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THE ROLE OF HORMONAL BACKGROUND IN THE DEVELOPMENT OF OSTEOPOROSIS

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Abstract: Osteoporosis is a chronic systemic metabolic disease of the skeleton, which is characterized by a progressive decrease in bone mass. The predominance of resorption processes and a decrease in bone formation it lead to a violation of bone microarchitecture and its shrinkage. Currently, osteoporosis and associated bone fractures are one of the main causes of disability and premature death in the elderly [1]. One of the main causes of osteoporosis is a violation of the hormonal background, which has been studied by many scientists. In particular, impaired activity of testosterone, estrogen, melatonin affects osteons.

Keywords: osteoporosis, testosterone, estrogen, melatonin, menopause

Quality Maria, Paula A. Melatonin effects on bone: potential use for the prevention and treatment for osteopenia, osteoporosis, and periodontal disease and for use in bone-grafting procedures It is reported that 8.9 million osteoporosis-related fractures occur worldwide each year, which is approximately one osteoporosis-related fracture every 3 seconds. According to the International Osteoporosis Foundation, more than 200 million women worldwide have osteoporosis, most of whom are 60 or older; the female-to-male ratio for fractures is 16:1. In the European Union, it is estimated that approximately 22 million women and 5.5 million men (aged 50 to 84) have osteoporosis; this number will increase by 23% by 2025. In the United States, approximately 57 million adults over the age of 50 suffer from bone disease, with 48 million adults having osteopenia and 9 million adults having osteoporosis, putting them at risk for fracture. If current trends continue, the prevalence of osteoporosis is projected to increase to 11.9 million and 64.3 million with osteopenia by 2030. [18].

Microstructural abnormalities in osteoporosis affect the trabecular and cortical layers.

A decrease in the thickness and number of trabeculae is characteristic of the pathogenesis of osteoporosis.

In the pathogenesis of osteoporosis, the cortical layer thins and becomes more porous, leading to a decrease in bone strength and the development of micro- and macro-fractures. [2].

In girls, changes in estrogen and testosterone activity begin after the onset of menstruation during puberty. This is because testosterone increases periosteal thickness, bone growth, and estrogens, through osteoclasts, affect the thickness of the cortical layer, restoring it on the endosteal surface of the bone. Thus, the increase in bone thickness occurs due to the predominance of periosteal synthesis processes over endosteal resorption processes.

During this period, the risk of fractures associated with growth is particularly high in the distal forearm, since bone volume increases more rapidly in this area. The effect of estrogen

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in this process is realized by inducing apoptosis of chondrocytes and osteoclasts of the tubular bone in the growth line of the bone.

The hormone melatonin is synthesized from the amino acid tryptophan in the pineal gland. Its main function is to act as a humoral messenger, transmitting information from the suprachiasmatic nuclei of the hypothalamus to the body's cells. Many structures in the body produce melatonin. These include, for example, the retina, bone marrow, platelets, skin, lymphocytes, the nictitating gland (Harder's gland), the cerebellum, and the gastrointestinal tract [12, 13]. However, this production is not cyclical and provides melatonin as an "internal" antioxidant agent. Melatonin performs many physiological functions in the body. These include:

1. Regulation of circadian rhythms (including the daily sleep-wake rhythm) [14].

2. Regulation of body temperature [15].

3. Reduction of age-related weight gain [15].

4. Pro-inflammatory (production of IL-2, IL-6, IL-12), strengthening the immune system (production of T-helpers).

The role of melatonin in the regulation of immunity has been proven,

Melatonin has a direct immunostimulating effect in animals and humans [16]. At the same time, the effect of melatonin on reparative osteogenesis of jaw bones

in bone fractures has been widely discussed, although the increasing possibilities of modern surgery are of great importance in dentistry and especially implantology.

The aim of the study was to study the effect of melatonin on the processes of osseointegration of jaw bones

in experimental conditions

Materials and methods. The changes in osteocytes stained with Hematoxylin-eosin by the method of Van Gison, Mallory, Masson were studied [19]. The effect of melatonin on bone turnover was studied in 7-8-month-old guinea pigs. The guinea pigs were anesthetized and injected with Zoletil 50. A 5-mm sample was taken from the lower jaw of the animals.

