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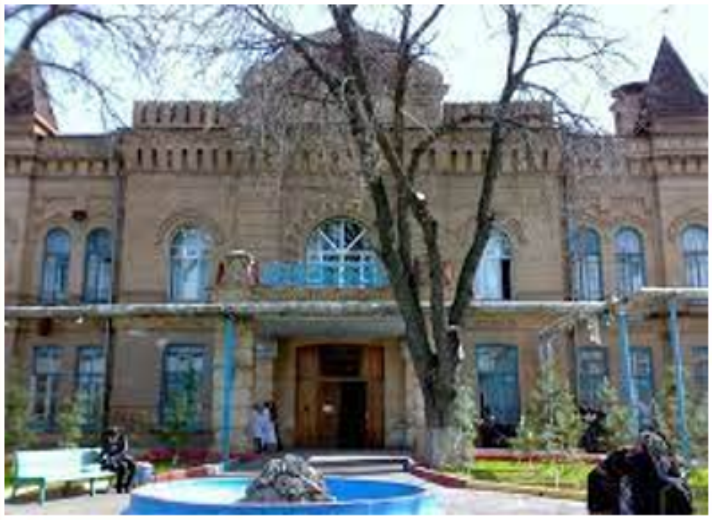

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The Role of Androgens in Osteoporosis

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ABSTRACT

Background. Osteoporosis in men is one of the most important medical and social problems. According to statistics, disability and death due to osteoporosis are 2 times higher in men than in women. But the problem of mineral disorders in men seems to remain somewhat secondary. Molecular mechanisms of changes in the bone system and the factors that affect them should be learned in detail, it is important to manage disorders of the bone system and to prevent them.

Materials. Databases were searched until February 23, 2019. A total of 34 articles were analysed including clinical trials and biological experiments. A planned meta-analysis was not possible because of heterogeneity and incomplete reporting of findings.

Conclusion. Bone remodeling consists of interrelated stages such as resorption and formation, in which osteoblasts, osteoclasts, and osteocytes together with immune cells and local cytokines participate. Beginning of remodeling begins once osteocytes receive physical load signals or due to endogenous factors (decreased calcium in the blood) due to parathormones. In this case, osteoclastogenesis is stimulated by osteocytes or osteoblasts. The continuous succession of resorption and formation processes, and bone formation in the resorbed amount, is carried out under the influence of stimulating factors such as colony-stimulating factor (KSF), activating ligand of NF-k receptor (RANKL), and inhibiting factors such as osteoprotegerin (OPG). The differentiation of osteoblasts increases under the influence of androgens, and androgens in physiological concentrations have the property of reducing the amount of PGE, whose synthesis is increased under the influence of IL-6 and parathormone.

Keywords: Osteoporosis, androgen deficiency, prostaglandin E, IL-6, parathyroid hormone

INTRODUCTION

Although modern medicine is conducting a lot of research on the bone system and its diseases and prevention, the problem of osteoporosis in men seems to remain somewhat secondary.

Osteoporosis in men is one of the most important medical and social problems. According to statistics, disability and death due to osteoporosis are 2 times higher in men than in women [1]. Osteoporosis in men occurs as a result of the complex interaction of various factors, including age-related sex hormone deficiency, genetic predisposition, and lifestyle [2].

Cellular mechanism of bone remodeling. This process consists of 2 processes that always go together - bone resorption and bone formation. Cells involved in bone remodeling are following [3]:

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A) osteoclasts are the only cells that resorb bone and are formed from myeloid cells in the bone marrow.

B) Osteoblasts are specialized bone-forming cells that have parathyroid hormone receptors and have the following properties in bone regeneration: expression of osteoclastogenic factors, production of bone matrix proteins, and bone mineralization Osteoblasts contain cells from different populations, including osteoblasts covering the bone surface, differentiated and mature osteoblasts at various levels [4]. Depending on the level of differentiation, osteoblasts perform different functions, immature osteoblasts direct osteoclastogenesis, while mature osteoblasts mainly provide bone matrix production and mineralization [5].

