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Perspective Article

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Calcitonin effects on cartilage and fracture healing

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Abstract

The literature about the effects of systemically administered calcitonin on fracture healing and in the prevention of disuse osteoporosis after fracture are reviewed in this study. Fracture healing is a biological process of great importance for the survival of the injured animal. Endochondral ossification is augmented in the fracture site followed by fast remodeling of the produced woven bone. There is strong evidence of the direct effects of calcitonin on cartilage proliferation as well as the vascularization of the callus. Calcitonin is found to promote the cartilaginous phase of fracture healing. On the other hand, the innervation of callus reveals an extensive distribution of sensory fibers containing a calcitonin gene-related peptide, a neuropeptide with potent vasodilatory actions. From several experimental studies, salmon calcitonin administration has been found to have a beneficial effect on fracture healing. Studies in humans also concur that calcitonin may speed up the time of fracture repair and facilitate early mobilization of the injured limb. Finally, calcitonin prevents post-fracture bone loss due to increased post-injury remodeling and lowers hydroxyproline and calcium excretion of patients who underwent internal fixation of fracture on the hip.

Keywords: Fracture Healing, Osteoarthritis, Internal Fixation of Fractures, Regional Osteoporosis, Calcitonin

The effects of calcitonin on various types of cartilage

Cartilage plays a vital role in musculoskeletal function. Growth plate and secondary ossification centers are the main loci of skeletal growth, and this process follows the mechanism of endochondral ossification[1]. The produced intermediate cartilaginous model helps osteogenesis, forming the necessary space and secreting paracrine substances. Another type of cartilage that is also of great importance for the function of the musculoskeletal system is the articular cartilage. This kind of cartilage gives joints the necessary viscoelasticity for the attenuation of vibrations during motion and muscular function. Finally, another vital function of cartilage is callus formation. Fracture healing is accomplished through the process of endochondral ossification, except in certain cases (i.e. stable internal fixation of fractures).

The importance of calciotropic hormones in the general function of cartilaginous tissue and especially in fracture healing has not been extensively studied until now[2-7].

The effect of calcitonin on the calcification of the growth plate has been shown *in vitro* in primary cultures of chicken growth plate chondrocytes[8]. Calcitonin's action upon the growth plate[9-12] can also be studied experimentally in growing rats because the growth plate has a strong metabolic function during growth. In a rat model of growing skeleton, 40 male rats aged 5 days were treated with 0.2 IU salmon calcitonin administered subcutaneously on a daily basis, while another 40 male rats of the same age received a placebo[13]. The growth plate and the metaphysis of the proximal tibia were examined histologically and histomorphometrically 7, 14, 21 and 28 days from baseline. Specifically, growth plate thickness, the cell number of the columns of the reproducing zone, the animal's weight and length of the right tibia were measured. An acceleration of skeletal growth was found in animals receiving calcitonin and this was noted by the increased thickness of the growth plate, the increased cell number of the growing cartilage and the increase in tibial length (Fig. 1). These results are in accordance with other reports[9,13,14].

In vitro studies in chondrocyte cultures using low concentrations of calcitonin (0.5%) as thyroid extract showed a more than twofold increase of cell proliferation and considerable increase of glycosaminoglycan production[14]. Similar results were found in the formation of the components of bone matrix, such as proteoglycans and type II collagen after treatment with calcitonin[15].

The effect of calcitonin on the produced bone in the

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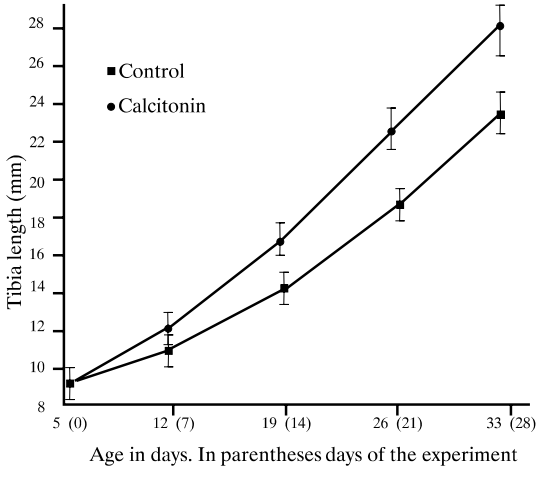

Figure 1. Changes in tibial length (mm) during the study. Calcitonin group shows increased skeletal growth in comparison with the placebo group. (Reproduced from GP Lyritis, 1983[3]).

metaphyseal area facilitates the development of good quality bone in the diaphysis, whereas cortical bone has a qualitatively better appearance than that observed in animals not treated with calcitonin[17].

