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**Perspective Article**

# Osteoporosis management in day-to-day practice. The role of calcitonin

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Osteoporosis is a silent condition characterized by reduced bone mass, abnormal internal bone architecture and an increased risk of fragility fracture. The commonest fractures involve the vertebral bodies and the most serious the femur (hip). Acute pain is also a common feature, and is frequently the initial reason why the patient consults a physician.

Osteoporosis is particularly prevalent in postmenopausal women but also occurs in men and in the elderly in general. Worldwide there are over 200 million sufferers, more than 75 million of whom sustain a femoral neck and/or vertebral crush fracture. It has been calculated that at least one osteoporosis-related fracture occurs somewhere in the world every 5 seconds, making osteoporosis an extremely costly condition both financially (in excess of US$75-100 billion per annum) and in human and social terms. A 50-year-old white woman has a greater-than-50% chance of suffering at least one major osteoporotic fracture, and the risk of institutionalization is substantial, with about 20-30% of previously non-institutionalized patients having been admitted to a nursing home by one year post-fracture. In addition, in the first year following hip fracture, mortality is 12-20% higher than in the population as a whole. Quality of life is also negatively affected, as accumulated functional deficits, deformity and pain lead to anxiety, depression and social dysfunction. And with life expectancy increasing at the rate of three months every year, the magnitude of the problem is clearly set to grow exponentially.

The causes of osteoporosis are multiple, three of the commonest being a deficiency of sex hormone secretion (primary osteoporosis), the adverse effect of drugs such as corticosteroids (secondary osteoporosis), and adverse environmental factors. Its pathophysiology is characterized primarily by impaired bone turnover, with more bone being resorbed by osteoclasts and less bone formed by osteoblasts. This leads to a loss of bone mass, resulting in increased fragility and rendering the aging patient's bone ever more liable to microfractures (microcracks) and even major fracture.

Diagnosis is relatively straightforward if there is a history of osteoporotic fracture. If not, other aids are becoming increasingly reliable, notably dual-photon absorptiometry (DEXA), currently the most commonly used technique and ultrasound, although this needs further clinical validation. Biochemical markers may also have some value as diagnostic aids and new techniques, such as peripheral quantitative computed tomography (pQCT) and magnetic resonance imaging (MRI), are being developed in an effort to learn more about bone quality.

Management comprises both prevention and treatment and uses many different approaches, including both pharmacological and non-pharmacological methods. Foremost among the latter are moderate exercise programs, dietary measures such as ensuring an adequate calcium intake, particularly in institutionalized elderly people, tobacco abstinence, and environmental measures to reduce the risk of falls, while a whole range of pharmacological treatments have been developed in the last few years. These include calcium and/or vitamin D, estrogen or estrogen/progestogen combinations (HRT), selective estrogen-receptor modulators (SERMs), bisphosphonates, and calcitonin, the principal property of all of which is anti-bone resorption activity. Bone formation stimulants are also beginning to emerge; some, like PTH, are already in an advanced stage of development, with an injectable form nearing market introduction for strictly limited uses.

Considerations of safety and patient compliance are particularly important in the choice of drug therapy. As we enter the 21st century with its promise of even greater longevity for more and more people, osteoporosis management calls for an integrated, three-dimensional strategy involving efficacy, safety and compliance, leading to effectiveness.

Calcium and vitamin D (0.5-1g and 400-800 IU) are mainly given as adjuncts to other treatments, but HRT with estrogen, in combination with progestogen where indicated, is a

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mainstay treatment for prevention of bone loss and fractures in postmenopausal women, as well as reducing coronary heart disease and stroke. In non-hysterectomized women, progestogen is added for 12-14 days each month to regularize uterine bleeding and protect against endometrial hyperplasia and carcinoma. There are limits to the use of HRT in osteoporosis, however; either women do not want to take it (fear of breast cancer) or it is contraindicated (risk of cancer during long-term use), or it has serious unwanted effects (e.g., asthma, migraine, phlebitis, breast tenderness, etc.), or else compliance is poor (average compliance time =9-12 months), leading to rapid bone loss when the treatment is stopped.

SERMs are a new class of drug that appear promising but, like all the other antiresorptive agents, have safety and tolerability limitations. Raloxifen, for example, has shown risk reduction for vertebral (but not hip) fracture at the recommended dosage of 60 mg/day but can cause hot flushes and, though rarely, venous thromboembolic events.

