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Effect of intermittent PTH administration in the periodontitis-associated bone loss in ovariectomized rats

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Parathyroid hormone (PTH 1–34);
Periodontal disease;
Estrogen deficiency

Summary

Objective: Parathyroid hormone intermittent administration has been considered to treat bone mass decrease in osteoporotic individuals. The present study evaluates whether PTH can affect alveolar bone loss in ovariectomized rats, since estrogen deficiency has been proposed as a risk factor for periodontal disease.
Design and methods: Thirty female rats were set in groups: ovariectomized (Ovx) and Sham operated. Ovx were divided in two groups: Ovx-PTH (1–34) treated and Ovx, which received vehicle. After 1 week, cotton ligature was placed around one lower first molar of all animals to induce periodontal disease. Ovx treated received PTH doses of 40 μg/kg, three times a week for 30 days. After that, the animals were sacrificed, the mandibles extracted, X-rayed and samples prepared for histological evaluation. Histomorphometry was performed using image analyzer software. Scanning electron microscopy (SEM) of the tibias was also performed in all animals to evaluate possible changes in bone structure caused by the estrogen deficiency. Optical densities of the radiographs were measured by aluminum step-wedge equivalent thickness.
Results: Histomorphomery indicated the anabolic PTH effect in ovariectomized rats with significant inhibition of periodontitis manifestation ($p < 0.05$) thus neutralizing the periodontitis inductor effects. The photo densitometry showed a lower mandibular optical density in the ovariectomized group that did not receive PTH ($p < 0.05$).

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SEM image confirmed the early effect of estrogen deficiency in osseous tissue and PTH anabolic effect.
Conclusion: PTH systemic intermittent administration was able to reduce alveolar bone loss in ovariectomized rats, despite the presence of a periodontal disease inductor and estrogen deficiency.

Introduction

Rat models are increasingly used in screening studies of agents for prevention and treatment of osteoporosis.[1] In human osteoporotic individuals the bone loss is especially pronounced in the cancellous bone of the spine and of the femoral neck.[1] Estrogen deficiency is the dominant pathogenic factor for osteoporosis in women.[2] Estrogen modulates some cytokines that are important regulators of the bone metabolism and also regulators of the host response to infections, among these cytokines are interleukin-1 alpha (IL-1α), interleukin-1 beta (IL-1β), tumor necrosis factor alpha (TNF-α), macrophage colony stimulating factor (M-CSF), thus estrogen deficiency promotes an unbalance on bone metabolism interfering in the bone mass density (BMD) in postmenopausal women.[2,3] The impact of estrogen deficiency and osteopenia/osteoporosis on periodontal disease is unclear.[4] Periodontal disease is an inflammatory disease of periodontal tissues resulting in loss of tooth supporting tissues and is one of the major causes of tooth loss in adults.[4,5] Periodontitis involves recruitment of inflammatory cells, generation of prostanoides and cytokines, elaboration of lytic enzymes and activation of osteoclasts leading to alveolar bone resorption and soft tissue attachment loss.[5–7] Due to the effect in the process of bone formation/resorption, the estrogen deficiency has been investigated in relation to the stability of alveolar bone structure and, several studies have reported a positive correlation between estrogen deficiency and periodontal disease.[6–8] Skeletal BMD has been related to interproximal alveolar bone loss and, to a lesser extent, to clinical attachment loss, implicating postmenopausal osteopenia as a risk indicator for periodontal disease in postmenopausal women.[7]

The ligature induced periodontitis model has been extensively used to evaluate the progression of periodontal disease and such method enables subgingival microorganisms to accumulate and it has been observed that 30 days of induction were enough to promote inflammation and periodontal destruction.[8,9] Individuals with decreased bone mineral density, indicative of osteoporosis, may be at a higher risk for periodontitis progression, the systemic increase of the BMD observed with the hormone/estrogen replacement therapy (H/ERT) has been demonstrated to be accompanied by the increase of alveolar BMD in postmenopausal women.[6] Although H/ERT in postmenopausal women is the main treatment for osteopenia and osteoporosis, recent studies indicate parathyroid hormone (PTH) treatment in intermittent doses as an efficient anabolic treatment, avoiding the bone loss due to estrogen deficiency.[10–12]

PTH functions as a major mediator of bone remodeling and as an essential regulator of calcium homeostasis, producing several distinct and independent effects on the bone remodeling process, resulting in both, bone formation (anabolic activity) and bone resorption (catabolic activity), e.g. continuous infusion of PTH decreases bone mass by stimulating osteoclast activity, while intermittent administration increases bone mass by stimulating osteoblast differentiation.[12] PTH capacity to promote an increase in the skeletal bone mass is also observed in mandibular bone of the ovariectomized rats.[13–17] Recently, Barros et al. (2003)[18] reported that intermittent PTH administration in a rodent model was able to protect against experimental periodontitis-associated bone loss.

Therefore, the purpose of the present study was to evaluate the effects of intermittent PTH administration in rats under estrogen deficiency (ovariectomy), analyzing the development of experimental periodontitis.

Materials and methods

Animals

A total of 30 female Wistar rats, aged 4 weeks old in the beginning of the experiment, were maintained in a room with 12 h day/night cycles and an ambient temperature of 21 °C, with food and water ad libitum. Experimental procedures were approved by the Institutional Animal Research Committee at the University of Campinas (São Paulo, Brazil).

Surgical protocols

General anesthesia was obtained by intramuscular injection of ketamine of 1.0 ml/kg body weight and xylazine at 10 mg/kg body weight. Bilateral ovariectomy was performed in 20 rats. Sham surgeries