Göteborg, 2018

Vitamin A and Bone

Studies *in vivo* and *in vitro*

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet, kommer att offentligen försvaras i Hjärtats aula, Vita stråket 12, Sahlgrenska Universitetssjukhuset, Göteborg, den 18 december 2018, klockan 9.00

av **Viktė Lionikaitė**

Fakultetsopponent:

Riku Kiviranta

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Avhandlingen baseras på följande delarbeten

I. **Lionikaite V**, Gustafsson KL, Westerlund A, Windahl SH, Koskela A, Tuukkanen J, Johansson H, Ohlsson C, Conaway HH, Henning P, and Lerner UH. Clinically relevant doses of vitamin A decrease cortical bone mass in mice. *Journal of Endocrinology*, 2018; 239(3): 389-402.

II. **Lionikaite V**, Henning P, Drevinge C, Shah FA, Palmquist A, Wikström P, Windahl SH, and Lerner UH. Vitamin A decreases the anabolic bone response to mechanical loading by suppressing bone formation. Submitted.

III. **Lionikaite V**, Westerlund A, Conaway HH, Henning P, and Lerner UH. Effects of retinoids on physiologic and inflammatory osteoclastogenesis in vitro. *Journal of Leukocyte Biology*, 2018; 1-13. Epub ahead of print.

IV. Henning P, **Lionikaite V**, Westerlund A, Conaway HH, and Lerner UH. Retinoids enhance osteoclastogenesis in periosteal bone cell cultures. Manuscript.

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Abstract

Background: Excess vitamin A is associated with decreased cortical bone and increased risk of fractures in humans. The aim of the present thesis was to assess the importance of vitamin A on the skeleton and bone cells in *in vivo* animal studies and mechanistic *in vitro* experiments. *In vivo*, we used clinically relevant doses of vitamin A to investigate its effects on bone after prolonged administration and on the anabolic bone response to mechanical loading. *In vitro*, we aimed to determine how retinoids affect inflammatory- and physiologically-induced osteoclast formation and how retinoids affect periosteal osteoclast progenitors.

Methods: *In vivo,* mice were fed diets containing clinically relevant doses of vitamin A for durations of 4 and 10 weeks and prior to and during 2-week mechanical loading of the tibia. *In vitro*, we investigated the effects of retinol on human monocytes and mouse bone marrow macrophages induced to form osteoclasts by physiological and inflammatory cytokines, and on periosteal cell cultures.

Results: *In vivo*, we found that clinically relevant doses of vitamin A are able to reduce cortical bone mass by means of increased resorption and to decrease the anabolic bone response to mechanical loading due to reduced bone formation. *In vitro*, our results indicate that all-trans retinoic acid (ATRA), the active metabolite of retinol, inhibits physiologically- and inflammatory-induced osteoclastogenesis, however, in mouse periosteal bone cell cultures, the addition of ATRA enhances osteoclastogenesis.

Conclusion: Our results demonstrate the importance of vitamin A status to bone health. Fortification of food with vitamin A and vitamin A supplementation should be re-examined as vitamin A status may be a risk factor for secondary osteoporosis, a disease of decreased bone mass and increased risk of fractures.

Keywords: vitamin A, retinol, osteoclasts, osteoblasts, cortical bone, osteoporosis

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