The effects of calcitonin on articular cartilage

Considering the beneficial effect of calcitonin on the growth plate and fracture healing, it could be of great interest if we could also find some beneficial effect of that hormone on articular cartilage, especially in osteoarthritis. The relative importance of cartilage and bone changes in the initiation and progression of osteoarthritis is still being debated.

In an experimental study with rabbits which underwent cartilage destruction by different means, it has been shown that calcitonin has a protective action on cartilage which is greater than the action of anti-inflammatory drugs[18]. The state of hyper-metabolism, that develops in unstable joints, involves bone, synovium and articular cartilage. The increased bone turnover is likely to contribute to cartilage breakdown. In an experimental knee osteoarthritis model involving dogs, an early and sustained rise in urinary and serum bone resorption markers was observed. Calcitonin markedly reduced the levels of these markers and the severity of osteoarthritic lesions[19]. The longer the duration of calcitonin therapy, the lower the score of osteoarthritic lesions (Fig. 2). In a rabbit model of experimental osteoarthritis, a group of animals treated with injectable calcitonin showed a regeneration of the surface of articular cartilage, an increase of the layers of the hyaline zone and a decrease of the osteophyte formation[20].

In an *in vitro* culture of chondrocytes from human osteoarthritic hips and knees, calcitonin appears to decrease collagenolytic activity and markedly stimulate attachment of chondrocytes on fibronectin[21].

The effects of calcitonin in callus innervation and vascularization

Callus vascularization plays an important role in its maturation because it contributes to the gradual replacement of cartilaginous callus by bone tissue. Paracrine substances (growth factors), such as prostaglandins, IGFs and TGF-β, promote angiogenesis. Calcitonin gene-related peptide (CGRP) has been considered as the causative neuropeptide for callus angiogenesis[22]. Bone neuropeptides can act as direct regulators of osteoblastic function[23]. This action in fracture healing is promoted by the indirect positive response of vascular endothelium cells, monocytes and histiocytes[23].

Recent experimental and clinical studies implicate bone nerves in different bone functions such as bone remodeling, fracture healing and pseudarthrosis[23,24]. It has been reported that intact innervation is essential for normal fracture healing because nerve injury induces a large, but mechanically insufficient, fracture callus[25]. An experimental study in rats with tibial fracture after sciatic nerve section showed an extensive concentration of CGRP in sensory nerve fibers of callus[23]. It is noticeable that CGRP has a strong vasodilative

