone turnover. Twenty-eight men with idiopathic osteoporosis aged 27–74 years (mean 52.4 years) were randomized to receive either nasal salmon calcitonin (200IU) or a nasal placebo daily for a period of 1 year. All men also received a daily supplement of calcium 0.5g. Those men who received calcitonin treatment had a mean increase in bone mineral density of 7.1 ± 1.7% at the lumbar spine, and those who received placebo had an increase of 2.4 ± 1.5% ($p > 0.05$) compared with baseline. The increase in lumbar bone mineral density in the calcitonin group was significantly greater than that in the placebo group ($p < 0.05$). There were no significant changes in the femoral neck, trochanter, or Ward's triangle relative to both baseline and placebo after 12 months. The authors also reported that treatment with nasal calcitonin resulted in a significantly pronounced suppression of bone resorption markers and to a lesser extent of bone formation markers, whereas the placebo did not. Therapy was well tolerated and there were neither treatment-related adverse events nor obvious signs of an escape phenomenon.

This study suggests that nasal salmon calcitonin appears to be a promising therapeutic approach for the treatment of men with idiopathic osteoporosis; however, long-term, well designed trials are necessary to confirm these results and to evaluate the osteoporotic fractures rate as endpoints in men.

2.3 Corticosteroid-Induced Osteoporosis

Corticosteroid-induced osteoporosis is a cause of morbidity in patients with chronic obstructive lung disease, asthma, and many rheumatologic disorders.[149,150] Corticosteroid treatment causes bone loss by a variety of complex mechanisms.[151] Corticosteroids increase bone resorption by stimulating osteoclastogenesis via increased expression of the RANK ligand and decreased expression of the decoy receptor, osteoprotegerin, although the most significant effect is an inhibition of bone formation. This results from a decrease in the number of osteoblasts and their function. The decrease in cell numbers is secondary to a decrease in osteoblastic cell replication and differentiation, and an increase in the apoptosis of mature osteoblasts.[152] Clinically, patients receiving corticosteroid treatment develop bone loss in the first few months of exposure, and modest doses of corticosteroids increase the risk of fractures of the spine and hip.[153,154]

Several approaches have been developed to prevent corticosteroid-induced bone loss. Calcitonin, given via subcutaneous injection or intranasal inhalation, has not been consistently shown to prevent bone loss compared with calcium and vitamin D supplementation alone, in patients starting corticosteroid therapy.[155-157] In a group of asthmatic patients, nasal calcitonin increased lumbar spine bone mineral density in the first year of treatment by 2.7% and maintained the gain for a second year compared with a decrease in the placebo group over the 2 years.[158] In corticosteroid-treated rheumatoid arthritis patients, nasal calcitonin prevented femoral neck but not lumbar spine bone loss compared with calcium alone.[159] In other studies, however, calcitonin did increase bone mineral density at the lumbar spine but not at the femoral neck in patients who had undergone prolonged corticosteroid treatment.[160,161]

To review the efficacy of calcitonin (subcutaneous or nasal) for the treatment and prevention of corticosteroid-induced osteoporosis, Cranney et al.[162] conducted a search and evaluation of the randomized controlled trials published up to May 1998. Nine trials met the authors predetermined inclusion criteria, including 221 patients randomized to calcitonin and 220 to placebo. The analysis shows that calcitonin was more effective than placebo at preserving bone mass at the lumbar spine after 6 and 12 months of therapy with a WMD of 2.8% (95% CI 1.4–4.3). At 24 months, lumbar spine bone mineral density was not statistically different between groups: WMD 4.5% (95% CI –0.6–9.5). Bone density at the distal radius was also higher with calcitonin after 6 months of therapy, but bone density at the femoral neck was not different between the placebo- and calcitonin-treated groups. The RR of fracture was not significantly different between calcitonin and placebo with a RR of 0.71 (95% CI 0.26–1.89) for vertebral and 0.52 (95% CI 0.14–1.96) for nonvertebral fractures. There was no consistent effect of different doses (50–100IU compared with 200–400IU). Reviewers concluded that calcitonin appears to preserve bone mass in the first year of corticosteroid therapy at the lumbar spine but not at the femoral neck, but efficacy of calcitonin for fracture prevention in corticosteroid-induced osteoporosis remains to be established.

