

Osteoporosis in men

To the Editor

The article by Rafat Faraawi¹ provided a good review of "Osteoporosis in men," a common global problem with its increasing significance in the growing elderly population worldwide. The author presented useful information about this metabolic disorder concerning with its epidemiology, risk factors, prevention, and treatment. However, although multiple mechanisms can lead to osteoporosis, the contribution of calcitonin, a bone tonic hormone, in both the pathogenesis and treatment of osteoporosis was not pointed out in this review. Hereby, I would like to comment on the possible role of calcitonin in bone metabolism, its imbalance in osteoporosis and its use in therapy. The activity of osteoclasts and osteoblasts is under control of system hormones and cytokines generated in the bone cells microenvironment.² The major 'calcium regulating hormones' are parathyroid hormone (PTH), vitamin D and calcitonin, which are under negative feedback control and regulation by ECF calcium concentration. Their effects on bone cells are partly responsible for calcium homeostasis, but their effects on the kidney and gut are probably more important. Bone resorption by osteoclasts is stimulated by PTH and vitamin D (PTH-dependent effect) and is inhibited by calcitonin. There are other 'calcium influencing hormones' that influence bone cell function, but they are not under negative feedback control by ECF calcium.² These include estrogens, progesterone, androgens, prolactin, growth hormone, gluco-corticoids, and thyroid hormones. During periods of increased demand for calcium as during pregnancy, lactation, growth, and reproductive ages, these hormones stimulate calcitonin release and one hydroxylation of vitamin D. This will ensure fulfillment of the body's demand for calcium through the gut absorption at minimum bone resorption.

Sex hormone deficiency is a major factor in women, especially after menopause, and apparently in men as well.³ The physiological decline in sex hormones (estrogens in women and androgens in men) will greatly reduce, at least partly, their stimulating effect on calcitonin secretion. This will, in turn, decrease the inhibitory effect on osteoclast function resulting in accelerated bone resorption with consequent reduced bone mass and strength in aging women and men. Multiple pathways, direct and indirect, have been described for the inhibitory effect of estrogens and androgens on osteoclasts.^{4,5} The unopposed effect of PTH on bone resorption will further contribute to the development of osteoporosis in the elderly population.⁶ Calcitonin

inhibits osteoclastic bone resorption through inhibiting the formation of osteoclasts, as well as inhibiting the mature cells.² Calcitonin receptors have been demonstrated at multiple steps in the osteoclast lineage. It also causes a transient contraction of the osteoclast cell membrane,⁷ an effect that has been related to its capacity to inhibit osteoclastic bone resorption. Osteoclasts may escape from the inhibitory effect of calcitonin by down-regulation of cell surface receptors.⁸ However, osteoclast response to calcitonin may be prolonged in the presence of the influencing hormones, a point of importance in the physiological effect of calcitonin as well as in its application in therapy.

Calcitonin is FDA approved in the treatment of hypercalcemia of malignancy, Paget's disease of bone and postmenopausal osteoporosis in women more than 5 years postmenopausal.⁹ Calcitonin therapy, particularly nasal calcitonin (200 IU/day), used daily has proved to be effective therapy in men with idiopathic osteoporosis.¹⁰ Nasal calcitonin is safe and effective but development of clinical resistance caused by the presence of antibodies or receptors downregulation has raised concern.⁸ An advantage of calcitonin that is not shared by other anti-resorptive therapies is its direct central analgesic effect on bone pain. So as more convenient routes of administration such as oral, pulmonary, and transdermal, or allosteric activators of calcitonin receptors become available, the demand for calcitonin in male idiopathic osteoporosis, with or without fractures, is expected to increase.¹⁰⁻¹²

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Reply from the Author

Professor Mula-Abed raised the question, "Why calcitonin was not discussed as a treatment option in my article Osteoporosis in men?" There are no specific guidelines for the treatment of men with osteoporosis. Based on substantiated data, compelling evidence of anti-fracture efficacy in men is lacking. However, bisphosphonates and PTH are the only 2 agents approved by the FDA for the treatment of men with osteoporosis. Calcitonin is not an approved medication for male osteoporosis. Little information is available on the efficacy of calcitonin in men. The antifracture efficacy of calcitonin is lacking. There is no strong evidence to support calcitonin as treatment for osteoporosis in men. Trovas et al,¹⁰ conducted a 12-month randomized, double-blind placebo controlled trial of the

effect of intranasal calcitonin on bone mineral density. Twenty-eight men were randomized to receive either nasal calcitonin (200 IU) or nasal placebo daily for one year. A significant increase in bone density in lumbar spine in the treatment arm was noted compared to placebo. There was no significant change in the femoral neck. In another open label study by Ludwig Erlacher et al¹³ 9 men received subcutaneous salmon calcitonin for 3 months without treatment. Total duration of the study was one year, and at the end of the study, a significant increase in bone mineral density occurred in all men. These studies were small and of short duration and cannot be used as evidence to rationalize treatment. To my knowledge, no other studies addressed calcitonin as a treatment for men with osteoporosis. In view of this, calcitonin is rarely used for treatment of osteoporosis in men. Furthermore, calcitonin is only approved for treatment and not prevention of postmenopausal women with osteoporosis. The only fracture study in postmenopausal women (PROOF STUDY) has major drawbacks. The dropout rate at 5 years was high with 59% of patients discontinuing the study prematurely. This study showed that the dosage of 200 IU per day can reduce the risk of vertebral fracture however 100 and 400 IU per day were not effective. The effect on the non-vertebral fracture was not significant. For these reasons, calcitonin is considered a second line treatment for postmenopausal osteoporosis.

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