Preventive anti-resorptive drug administration in disuse osteoporosis might preserve trabecular connectivity

PREVENTIVE ANTI-RESORPTIVE DRUG ADMINISTRATION IN DISUSE OSTEOPOROSIS MIGHT PRESERVE TRABECULAR CONNECTIVITY

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INTRODUCTION

Osteoporosis is caused by altered bone forming osteoblast and bone resorbing osteoclast activities, causing degenerated bone structure. In *disuse* osteoporosis reduced loads cause this condition. It is often treated with *anti-resorptive drugs* (ARD), which preserve bone mass and fracture resistance. We developed a theory for bone modeling and remodeling as governed by mechanical forces (Huiskes, 2000). In this work we investigated whether the theory can describe the known morphological effects of osteoporosis and anti-resorptive drug treatment on trabecular structure. We then asked the question whether *preventive* treatment could preserve bone mass and structure on the long term.

METHODS

We incorporated our theory in a computational model. Starting from a conceptual morphology, representing bone tissue at the post-mineralized fetal stage, the modeling simulation was continued to morphological homeostasis, representing mature bone where only remodeling still occurred (Ruimerman, 2003). After this stage disuse *osteoporosis* was invoked by reducing the mechanical loading magnitude by 50%. In the resulting osteoporotic structure the osteoclastic activation frequency was reduced by 70% in order to mimic the effects of – therapeutic or *late* - anti-resorptive drug administration (Steiniche, 1991). To study the effects of *preventive* treatment, we repeated the simulation of inducing disuse osteoporosis and reduced osteoclastic activation prematurely, i.e. at the moment of reducing the loading magnitude.

RESULTS

Starting from the post-mineralized fetal stage, the simulation produced a mature trabecular structure, aligned to the external loads, in approximately 8 simulated years. After that stage no more significant morphological changes occurred. After 20 simulated years the analysis was discontinued (fig 1a-b).

Invoking mechanically induced *osteoporosis* resulted in loss of bone due to trabecular thinning and loss of connectivity (fig 1c, table 1) until finally homeostasis was restored. Simulated anti-resorptive drug administration (*late* treatment) in the osteoporotic structure resulted in trabecular thickening but connectivity was not restored.

Simulated *preventive* anti-resorptive drug administration resulted in slower loss of bone tissue. Compared to *late* treatment, it did not preserve more bone mass on the long term. Trabecular connectivity however, was preserved (table 1).

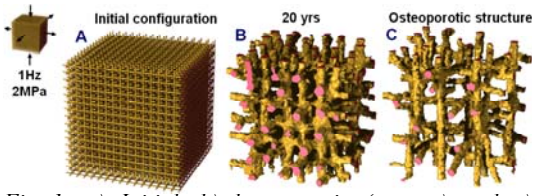

Fig 1: a) Initial, b) homeostatic (mature) and c) osteoporotic trabecular structure.

	VF	Nett full turnover (years)	Tr.Th. (µm)	Reduction in number of trab (%) *
Reference situation	0.192	3.9	183	-
Forces 50%	0.108	3.1	147	20
Late treatment	0.126	6.1	155	21
Preventive treatment	0.127	5.9	147	7

* Compared to the reference situation

Table 1: Morphological characteristics for the mature homeostatic (reference), osteoporotic (Forces 50%) and ARD-treated structures.

DISCUSSION

The simulations explain the structural developments observed in trabecular bone growth (modeling), adulthood (remodeling) and osteoporosis (Mosekilde, 1988). The effects of anti-resorptive drugs (*late* treatment) on bone mass were realistic as well (Liberman, 1995). Simulated *preventive* anti-resorptive drug administration reduced the rate of bone loss. Compared to *late* treatment it did not preserve bone mass on the long term. Trabecular connectivity, however, was preserved, which results in higher resistance to un-physiological - "error" - loads. The treatment increases tissue age with a risk of enhanced crack propagation.

REFERENCES

Huiskes et al., *Nature 405*:704-706, 2000; Liberman et al., *New Engl. J. Med. 333*:1437-1443, 1995; Mosekilde et al., *Bone 9*: pp 247-250, 1988; Ruimerman et al., ORS, 2003; Steiniche et al., *Bone 12*: pp 155-163, 1991;