Bisphosphonates are potent inhibitors of osteoclastic resorption, reducing bone turnover and thereby maintaining bone mass. They may also induce a long-term gain in bone mass and a reduction in fracture rate. Here, too, however, there are disadvantages; bisphosphonates are poorly absorbed by the oral route, making extremely complex dosing regimens necessary (e.g., "One tablet every morning with a glass of water with low calcium and magnesium content half an hour before breakfast followed by half an hour in the upright position"). Such dosing instructions inevitably raise concerns about compliance and about actual therapeutic effect if not properly followed. In addition, serious adverse events have been reported at the upper GI tract level. Long-term safety is also an open issue, especially as there is no antidote, since bisphosphonates are deposited in bone, where they have an extremely long half-life.

Another potent weapon in the therapeutic war against osteoporosis is calcitonin, particularly the salmon variety of the hormone.

Calcitonin is an endogenous hormone that has been identified in different forms in more than 15 species of mammals, birds, amphibians and fish, and even in unicellular organisms such as *Escherichia coli*. The only forms currently in therapeutic use, however, are the fish varieties (native salmon, native eel and an aminosuberic derivative of the latter) and two mammalian calcitonins, porcine and human. Extracted porcine calcitonin was the first to be used therapeutically in man, but the synthetic analogs of the fish calcitonins are now generally acknowledged to be more potent than the mammalian types in their pharmacological effects, with salmon calcitonin one of the most active of all the calcitonins (20-40 times more potent than human calcitonin).

The primary pharmacological effect of salmon calcitonin is its activity at specific osteoclast receptors, resulting in diminished osteoclast activity at extremely low concentrations (inhibitory effect on bone resorption via reduction of osteoclast attachment and release of enzymes, H+ etc.) and leading to the normalization of bone resorption and the formation and maintenance of functional bone. It also promotes the mineralization of bone, as acute studies in rats, rabbits and young pigs have shown, as well as exerting a regulatory effect on renal electrolyte excretion. The overall result is that bone mass is maintained or increased, with no adverse effect on cortical bone. Moreover, the bone retains – or regains – the biomechanical properties necessary for proper function, with slight enhancement in some cases.

Bone strength (i.e. resistance to fracture) is determined by bone quantity and bone quality together. Bone quantity is currently assessed by densitometry, while several techniques – mostly *in vitro* – are available for the evaluation of bone quality. Its mechanical properties, for example, can be studied at two levels, at the material level, by performing standardized tests on uniform specimens, and at the structural level, by examining the mechanical behaviour of a given bone as an anatomical unit.

If a bone is constrained so that it cannot move and is then subjected to a force, deformation will occur, resulting in the generation of internal resistance to the applied force. This internal resistance, known as 'stress', is equal in magnitude but opposite in direction to the applied force and is distributed over the whole cross-sectional area of the bone. The extent of the resultant deformation is called 'strain'. Such tests, performed under controlled laboratory conditions, enable a stress-strain curve to be plotted from which properties such as stiffness and strength can be calculated. If the ultimate strength of a bone is exceeded, fracture will result.

Another important parameter of bone quality is its microarchitecture, which can be studied by means of histomorphometry and/or microcomputer tomography (μCT) on biopsies to assess variables such as connectivity, trabecular perforations, erosion depth and activation frequency, and/or by Magnetic Resonance Imaging (MRI).

Experimentally, calcitonin has been shown to preserve/improve bone strength in several animal studies. One of the most important of these demonstrated a dose-dependent increase in the ultimate strength of the femoral neck in ovariectomized sheep following administration of calcitonin[1].

Clinically, salmon calcitonin is effective in various disorders of bone metabolism, most notably in established postmenopausal osteoporosis (FDA-approved use). Moreover, the higher the rate of bone turnover, the greater the response to salmon calcitonin, enabling the dose to be adjusted accordingly to 50 or 100 IU with the injectable form and, in most cases, 200 IU with the nasal spray, daily or every other day. In postmenopausal osteoporotic women, several studies[2-6] have shown that calcitonin significantly reduces fracture rate, even in the absence of a substantial increase in bone mass. This apparent non-correlation between bone mass and reduced fracture rate is currently under investigation (QUEST study).

It seems likely that the reduction brought about by calcitonin in the increased remodeling activity that is characteris-

tic of osteoporosis leads to improved bone quality, and hence increased bone strength. And bone strength reflects resistance to fracture, which is the primary end point in the management of osteoporosis.

