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INDIRECT OSTEOBLAST-OSTEOCLAST COUPLING THROUGH MECHANICS EXPLAINS ELEVATED OSTEOBLASTIC BONE FORMATION AS A RESPONSE TO INCREASED OSTEOCLASTIC ACTIVITY

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Introduction: Osteoporosis is a condition of reduced mass and increased fragility in trabecular bone. *Post-menopausal* osteoporosis, occurring in women, is caused by estrogen deficiency, leading to an increased remodeling rate (increased activation frequencies of both osteoclasts and osteoblasts), reduced trabecular number and thickness, and reduced strength. *Senile* osteoporosis occurs in the elderly of both genders, leads to similar morphological adaptations, but lacks the metabolic accelerations; it is believed to be associated with reduced loads and physical activities. We have developed a unified, quantitative theory of bone modeling and remodeling, that provides an explanation for the emergence, maintenance and adaptation of trabecular structure as governed by external forces [1]. This theory assumes that mechanical load transfer governs osteoblast-osteoclast coupling implicitly. The theory was implemented in a 3-D FEA computer-simulation model, allowing predictions of the morphological consequences following metabolic or biomechanical perturbations.

For the present work we asked the question whether the morphological changes seen in osteoporotic trabecular bone can be explained by increased osteoclastic activation frequency (postmenopausal) or reduced loading (senile) by themselves.

Methods: The theory describes the separate activities of osteoclasts and osteoblasts in both *modeling* and *remodeling* of trabecular structure [1]. We assume local dynamic loading variables (SED-rate) to activate osteocytes in the bone matrix to transfer osteoblastic bone-formation stimuli to trabecular surfaces, through the canalicular network. The stimulus received at the surface depends on osteocyte density, mechano-sensitivity and signal decay by distance. Bone is formed at trabecular surfaces, where and while the stimulus exceeds a threshold value. Concurrently, osteoclasts are assumed to resorb bone which is (micro)damaged, the sites of which are determined at random per iteration. Coupling between osteoclastic and osteoblastic activities in remodeling is governed *implicitly* by the mechanics through SED concentrations around resorption cavities, due to a notching effect (fig 1).

The simulations were effected in a (2x2x2 mm^3) cubical FEA model containing 60x60x60 cubic voxel elements, which can be bone or marrow. The cube was loaded by distributed stresses, perpendicular to its faces, of 2 MPa, cycling at 1 Hz. Starting from a conceptual morphology, representing the post-mineralized fetal stage of a vertebral bone cube, the simulation was continued until no more gross morphological changes occurred (remodeling still continues), representing a homeostatic mature stage. Postmenopausal osteoporosis was invoked by increasing the osteoclastic activation frequency by a factor 3 [2] at the mature stage. Senile osteoporosis was invoked in 2 ways, at the same mature stage: by reducing the loads at all faces of the cube by a factor 2 (simulating overall reduction of physical activity) and by reducing only the horizontal loads by a factor 2, while maintaining vertical loading values (simulating simplified activity patterns, with reduced error loads).

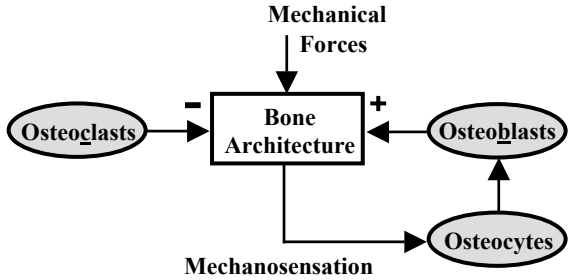

Fig 1: *Proposed regulation mechanism of bone cell metabolism: (i) Osteoclasts are assumed to resorb bone on locations where microdamage occurs, the trabecular surface locations of which are selected at random. (ii) Osteocytes locally sense a mechanical signal due to external load transfer through the architecture and locally recruit (iii) osteoblasts to form bone tissue.*

Results: Starting from the post-mineralized fetal stage, the simulation produced a mature trabecular structure, aligned to the external loads (fig 2a-c). The bone volume fraction of the cube initially rose sharply, overshot, and then stabilized. At an early stage, the structure was unorganized and trabeculae were thin (fig 2b), while later trabecular alignment and thickness gradually increased (fig 2c).

