

Large animal models for osteoporosis research: The small ruminants (sheep and goat)

In the healthy skeleton, constant bone remodeling occurs in which mature bone tissue is removed, in a process called resorption, and new tissue is formed in order to maintain bone strength and mineral homeostasis in continuum with a strict coordination between their phases, not only for the amount of bone resorbed and reconstructed but also in what exact location it must occur. The bone remodelling cycle has three phases: the initiation, the transition (reversal) and the termination phase of bone formation.

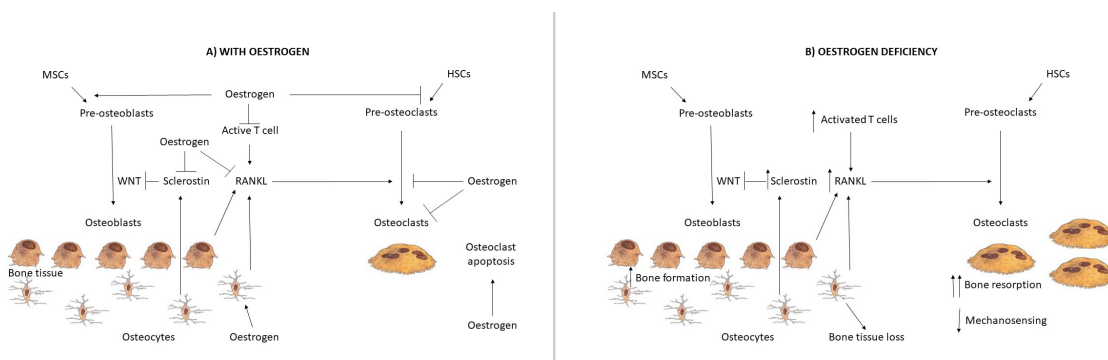


Fig. 1. Role of oestrogen in bone remodeling. A) Normal bone remodeling and B) oestrogen deficiency: Increased RANKL production, increased osteoclast number and activity, osteoblasts suppression and osteocytes deregulation.

During bone remodeling, the receptor activator of nuclear factor κ B ligand (RANKL) and macrophage colony stimulating factor (M-CSF) promote the osteoclast maturation and, consequently, bone resorption forming lacunae and inhibit the osteoblast differentiation and activity. The osteocalcin and collagen-I attract the precursors to bone resorption and prepare also the bone surface for osteoclasts. Then, osteoclasts attaches to the bone matrix. At this stage, osteoclasts polarize, resorptive lacunae acidify and lysosomal enzymes are released into it. Thus, the matrix is dissolved and its elements are removed. The accumulation of extracellular calcium induces osteoclast apoptosis. After, phagocytes forms a reversal line on the newly resorbed surface and modify it for the osteoblast recognition. Moreover, the release of growth factors stored in bone matrix, such as transforming growth factor β (TGF- β) and insulin-like growth factor 2 (IGF-2), stimulate osteoblast differentiation and activate bone formation in resorption lacunae. Finally, osteoblasts produces osteoprotegerin (OPG) and semaphoring 3 that suppresses osteoclast differentiation and consequently bone resorption. To end this cycle, osteoblasts differentiate into bone lining cells, and the bone surface is again covered by them, or differentiate into osteocytes. Osteoblasts and osteoclasts activities are controlled by a variety of cytokines and hormones, such as oestrogen. Thus, the lack of estrogen leads to unbalanced remodeling, enhancing the expression of M-CSF, RANKL and tumor necrosis factor α (TNF- α) and fails to express OPG. Consequently, there is an enhancement of osteoclasts formation and of bone resorption because there is no osteoclasts apoptosis performed by oestrogen. Moreover, the lack of oestrogen suppress osteoblast differentiation and activity by mesenchymal stem cells and consequently, inhibits the production of IGF-2 and TGF- β (Fig. 1).

Osteoporosis is the most common metabolic disorder of the skeleton, characterized by a systemic loss of bone mass and structure, increasing the risk of fragility fractures. So, efforts to improve the implant fixation in osteoporotic bone tissue have resulted in an increasing demand for suitable large animal models for research within biomaterials, prosthetic components and medical devices. The most frequent osteoporotic small ruminant model used is by far the ovariectomized (OVX) sheep with 12 months post-operatively or more as a surgical model for biomaterial research, bone augmentation, efficacy of implant fixation, fragile fracture healing process improvement or bone defect repair studies in the osteopenic or osteoporotic bone, or by the combined treatment of OVX sheep associated to calcium/vitamin-D deficient diet and glucocorticoid applications for 6 months. The goat model for osteoporosis research has been used in a very limited number of studies in osteoporosis research relative to sheep, using specially the OVX model after a post-operative period of 24 months. Recently, the pathophysiological mechanism underlying osteoporosis induction in the glucocorticoid treated OVX aged sheep was clarified, being similar to what occurs in postmenopausal women with glucocorticoid-induced osteoporosis. This mechanism result in a significant bone loss promoted by an arrest of the reversal phase, resulting in an uncoupling of bone formation and resorption during this reversal phase, supporting the importance of this large animal model for the study of the pathophysiology of osteoporosis and as a preclinical model for orthopedic implant and biomaterial research. Another very recent study elucidates the osteocyte regulation of RANKL/OPG in a sheep model of osteoporosis, concluding that in the late progressive phase of the osteoporosis induced by steroids, the RANKL expression is stimulated in osteocytes. With the increase in the knowledge of the pathophysiological underlying mechanisms involved in the induction of osteoporosis in the small ruminants, the studies in these animal models should be carried out with greater confidence in obtaining transposable results for humans.

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