For 14 days before surgery, a group of guinea pigs (24 animals) were given insulin orally using a laboratory pipette into an insulin syringe from 4:00 PM to 5:00 AM. The second control group (24 animals) was given melatonin (in the form of Melaksen®, Unipharm) in a physiological solution of sodium chloride at a dose of 5 mg / kg body weight of the animals. Melatonin was removed from the water and food of the animals. [6].

Experimental and control guinea pigs were examined on days 14, 30, 60 and 120 after surgery. The lower jaw was examined radiographically, fixed with 10% neutral formalin and stained with Hematoxylin-Eosin, and a preparation was prepared using the Van Gison,

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Mallory, and Masson methods. When examining the guinea pigs in the control group at 60 days, it was found that the structural structure of the lower jaw bone was preserved. During the same period, when melatonin was administered, histologically dense fibrous tissue was detected. Histological examination of the preparations obtained up to the 120th day of the experiment showed that only the use of melatonin provided secondary restructuring of regeneration in the peripheral area.

Histochemical analysis showed that the speed and duration of changes in the redistribution of acidic mucopolysaccharides in the tissues increased.

On the 30th day of the experiment, the same dynamics of changes in the composition of neutral mucopolysaccharides was observed when melatonin was used for 28 days. Together

However, their concentration, unlike acidic mucopolysaccharides, remained high in the experimental and control groups from the moment of stabilization on the 30th day after surgery to the 60th day of the experiment.

When studying the activity of cells under an electron microscope, significant changes were detected in the cytoplasm of osteoblast cells 2 weeks after surgery. Indicative changes were detected in the endoplasmic reticulum, Golgi complex, and ribonucleotide granules (7)

Histological examination of preparations obtained up to the 120th day of the experiment showed that

only the use of melatonin provided secondary restructuring of regeneration at the periphery of the defect, with the development of bone tissue.

Histochemical analysis showed significant differences in the quantitative redistribution of mucopolysaccharides in the regeneration tissues, including the speed and duration of such changes. In particular, while the amount of acidic mucopolysaccharides in intact bone callus cells increased on day 30 of the experiment, melatonin administration for 28 days provided such a restructuring by day 14 of the experiment. Thus, according to the data of visualization research methods, chronic intake of melatonin alone within 14 days after surgery ensures the formation of bone structures, and not dense fibrous tissue, as in the control group of animals.

It is noteworthy that throughout the entire experiment, the process of bone tissue regeneration with melatonin administration was 14–30 days ahead compared to those who did not receive it. Changes in regenerative activity are mainly associated with the activation of cellular metabolic functions, particularly those of osteoblasts, and their structural reorganization under the influence of melatonin pre-administration. This is evidenced by the early and quantitatively expressed manifestation of mucopolysaccharides in the regeneration of animals in the main group.

In scientific articles by Brailova N.B., Kuznetsova V.A., Dudinskaya E.N., and Tkacheva N.E., the aging process is examined in relation to collagen and gene cells. In 1961, Hayflick determined the division limit of somatic cells due to the onset of critical telomere length, after which all signs of cell aging appeared and apoptosis occurred. As in any tissue, aging in bone — which includes extracellular matrix components such as non-cellular proteins,

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calcium phosphate, and hydroxyapatite-mineralized collagen fibers — leads to a decrease in the number of osteoblasts and osteocytes due to apoptosis and an increase in adipose tissue volume. Qualitative changes also occur in bone cells. For example, in aging osteoblasts, the production of type I collagen (the organic matrix of bone) gradually declines, and aged cells exhibit irregular morphology, flattening, and accumulation of cellular debris.

Interestingly, in experiments involving prolonged administration of troglitazone (a low-affinity thiazolidinedione) to mice, an increase in the number of adipocytes was observed without affecting bone mass. In contrast, injections of rosiglitazone (a high-affinity thiazolidinedione) were associated with decreased joint mineral density. This, as well as the stimulation of osteoblast and osteocyte apoptosis, explains the increased incidence of fractures in individuals treated with thiazolidinediones for diabetes mellitus. Two isoforms have been identified in mice — PPARγ1 and PPARγ2. PPARγ2 is expressed only in adipose tissue, whereas the other isoform is expressed in various other tissues.

Studies have shown that PPARγ promotes adipogenesis, and its absence in mice leads to a lack of terminally differentiated adipose tissue, fatty liver dystrophy, and lipodystrophy. In humans, somatic mutations of the **PPARG** gene that activate aging contribute to metabolic disorders, including insulin resistance and the development of arterial hypertension. Selective PPARγ ligands, particularly thiazolidinedione drugs, are used to treat type 2 diabetes by suppressing insulin resistance.

