

The osteocyte as a director of bone metabolism

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It is well known that bone is a living tissue. Continuous turnover in bone tissue is driven by numerous factors. Among those, bone cells stand as the essential components of bone turnover. Osteocytes, which occupy 95% of the total cell count in bone tissue, are one of the longest-lived (average half-life of 25 years) cell types in human body. On the other hand, osteoblasts and osteoclasts account for approximately 5% of the total bone cell population with a life period of few days or weeks.^{1,2}

Earlier, it was considered that osteocytes were just placeholders in bone tissue. Nevertheless, it is now well documented that osteocytes act as important orchestrators not only in bone-related clinical conditions, but also in some non-bone diseases.²⁻⁴ The majority of the literature data regarding osteocyte functions concentrate on bone-related conditions, particularly on osteoporosis. Osteoporosis affects not only postmenopausal women and elderly individuals, but also patients with certain diseases such as neurological conditions (i.e., multiple sclerosis) and rheumatologic diseases (i.e., rheumatoid arthritis).^{5,6} Bone remodeling is a physiological process involving the regulated balance among bone cells (bone-lining cells, osteocytes, osteoclasts, and osteoblasts).⁷ Osteocytes are descended from mature osteoblasts.

The osteocyte's body is surrounded within a hydroxyapatite cave of lacuna and the dendritic processes lie in canaliculi. Distinct signaling molecules such as receptor activator of nuclear factor kappa-B ligand (RANKL), osteoprotegerin (OPG), Dickkopf-1 (Dkk-1) and sclerostin provide osteocytes to communicate with osteoblasts and osteoclasts.^{1,8} They also secrete molecules such as parathyroid hormone related peptide (PTHrP), prostaglandin E2 (PGE2), and osteopontin (OPN).⁹ Osteocytes are mechanosensory cells responding to mechanical stimulation applied to the bone. Osteocyte mechanotransduction modulates the function of osteoblasts and osteoclasts, thereby regulating bone homeostasis.⁴ In addition to their effects on local bone environment, osteocytes have paracrine/autocrine effects. They can also regulate phosphate and calcium hemostasis, modulate myelopoiesis/hematopoiesis, and enhance muscle myogenesis and muscle function.²

Given the important role of osteocytes in bone metabolism, neutralizing antibodies against osteocyte-secreted proteins are used for the treatment of osteoporosis.⁹ Denosumab, a human monoclonal antibody against RANKL, has been used with favorable results in men and postmenopausal women with osteoporosis and at a high risk for fracture, as well as in patients

Received: December 06, 2020 **Accepted:** December 28, 2020 **Published online:** January 15, 2021

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Citation:

Coşkun Benlidayı İ. The osteocyte as a director of bone metabolism. Arch Rheumatol 2021;36(4):617-619.

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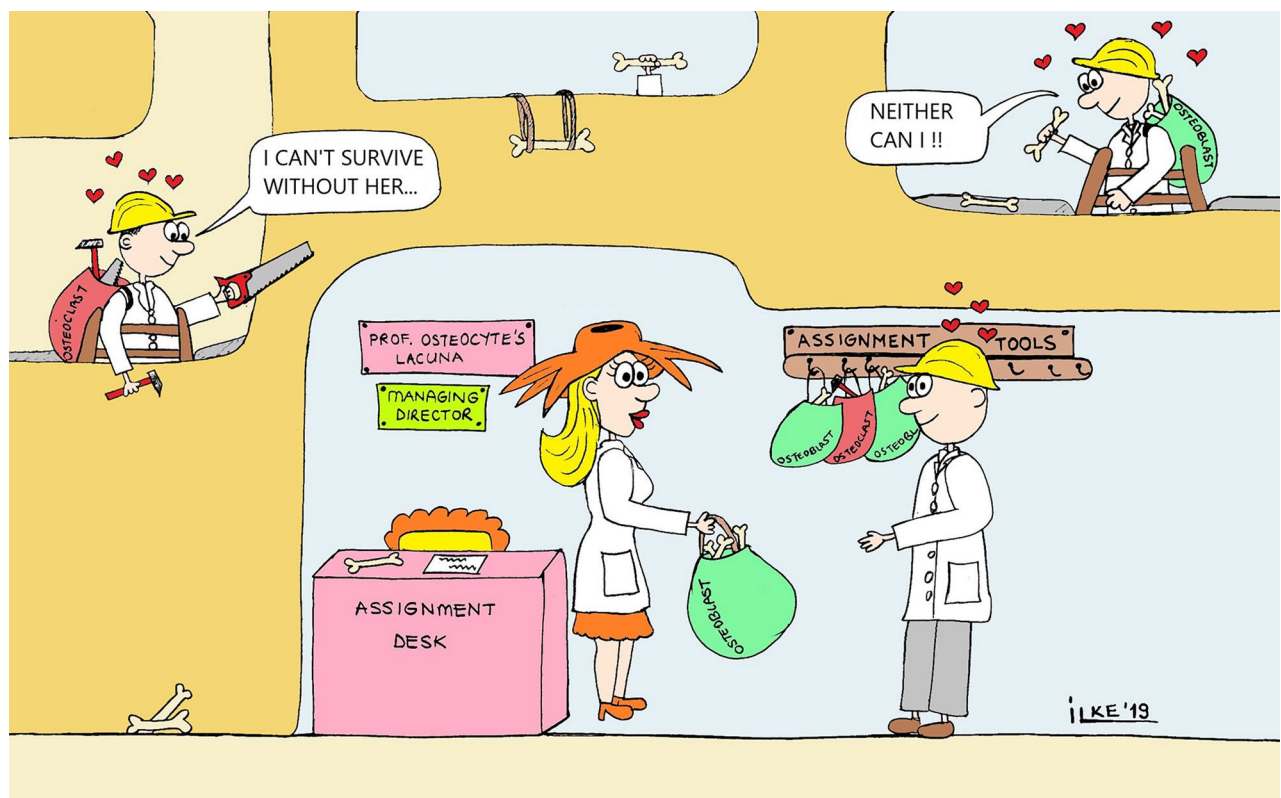


Figure 1. Cartoon.

with glucocorticoid-induced osteoporosis.¹⁰ Romosozumab, a sclerostin inhibitor, has been recently approved for the treatment of osteoporosis in postmenopausal women at a high risk for fracture. Of note, the drug has a black box warning given its relation to an increased risk for serious cardiovascular events.⁸

In conclusion, osteocytes are directors of bone metabolism. They coordinate the activity of both osteoblasts and osteoclasts (Figure 1). In addition to their role in bone regulation, they have also the potential to modulate other cell and/or organ functions. Further understanding on the capabilities of osteocytes would be valuable for developing new treatment strategies for osteoporosis and other bone-related diseases.

Declaration of conflicting interests

The author declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The author received no financial support for the research and/or authorship of this article.

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