C) A certain population of osteocytes-osteoblasts, after terminal differentiation, become osteocytes, which are located in mineralized bone lacunae and have various protrusions, through which they communicate with other osteocytes and osteoblasts [6] these cells increase the load placed on the bone and, according to some scientists, induce the process of bone regeneration.

D) Immune cells. T and B lymphocytes also participate in normal bone formation, as evidenced by the development of osteoporosis in mice with low numbers of B or T lymphocytes. [7] More than 50% of bone marrow-derived OPG (osteoprotergin) is produced by B-lymphocytes (the importance of OPG is discussed in detail in the molecular mechanism), the exact molecular mechanism of T-lymphocytes is not well known, but experimentally, the number of T-lymphocytes is low. development of osteoporosis in mice confirms its involvement in bone formation [8].

Molecular mechanism of remodeling process. Bone resorption takes place in the multicellular bone unit (MBU) and consists of an interconnected process of resorption and formation. [9]

The process initially begins with activation, which may involve the following mechanisms:

1) osteocytes generate biological signals when the load on the bone increases [10] and stimulates osteoclastogenesis, and when there is damage to the bone, osteocytes undergo apoptosis and osteoclastogenesis is activated [11], because normally, osteocytes produce TGF-, which inhibits osteoclastogenesis, and apoptosis causes a decrease in the amount of this substance, and osteoclastogenesis is activated [12].

2) PTH - parathormone responds to the homeostasis of calcium in the blood, and when the amount of calcium in the blood decreases, it acts on PTH receptors in osteoblasts, activates protein kinase A, protein kinase C and intracellular calcium channels, attracts osteoclast procusors and ensures the differentiation and activity of osteoclasts [13]. Thus, osteoblasts attract and activate osteoclasts to the bone remodeling site due to signals from osteocytes or endocrine changes. As a result of the effect of PTG on osteoblasts, they produce a chemoattractant that attracts osteoclasts, and also stimulate the production of KSF, RANKL, and the expression of OPG decreases.These molecules have following functions: KSF-1 ensures the proliferation and active state of osteoclasts.

RANKL binds to RANK receptors on osteoclasts and ensures their differentiation and activation. [14]

OPG is a receptor for RANKL, a soluble molecule that binds and inactivates RANKL and inhibits osteoclastogenesis. Thus, osteoglastogenesis increases due to increased synthesis of RANKL, KSF, decreased expression of OPG. Also, in response to mechanical stress or endocrine [15] changes, osteoblasts produce matrix meta-proteinases (MMPs), which break down unmineralized osteoid tissue on the bone surface, making room for osteoclast adhesion, the osteoclasts attached there create a microenvironment and produce H+ ions, in which the mineralized matrix begins to dissolve in an acidic environment and forms the resorption lacunae of Hovship. The organic matrix of the bone is dissolved in the presence of collagenases, these enzymes are active in a highly acidic environment (in particular, Cathepsin K). [16]

Even after resorption of osteoclasts, undigested collagen residues remain and are broken down by reversal cells and a place is prepared for bone formation. The cell type of reversal cells is controversial. point out that because reversal cells have the morphological features of these two groups of cells, this requires further research [17].

Bone formation phase. Although the molecular mechanism of bone resorption has been studied in great detail, the process of bone formation is still not fully understood. are explained as a process, these mechanisms will be explained below. Initially, it was thought that growth factors that stimulate formation are released from the bone matrix during the resorption process, such as insulin-like growth factor (IGF) and TGF-beta [18], but formation occurs even in the presence of osteoclasts that cannot resorb bone, and then the formation process occurs. it was concluded that osteoclasts activate.

Several mechanisms have been proposed for osteoclasts to produce osteoblast-activating factor and initiate the formation process.

1) sphingosine 1-phosphate is produced by osteoclasts and attracts osteoblasts to the site of resorption and accelerates their maturation [19].