Adipocytes secrete several proteins (adipokines) that function as hormones via endocrine pathways, such as leptin. In studies on mice, bone strength loss with age was accompanied by a decrease in serum leptin levels. Leptin-deficient mice had shortened femurs, reduced mineral content, and lower mineral density in the femur, while the mineral content of the lumbar vertebrae was increased.

Leptin is believed to differentially regulate chondrogenic proliferation and differentiation in appendicular and axial skeletal regions. Thus, primary tibial epiphyseal chondrocytes cultured in mice proliferated faster than vertebral epiphyseal chondrocytes. Leptin inhibits apoptosis in tibial epiphyseal plate chondrocytes but promotes apoptosis in vertebral epiphyseal plate chondrocytes. It regulates osteoclast development by reducing the production of RANK and RANK ligands. Research results indicate that the level of BMP-7 in tibial epiphyseal chondrocytes is significantly higher than in vertebral epiphyseal chondrocytes.

In scientific articles by Sifat Maria and Paula A., one of the mechanisms underlying melatonin's bone-strengthening effect is its stimulatory action on osteoblasts. Numerous studies have shown that melatonin promotes the differentiation of hMSCs and preosteoblasts into mature osteoblasts via multiple signaling pathways involving ERK1/2 and Wnt/β-catenin. As shown in Figure 2, activation of melatonin receptors by melatonin leads to increased MAPK activity (ERK1/2, p38, or JNK); for MEK1/2/ERK1/2, this activation is associated with MT2 melatonin receptors and MT2R/Gi/β-arrestin/MEK/ERK1/2 pathways, which in turn lead to ALP activation in the cytoplasm and the induction of osteogenic gene expression involving Runx2, followed by bone morphogenetic protein 2 (Bmp2), osterix, and osteocalcin (OCN).

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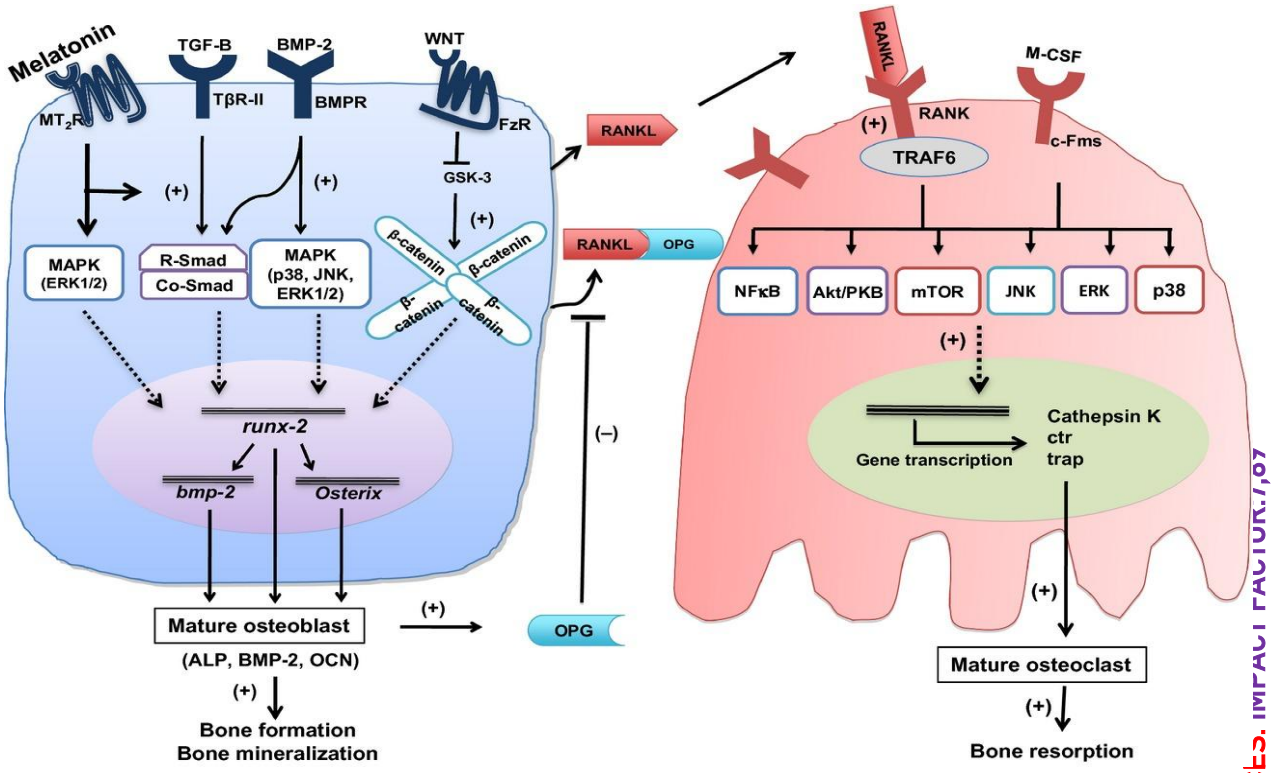
Bone morphogenetic proteins (BMPs) play a crucial role in osteoblastogenesis and are currently used clinically (INFUSE™) in bone grafting procedures.