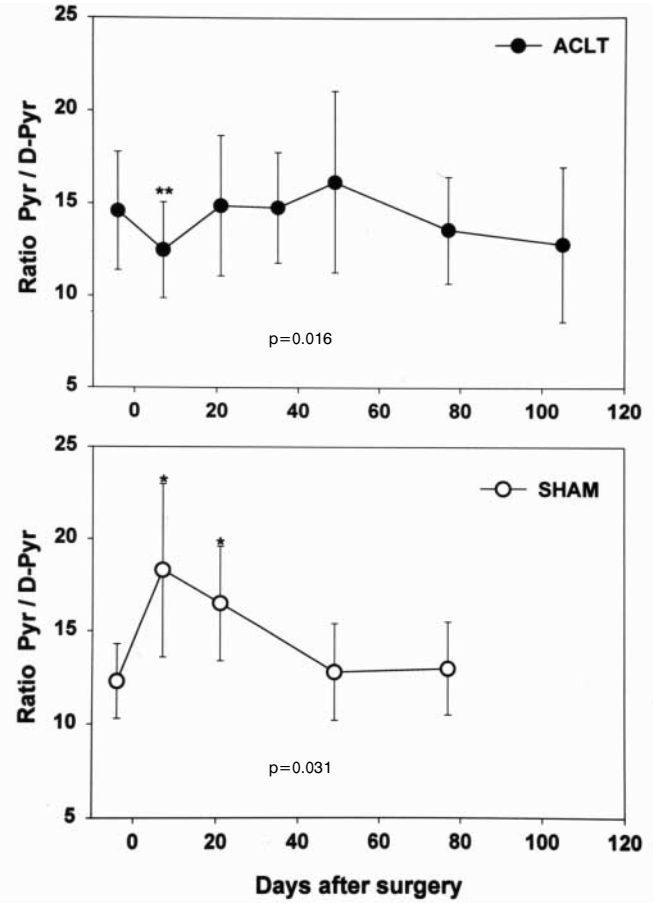

Figure 2. Changes in the molar ratio of pyridoline (Pyr) / deoxypyridoline (D-Pyr) at different times after anterior cruciate ligament transection (ACLT) (upper panel) or SHAM-operation (lower panel) (Manicourt et al. 1999, with permission).

action. This way, the huge callus observed after sciatic nerve section can be explained[24]. Calcitonin, and such other calciotropic hormones (PTH, 1,25-$(OH)_2$-D_3), are supposed to contribute to the production of other promotive substances of bone matrix, like neutral proteases[26].

Experimental data for the effects of calcitonin on fracture healing

There are numerous experimental studies in the literature investigating the action of calcitonin on fracture healing[27-43]. All these studies have been done in rats or rabbits where a fracture of the peripheral skeleton was performed. The dose administered corresponds to 2-5 IU of salmon calcitonin depending on the type, age and weight of the animal. The parameters examined are the histological study of callus, calcium content, radioactive isotope retention, bone enzyme and biochemical indices of callus, as well as of serum and urine and finally, the mechanical strength of the callus.

Of the above studies, 16 examine the effect of calcitonin upon secondary (osteocartilaginous) callus formation. In 5 of these studies it was not possible to detect any beneficial effect of calcitonin on fracture healing between the animals[29,32,35,39,43]. In 2 other studies[38,39], calcitonin was found to have an adverse effect by way of decreased collagen formation and mineralization as well as decreased callus strength.

However, in the other 9 studies[27,28,30,31,34,35,36,37,41] a positive effect on fracture healing was found, which is shown from the histologic appearance of callus, biochemical and immunohistochemical findings and radiological appearance. The conclusion in the majority of these studies was that calcitonin stimulates endochondral ossification during fracture healing, causing an increase in cartilaginous callus and faster maturation. The differences found[29,32,35,39] may be caused by inadequate[29,32] or very high[35,39] doses of calcitonin, resulting in secondary hyperparathyroidism due to hypocalcaemia.

In cases of primary fracture healing[34,42] without the process of endochondral ossification, calcitonin has no effect, although its administration inhibits regional osteoporosis under the materials of fixation[42].

The effects of calcitonin on fracture healing in humans

The action of calcitonin on fracture healing in humans has not been extensively studied. In some clinical studies[44-46], it has been established that there is a clinical and radiological improvement in patients with recent fractures of the peripheral skeleton[45], an acceleration in the formation of radiologically visible callus, and clinical improvement in Paget's disease patients with multiple fractures[44].

Calcitonin has also been used in clinical settings of patients with injuries of the musculoskeletal system, such as incorporation of bone grafts after local injections of calcitonin[47], restoration of bone cysts after dental extractions[48] and an improvement in delayed fracture healing after local administration of calcitonin in patients with neglected fractures[49]. Finally, the analgesic effect of calcitonin (Fig. 3) in patients with recent osteoporotic vertebral fractures[50] is of great importance.

The effects of calcitonin on regional and immobilization osteoporosis

Immobilization is one of the main causes of disuse or regional osteoporosis. The pathogenesis of immobilization osteoporosis is multifactorial, but the main cause is bone unloading from mechanical strains. Immobilization is very common in fractures and usually lasts for a long period. Bone loss in these cases is extensive and fast[51-53]. Recovery from bone loss due to disuse is in most cases gradually achieved after the return of the usual mechanical loadings. In cases where this is not possible, it is advisable to add antiresorptive drugs. Calcitonin seems to be effective in partially reversing this bone loss[51-54].

Fracture regional osteoporosis is a specific form of immobilization osteoporosis found at the site of the fracture and periarticular regions near the fracture. Osteoporosis is the result not only of immobilization but also of vasomotor disorders. Osteoporosis found after fracture and immobilization for a long period of time in plaster especially affects the metaphyseal regions and carpal and tarsal bones[55].

