

Effects of antiresorptive agents on inflammation and bone regeneration in different osseous sites

- experimental and clinical studies

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien vid Göteborgs Universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Academicum, Medicinaregatan 3, fredagen den 17 oktober 2014, kl 13.00

av

Carina Cardemil
Leg tandläkare

Fakultetsopponent:

Associate Professor Bente Brokstad Herlofson
Department of Oral Surgery and Oral Medicine, Faculty of Dentistry,
University of Oslo, Oslo, Norway

Avhandlingen baseras på följande delarbeten:

- I. Cardemil C, Omar O, Norlindh B, Larsson Wexell C, Thomsen P. The effects of a systemic single dose of zoledronic acid on post-implantation bone remodelling and inflammation in an ovariectomised rat model. *Biomaterials*. 2013; 34: 1546-1561.
- II. Cardemil C[#], Elgali I[#], Norlindh B, Xia W, Emanuelsson L, Omar O, Thomsen P. Strontium-Doped Calcium Phosphate and Hydroxyapatite Granules Promote Different Inflammatory and Bone Remodelling Responses In Normal and Ovariectomised Rats. *PLoS One*. 2013; 8: e84932.
[#] Equal contribution.
- III. Cardemil C, Thomsen P, Larsson Wexell C. Jaw bone samples from bisphosphonate-treated patients: a pilot cohort study. Submitted.
- IV. Cardemil C, Granéli C, Palmquist A, Windahl SH, Emanuelsson L, Norlindh B, Larsson Wexell C, Omar O, Thomsen P. Molecular and structural differences in bone remodelling and inflammation in different bone types of the mature OVX rat model. In manuscript.



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ABSTRACT

The biological mechanisms involved in bone regeneration in osteoporotic bone and the effect of antiresorptive drugs in relation to surgically inserted biomaterials are not fully understood. Improved osseointegration of titanium implants but also adverse effects of antiresorptive therapies, such as osteonecrotic jaw have been described in the literature. The aims of this research project were, firstly, to investigate and to understand the biological events determining bone regeneration and implant integration, after administration of antiresorptive agents; secondly, to determine the cellular and molecular patterns of bone regeneration at implants and synthetic bone substitutes under osteoporotic conditions and, thirdly, to determine how different skeletal sites are affected. The present research included a study of jawbone morphology and gene expression in patients treated with systemic bisphosphonates. When compared to controls, higher gene expression levels of IL-1 β was observed in bisphosphonate treated patients with osteonecrosis while bisphosphonate treated patients without necrosis showed lower expression levels of caspase 8, an apoptosis marker involved in the immune response. In ovariectomised rats, zoledronic acid resulted in site-specific differences in the rate of osseointegration and also of gene expression involved in bone healing and regeneration. Strontium-doped calcium phosphate inserted in the rat femur induced lower expression of osteoclastic markers compared to hydroxyapatite and higher bone formation in the periphery of the defects. Whereas major structural changes were demonstrated in the long bones of the ovariectomised rat, less structural alterations were shown in the mandible. However, ovariectomy resulted in lower expression of genes coding for bone formation and angiogenesis in the mandible. In conclusion, the present study shows that the mandible is differently affected by experimentally induced estrogen deficiency than the long bones. Bisphosphonates, administered systemically to estrogen deficient animals, impair osseointegration in the mandible, at least partly related to a downregulation of genes important for the osteogenic process. These observations may have implications for understanding the mechanisms involved in the deranged bone healing observed in the jawbone of bisphosphonate treated patients.

Keywords: antiresorptive agents, ovariectomised rat, osteoporosis, skeletal site differences, osteonecrosis of the jaw, osseointegration, bone substitute, inflammation, bone regeneration, gene expression, histomorphometry, Micro-CT.

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