2) Osteoblasts have EphB4 receptors, which under the influence of the ephrin-B2 ligand present in osteoclasts, enhance the differentiation of osteoblasts, and also inhibit osteoclastogenesis by inhibiting resorption by opposing binding, this mechanism explains the process better because it is bidirectional, but always osteoclasts and osteblasts do not contact each other, so both sphingosine and EphB4–Ephrin-2 mechanisms may be required for this process. Activated osteoblasts attracted to lacunae synthesize osteoid-organic bone matrix consisting of organic compounds, and hydroxylapatite is absorbed into this tissue and mineralized. The process ends when sufficient bone tissue is formed in place of the destroyed bone. The mechanism in this process is not fully understood, and there are opinions that osteocytes participate in it. At the end of the process, osteoblasts undergo apoptosis or become osteocytes [20].

Effects of androgens on bone metabolism. Above, we considered the cellular and molecular mechanisms of the bone regeneration process, now we will focus on how androgens affect this process.

Effects of androgens on bone cells. The main circulating androgen is testosterone, which can be converted to dihydrotestosterone (DGT) by 5-alpha reductase in peripheral tissues or to Estradiol (E2) by aromatase enzyme, (AR) [21].

Depending on the local action of the enzyme 5-alpha reductase or aromatase, testosterone can act on androgen receptors (AR) or estrogen receptors in bone [15]. Osteoblasts and osteocytes have androgen receptors, cortical bone osteoblasts have a higher sensitivity to androgens than trabecular bone osteoblasts [22]. Testosterone and estradiol are important in maintaining bone formation and strength in both men and women. Osteoblasts and osteocytes have ERα and ERβ receptors, and osteoclasts also have these two types of receptors, and AR has not been detected [23]. However, testosterone has a direct inhibitory effect on osteoclast differentiation, while the inhibitory effect of E2 is indirect through osteoblasts [24]. Also, Rochira and his colleagues observed the effect of testosterone and testosterone+estradiol in men with mild hypogonadism and aromatase deficiency for 7 years. He concluded that estradiol increased bone mineral density more when used with testosterone than when testosterone was used alone. He concluded that estradiol increased bone mineral density more when used with testosterone than when testosterone was used alone. The effect of androgens on bones is realized through 3 factors: TGF-beta, IGF (insulin-like growth factor) and IL-6. Androgens stimulate TGF-beta, IGF, which increases bone formation, and suppress IL-6, which stimulates osteoclastogenesis [26].

Testosterone increases trabecular and cortical bone mass in androgen-deficient adolescents [27]. In one study, testosterone increased bone mineral density by 20% in the first year in androgen-deficient older men. In a study of men over 65, testosterone therapy increased bone mineral density by 10.2% over 3 years [28].

Effects of androgens in eugonadal males. The effect of testosterone is more pronounced in eugonadal men. Testosterone's effect on bone mineral density is more effective when administered intramuscularly than when administered transdermal, and higher doses of testosterone are required to achieve a positive effect. In men over 65 years of age, transdermal testosterone administration did not increase bone density [29], while intramuscular testosterone increased bone mineral density in osteoporotic patients. However, dangerous side effects of testosterone therapy, such as polycythaemia, sleep apnoea, benign prostatic hyperplasia, and prostate tumours, limit its use in men without androgen deficiency. During bone remodelling, ERα is necessary for the growth of long bones, AR receptors have a positive effect on periosteal bone growth, and ERα has a negative effect.

Effects of androgens on parathyroid hormone and IL-6 function. To understand the effect of androgens on parathormone function, let's look at the effect of parathormone on bone metabolism. Parathyroid hormone is produced by the thyroid gland and its main function is to maintain calcium homeostasis in the blood by increasing calcium excretion from bones, increasing intestinal calcium absorption and decreasing renal calcium excretion [30]. The effect on bones is through the following mechanism: parathyroid hormone binds to PTH receptors in stromal cells and preosteoblasts. PTH receptor activation increases RANK-ligand expression and inhibits OPG and enhances osteoclastogenesis, as well as the local and systemic synthesis of IL-6 [31]. Under the influence of these two peptides, osteoclasts are differentiated, activated, and attracted to the resorption area, and the resorption process begins. Also, under the influence of parathyroid hormone, the synthesis of PGE (prostaglandin E) from osteoblasts covering the bone surface increases, and PGE has a two-phase effect on bone formation. At a relatively low concentration and in the presence of glucocorticoids, it increases bone forma-

tion by increasing the replication and differentiation of osteoblasts.