Reducing loads to 50% of the original level resulted in loss of trabecular thickness as well as trabecular number (connectivity) until finally a new homeostatic state was reached (fig 1d). Reducing the load 50% in only horizontal directions led to a strong anisotropy, favoring the vertical direction (fig 1e).

Increasing the osteoclastic activation frequency by 300% to mimic the effects of estrogen deficiency led to loss of trabecular thickness and number (connectivity) until a new homeostatic state was reached (fig 2f). It also increased the osteoblastic activation rate, hence the new homeostatic condition was characterized by an increased remodeling rate

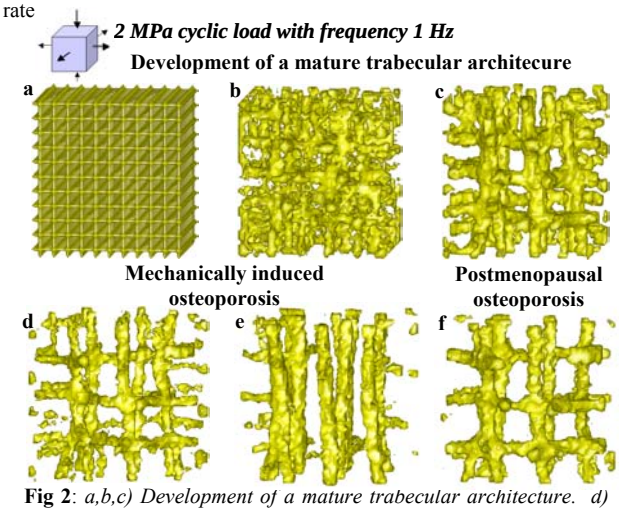

Fig 2: *a,b,c) Development of a mature trabecular architecture. d) Reducing external force leads to loss of bone and trabecular connectivity. e) After reducing horizontal loads only, the structure becomes aniotropic. f) Increased osteoclastic activation frequency leads to trabecular thinning and loss of connectivity*

Discussion: The morphological developments in simulated growth (fig 2a-c) were realistic relative to bone-density development, trabecular thickness and orientation, compared to measurements in growing pigs [3]. Remodeling space and rate also attained realistic values in this simulation [2]. The reduction of trabecular thickness after simulated reduction of overall loading is also seen in reality [4], but not very surprising, as it is an inherent ('predictable') capacity of the model. The predicted loss of trabecular number (connectivity) in this case is less obvious, pointing at 'stress shielding' in the trabecular structure. Reducing only horizontal ('error') loads produced the same kind of anisotropy as found from measurements in post-mortem vertebrae from the elderly [5].

It is known that postmenopausal osteoporosis is associated with increased remodeling rates, hence accelerated activation frequencies of both osteoclasts and osteoblasts [6]. Our results suggest that the increased osteoblastic activation rate may be an effect, not of estrogen deficiency, but of the increased osteoclastic activation frequency alone. Hence, the theory explains both postmenopausal bone loss and increased remodeling rate as effects of increased resorption rate.

References: [1] Huiskes et al., *Nature* ***405***, pp704-706, 2000. [2] Kanis, Osteoporosis, Blackw. Healthc. Comm., 1997. [3] Tanck et al., *Bone* ***28***, pp 650-654, 2001. [4] Zerwekh et al., *J.Bone Min.Res.* **13**, pp 1594-1601. [5] Mosekilde, *Bone* ***9***, pp 247-250, 1988. [6] Chambers, *Adv in Organ Biol* ***5B***, pp 627-638, 1998.