Thus, the role of calcitonin in corticosteroid-induced osteoporosis remains controversial, and it can only be considered a second-line agent for the treatment of patients with low bone mineral density who are receiving long-term corticosteroid therapy, especially those who have contraindications to or cannot tolerate other more effective therapies. There is no evidence to recommend calcitonin use for the prevention of bone loss in patients beginning corticosteroid treatment.[163-166]

3. New Approaches

A relevant limitation to the clinical usage of calcitonin is its bioavailability. Several new approaches are currently being investigated to enhance calcitonin access to the osteoclast.

Novel allosteric activators of the calcitonin receptor might make the receptor more sensitive to circulating calcitonin.[167-170] Preliminary data have shown that such lead compounds can be synthesized and used *in vivo*. Furthermore, drugs targeting a specific transmembrane domain may abolish certain receptor functions while sparing others. Drugs targeting one isoform over another could reduce adverse effects or, preferentially, target forms of osteoporosis that have high or low bone turnover rates. Theoretically, the possibility could exist of modulating the release of endogenous calcitonin itself by a drug that activates the C-cell Ca^{2+}-sensing receptor. This strategy has been achieved for the parathyroid cell Ca^{2+}-sensing receptor, another G-protein-coupled, seven-pass receptor, wherein an oral calcimimetic (or Ca^{2+} receptor agonist), cinacalcet, has been evaluated for use in hyperparathyroidism.[171-174]

As outlined in section 1.5, oral calcitonin formulations are under development, and the pulmonary and transdermal routes are also under consideration. These approaches could improve the bioavailability of calcitonin.

Finally, given the fact that low-dose teriparatide (recombinant human parathyroid hormone 1–34) reduces fracture risk through its dramatic effects on bone formation,[175,176] the possibility of combining this agent with calcitonin makes solid therapeutic sense. During the past decade, Hodsman et al.[177-180] have conducted several studies evaluating this hypothesis, but their results show that sequential calcitonin therapy does not appear to act synergistically with teriparatide in cyclical therapeutic protocols.

In one study,[180] the authors included 30 women with osteoporosis, who completed a 2-year protocol comprising 28-day courses of teriparatide (800 U/day) given by daily subcutaneous injections immediately followed by either sequential parenteral calcitonin or placebo for 42 days. At the end of the 2 years, the lumbar spine bone mineral density increased 10.2% in the teriparatide group and 7.9% in the teriparatide + calcitonin group ($p < 0.001$ for both groups versus baseline). Although the final 2-year lumbar spine bone mineral density was not significantly different between the two treatment groups, those patients receiving sequential calcitonin injections gained bone mass at a consistently slower rate. Changes in bone mineral density at the femoral neck were not significant. Thus, the authors concluded that short cycles of daily teriparatide injections result in significant increases in lumbar spine bone mineral density, without significant changes in cortical bone mass at the femoral neck; however, there was no evidence that sequential antiresorptive therapy with calcitonin could be of any benefit over that conferred by cyclical teriparatide alone.

Moreover, DeLuca and Dani[181] reported similar outcomes in a study evaluating the effect of teriparatide alone or in combination with salmon calcitonin in ovariectomized rats. Clinical research during the next years could focus on sequential therapy; using teriparatide first, followed by an antiresorptive calcitonin.

4. Conclusions

Calcitonin has been used for many years in the treatment of osteoporosis; however, the development of new pharmacological agents with proven efficacy such as bisphosphonates, raloxifene and teriparatide raises the question of whether a role remains for this naturally occurring peptide.

Nasal calcitonin stabilizes and in some cases produces short-term increases in bone mineral density at the lumbar spine level. Parenteral administration is also effective, but long-term use in the clinical setting is precluded by its more frequent adverse effects. As evaluated in the PROOF study and a recent meta-analysis, calcitonin appears to reduce vertebral fracture risk, however benefits on hip and other non-vertebral fractures are less clear. The decrease in fracture risk is more evident in the population with established osteoporosis. An interesting effect of calcitonin is its analgesic activity on bone pain in the vertebral crush fracture syndrome. Calcitonin has no serious adverse effects or toxicity, and the intranasal formulation is particularly well tolerated. A recent study suggests that nasal calcitonin appears to be a promising therapeutic approach for the treatment of men with idiopathic osteoporosis, although long-term trials are necessary to confirm these results and to evaluate fracture as an endpoint in men. At the present time, the role of calcitonin in corticosteroid-induced osteoporosis remains controversial.

New approaches to calcitonin therapy offer an interesting perspective, such as the development of novel allosteric activators of the calcitonin receptor, oral formulations, and sequential therapy with anabolic agents such as teriparatide.

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