As shown in the figure, BMPs bind to bone morphogenetic receptors (BMPRs), which are membrane-bound and located in osteoblasts and phosphorylated Smad proteins. This leads to their interaction with common-partner Smads (Co-Smads), resulting in nuclear translocation and activation of osteogenic genes such as **Runx2**, **Bmp2**, and **osterix**. Melatonin can also activate **Wnt/β-catenin** in osteoblasts, which enhances **Runx2** expression. The Wnt/β-catenin pathway is a well-known signaling route involved in osteogenesis. Many other signaling mechanisms also participate in osteogenesis (e.g., fibroblast growth factors); it would be interesting to explore how melatonin interacts with these pathways to stimulate osteoblastogenesis.

Overall, these studies confirm the claims that melatonin accelerates the synthesis and mineralization of new bone. Indeed, the influence of melatonin on bones supports its use as an adjunct therapy in osteoporosis populations, alongside other systemic hormones such as **PTH**, **estrogen**, and **calcitonin**, to improve or maintain bone health. (18)

Scientific research also shows that **epigenetic factors** in elderly women are directly related to **physical activity**. For example, regular physical activity is positively associated with enhanced bone formation and bone strength, and it positively affects bone metabolism and remodeling. (10)

During menopause, the rapid decline in estrogen is associated with decreased bone density. Paradoxically, an increase in bone volume is observed due to an increase in periosteal diameter, which partially maintains bone strength. Bone resorption and bone formation processes continue, but resorption predominates, which is linked to increased osteoclast

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activity in trabecular bone. Trabeculae begin to thin, lose their layered structure, become cylindrical, and are destroyed if mechanical load persists.

Research data suggest that changes in estrogen levels are associated with the secretion of immune factors by mononuclear cells, and alterations in the local production of bone-forming cytokines may underlie changes in bone metabolism.

Conclusion. Melatonin has an optimizing effect on the renewal of jaw bone tissue. Continuous administration of the drug stimulates osteogenesis and enhances the functional and morphological reorganization of cells in the early stages of reparative regeneration. (8)

Regarding the treatment of osteoporosis, currently, there is no medication that completely cures the disease. The treatment of senile osteoporosis mainly involves managing low-energy fractures in patients with limited mobility, which slows down the bone regeneration process. However, **bisphosphonates** can be used as drug therapy, providing **anti-apoptotic effects** on osteoblasts through mechanisms involving **extracellular signal-regulated kinases (ERKs)** and **connexin 43 channels**. (11)

Scientific findings have confirmed that **melatonin levels decrease with age**, particularly during **menopause**. Therefore, restoring nighttime melatonin levels can positively affect bone health in menopausal women, as shown in studies. Melatonin increases bone density and accelerates new bone growth, targeting multiple stages of bone regeneration.

Moreover, melatonin improves sleep quality and psychological condition in middle-aged and elderly individuals. These attributes of melatonin may enhance the patient's overall condition, ultimately contributing to better health, as sleep disorders and increased depression are common symptoms reported by older and menopausal women, the populations most affected by **osteopenia** and **osteoporosis**.

In addition, melatonin's **availability over the counter** and its **low cost** make it especially beneficial from an economic perspective in promoting health.

Our objective is to study the effect of melatonin on **osteocytes** when sleep activity is disrupted and melatonin levels are reduced.

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