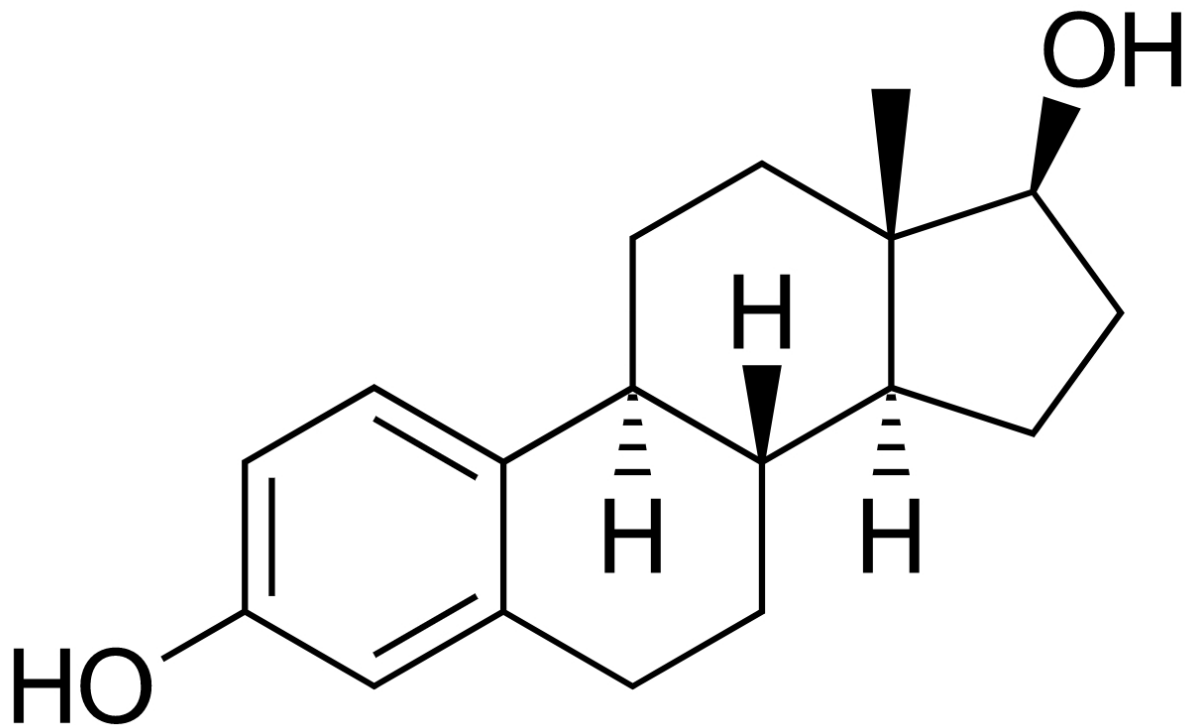


Estrogen regulates pathological changes of bones via bone lining cells

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Estradiol, the major estrogen sex hormone in humans and a widely used medication. Credit: Public Domain

The female sex hormone estrogen plays an important role in the structural stability of bones. To date, however, it had been unclear exactly which cells were involved in the hormone's protective function in

preventing changes in bone density. Researchers at Vetmeduni Vienna were able to show for the first time that estrogen uses a certain cell type as a "mediator" for its beneficial effects on bone. When estrogen binds to these so-called "bone lining cells", which cover the bone surfaces, it regulates the expression of a protein called RANKL in these cells. Estrogen deficiency leads to uncontrolled expression of RANKL, which can trigger pathological changes in the bones. The results were published in *Scientific Reports*.

The most important female sex hormone, estrogen, plays a crucial role in the regulation of [bone mass](#). Estrogen deficiency is known to be a major cause of postmenopausal osteoporosis, or [bone](#) weakness. Skeletal stability and pathological skeletal changes thus depend directly on the hormone's availability and its interaction with the [bone cells](#).

Until now, however, the actual target cells responsible for mediating the effect of estrogen on bone had still been unknown. Researchers at Vetmeduni Vienna have now demonstrated that bone lining cells act as "gatekeepers" for the hormone. By binding to these cells, estrogen controls the expression of RANKL, an important factor in bone turnover and remodelling.

Estrogen uses a certain cell type to mediate its effect on bone density

The development of bone structure depends on a complex system of hormones and proteins. One important component is the signalling molecule RANKL. It influences the development of special cells, the so-called osteoclasts that are responsible for [bone resorption](#). A lack of estrogen or the corresponding cell receptors where it can bind results in the overproduction of RANKL, which triggers a variety of pathological bone changes.

Several studies confirm estrogen's role in regulating RANKL production and thus in protecting skeletal integrity. "Which cells it must bind to in order to have this effect, however, had been a matter of debate," says study director Reinhold Erben from the Unit of Physiology, Pathophysiology and Experimental Endocrinology. "We were now able to confirm that estrogen's effect on bone occurs primarily through binding to the bone lining cells."

The bone lining cells cover the bone surfaces and contact other bone cells, such as the osteocytes that reside inside the bones, through cell-to-cell contact. They had been suspected of being involved in the regulation of bone resorption through the osteoclasts. The fact that the bone lining cells, as target cells for estrogen, play a role in bone maintenance confirms this suspicion.

Tissue cells surrounding the bones act as mediator of the hormonal effect

Erben and his team based their study on the use of a special mouse model and new experimental methods. "We used different groups of mice, in which either the estrogen receptor or RANKL was inactivated in hematopoietic cells or in mesenchymal cells, to be able to identify the target cells of the hormone. The effect we were looking for was found only in mesenchymal cells," explains Erben.

To identify the cells, the research team used a special method called laser capture microdissection to exactly separate individual cell types from the remaining tissue. They then determined the gene frequency using RNA analysis and were so able to confirm the bone lining cells as the primary [target cells](#). "The bone lining cells also make sense as gatekeepers or mediators for the effect of the bound hormone because of their position on the bone and their connection to the other bone

cells," says Erben. "Future studies are needed to answer whether other hormones also influence bone turnover via this cell type or if they use other [cells](#). The aim of our study was merely to answer the question of how the interaction of [estrogen](#) with bone functions."

More information: Carmen Streicher et al. Estrogen Regulates Bone Turnover by Targeting RANKL Expression in Bone Lining Cells, *Scientific Reports* (2017). [DOI: 10.1038/s41598-017-06614-0](https://doi.org/10.1038/s41598-017-06614-0)

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