Following the internal fixation of fractures with metal plates and screws, without immobilization in plaster, local osteoporosis is found under the metal plate[55]. This type of osteoporosis is due to the stress-shielding phenomenon as well as the local endosteal and periosteal vascular damage.

Calcitonin partially inhibits osteoporosis under the plate[42,56] and improves the mechanical properties of experimental osteotomies[57]. It has been found that, apart from the mechanical improvement in the region of the osteotomy,

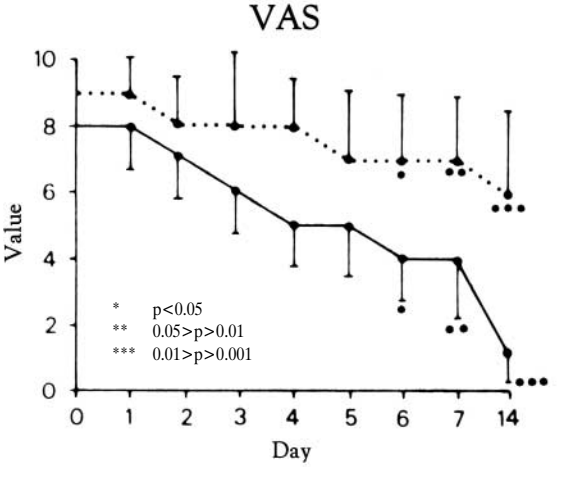

Figure 3. Pain rating (VAS scale) in the standing position. Calcitonin-treated patients can be mobilized from 14th day of the study.

there is an improvement in the mechanical parameters of the non-affected leg. This finding supports the effectiveness of calcitonin in bone microarchitecture.

Finally, it is important to note the effect of calcitonin administration for the prevention of post-surgical bone loss, especially in patients with hip fractures[58]. This effect is confirmed with the reduction of hydroxyproline/creatinine and calcium/creatinine ratios. In elderly patients with fractures, calcitonin administration immediately after surgery is of great clinical importance as it accelerates fracture healing, prevents disuse or regional osteoporosis and promotes faster mobilization of patients due to its analgesic effect.

In a prospective clinical study on the effect of 200 IU nasal salmon calcitonin administered daily for a period of three months in patients with a recent hip fracture, it was found that calcitonin protected the bone loss in the non-fractured hip after the end of the three month period of calcitonin treatment[59]. This beneficial effect on the bone of the femoral neck remained statistically significant after the discontinuation of the treatment.

Effect of calcitonin on the mechanical properties of bone

In the rabbit a higher fracture load and stiffness is observed after calcitonin treatment for 12 weeks (6 IU daily)[56]. Moreover, in the lumbar spine of retired breeder female ovariectomized Wistar rats, improvement in stiffness values and load-bearing capacity is a lot greater with combined administration of salmon calcitonin (10 μg/kg five times per week) and hPTH (1-38) (100 μg/kg five times per week)[60].

In ovariectomized ewes, torsional strength and stiffness on torsion of the femur was significantly improved, using 50 or 100 IU doses of calcitonin[61]. This phenomenon was not dose-dependent and differences in the parameters studied were not statistically significant. On the other hand, ultimate compressive stress was significantly improved in a dose-related response in the calcitonin group.

There are only a few animal model studies investigating the effect of calcitonin on mechanical properties of bone. No clinical studies have been published on this issue and further research is justified from the already existing results.

Conclusions

Systemically administered calcitonin interacts with cartilage and musculoskeletal trauma to a significant degree. Calcification of the growth plate and an acceleration of skeletal growth is evident in experimental studies with animals receiving calcitonin. Moreover, calcitonin seems to reduce the severity of osteoarthritic lesions on the articular cartilage of animals with experimental osteoarthritis. Cartilaginous callus maturation seems to increase in experimental studies using calcitonin, although further research on appropriate doses is required. Data from human studies on the effects of calcitonin on musculoskeletal trauma in humans are scarce. There are indications of clinical and radiological improvement of trauma patients receiving calcitonin, with special reference to pain and immobilization osteoporosis. These encouraging results call for more clinical stuides on the effects of calcitonin on musculoskeletal trauma.

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