Salmon calcitonin has also been shown to possess analgesic properties in a number of animal models, including electrical stimulation of the dental pulp in rabbits and cats, acetic acid-induced inflammation in mice, posterior rhizotomy in rats, the hot-plate test in rats, and Freund's adjuvant-induced inflammation in rats. A number of possible mechanisms have been postulated for this effect, which is not antagonized by naloxone and is additive to that of morphine. They include both central (effect on specific central calcitonin receptors, modulation of calcium flow, interaction with GABAergic, serotoninergic and catecholaminergic systems) and peripheral (increase in beta-endorphin release, modulation of calcium flow, inhibition of the synthesis of prostaglandins and other inflammation mediators) mechanisms, although primary involvement of a central site of action at specific calcitonin receptors seems increasingly likely.

Most of the evidence for the analgesic effect of salmon calcitonin has been reported in published studies in cancer-related bone pain, Paget's disease and osteoporosis; in one study, in terminal cancer patients with severe bone pain, its analgesic effect as rated using a visual-analog scale was reported to be as potent as that of morphine in some cases.

There are no major safety or compliance concerns with salmon calcitonin. Although it has a relatively long duration of effect, its elimination half-life is short and, most importantly, its residence time in bone is limited. No specific antidote is necessary and there are no known food or relevant drug interactions and no GI or renal issues that impose restrictions on its use.

The injectable form of salmon calcitonin was first introduced in 1974 and the intranasal form in 1987. Both dosage forms are already available in over 70 countries, including the USA. The injectable form (a solution presented in ampoules or multidose vials), which is now used mainly in the management of acute situations involving metabolic bone diseases, has certain disadvantages, such as the "discomfort and inconvenience" normally associated with injections, some hypersensitivity reactions, and unpleasant side effects in 20% of osteoporotic patients.

The principal advantages of the nasal spray are that it is more suitable for long-term use, well tolerated locally and systemically (with almost no adverse effect on nasal function), and flexible from the point of view of dosage. Local tolerance has so far been good with the exception of cases of rhinitis, confirming the results of laboratory studies in guinea pigs and rabbits, which showed that the solution has practically no effect on the nasal mucosa, especially on the important parameter of nasal function, ciliary beat frequency.

The systemic tolerance of the intranasal form of salmon calcitonin is also notably superior to that of the injectable form, particularly with regard to the drug's most troublesome side effects, nausea and flushing. With intranasal treatment these adverse reactions are almost entirely absent, and the overall incidence of severe reactions – and thus of treatment withdrawal – is very much lower. Thus, it can safely be asserted that the nasal spray is a more acceptable form of calcitonin treatment as far as the patient is concerned because of its much lower "discomfort rating" and lower incidence of troublesome side effects compared with the injectable form. These features are also important from the physician's point of view since they tend to enhance patient compliance and thus the effectiveness of the treatment.

These claims are supported by extensive clinical trial and post-marketing surveillance data. With exposure now totalling more than 2,300,000 patients-years, there have been very few reports of adverse reactions and very few cases of hypersensitivity. Where side effects have occurred, they have been mostly minor and transient and related to the pharmacological properties of calcitonin.

Thus, salmon calcitonin, particularly the intranasal form, is gaining increasing recognition as a practical, safe, effective, well-tolerated (both locally and systemically) and high-compliance drug in the management of metabolic bone disorders, especially in cases where the disease is neither manifest nor troublesome to the patient, as in early osteoporosis (ease of administration, an uncomplicated dosing regimen, no limitations on use, no relevant drug interactions, no adverse GI effects).

Pursuing the same objective of improved patient convenience that had led to the development of the nasal spray, it was decided some 15 years ago to try to devise a technology that would enable calcitonin – and other peptides – to be given orally. This exciting project has now resulted in a very promising oral form of salmon calcitonin (SCT), which is currently under evaluation. The basic principle of the technology involves the use of a specific carrier that transports SCT across the GI tract wall.

A Proof of Concept study (ascending single doses) carried out in 40 healthy volunteers confirmed the relevant SCT absorption levels found in animals.

Cmax levels were also relevant, showed acceptable variability, and were similar to those obtained after s.c. injection of 50 IU (Cmax ~ 100 pg/ml). In addition, the safety and tolerability data did not reveal any impediment to continued development of this oral form of SCT.

Work is now ongoing to determine the optimal carrier: SCT ratio, minimum effective active ingredient content and ideal pharmacokinetic profile, and to assess pharmacodynamics, tolerability and clinical response.

An oral form of calcitonin will be a useful new tool in osteoporosis management, promising high compliance and safety. Its principal role will be to complement the highly successful nasal spray and, potentially, to facilitate the extension of the use of SCT to other indications. The technology involved might also prove to be the answer to problems of oral delivery for other peptides and other poorly absorbed drugs with a wide safety margin.

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