However, in high concentrations and in the presence of IGF, it stimulates osteoclast genesis and increases bone resorption [32]. Thus, PTH enhances bone resorption and catabolic effects through the above mechanisms but is currently being used to treat severe osteoporosis in postmenopausal women by intermittent administration of PTH, in which daily intermittent administration increased bone mineral density and bone mass, although the exact molecular mechanism of this process is currently not fully understood, the effectiveness of PTH in osteoporosis due to its anabolic effect has been confirmed in several animal experiments as well as in human clinical trials [33].

Experiments also show that androgens have the property of reducing the catabolic effect of PTG on bone, which is mainly related to the reduction of the amount of PGE stimulated by PTH. the same 2 peptides were added to the control cultures that were not treated with T and DHT, according to the obtained results, PTH increased the amount of PGE in the control groups by an average of 9 times, in the control group, testosterone reduced the synthesis of PGE by 50%. IL-1 increased it by an average of 20-22 times, and testosterone and DGT reduced it by 60% and 70%, respectively, and T and DHT did not reduce the calcium release from bone by PTH, but the amount of calcium released by IL-1 was 20-30 reduced by %. This suggests that, apart from direct effects on bone cells, androgens can reduce PTH- and IL-1-induced PGE production in vivo, but not PTH-induced calcium release [34].

CONCLUSION

Although the consequences of osteoporosis in men have a worse prognosis than in women, many molecular mechanisms in men are not yet fully understood.

According to currently known information, androgen and estradiol are important in men and women. Also, the specific characteristics of the skeleton in men are realized through androgen receptors. Also, androgens have the ability to reduce the amount of PGE, whose synthesis is increased due to inflammatory mediators Il-6 and parathormone, which is not possible in cases of androgen deficiency.

This process has been proven in animals and has not been confirmed in clinical experiments, the full study of this mechanism will allow the development of more effective methods of treating osteoporosis in men.

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OSTEOPOROZDA ANDROGENLARNING ROLI

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Abstrakt

Dolzarbligi. Erkaklarda osteoporoz muammosi muhim ijtimoiy va tibbiy muammolardan biri hisoblanadi. Statistik ma'lumotlarga qaraganda erkaklarda osteoporoz ayollarga qaraganda kam uchrasada, osteoporoz tufayli nogironlik va o'lim ko'rsatgichlari erkaklarda ayollarga qaraganda 2 barobar ko'p uchraydi.

Materiallar. 2018 –yil 23-fevralga qadar bo'lgan ma'lumotlar o'rganib chiqildi. Ja'mi 34 ta klinik va biologik tajribalar natijalari tahlil qilindi. Tajribalar, obyekti va usullari turli xil bo'lganligi sababli meta-analiz o'tkazilmadi.

Xulosa. Suyak remodelizatsiya rezorpsiya va formatsiya kabi o'zaro bog'langan bosqichlardan iborat bo'lib, bunda osteoblastlar, osteoklastlar, osteositlar bilan birgalikda immun hujayralar va mahalliy sitokinlar ishtirok etadi, remodelizatsiya boshlanishi osteositlar tomonidan jismoniy yuklama signallari qabul qilinganda yoki endogen faktorlar tufayli (qonda kalsiyning kamayishi) paratgormonlar tufayli amalga oshadi. Bunda osteoklastogenez osteositlar yoki osteoblastlar tufayli stimullanadi. Rezorbsiya va formatsiya jarayonlarining doimo ketmaket kelishi, va rezorpsiya qilingan miqdorda suyak hosil bo'lishi, koloniya stimullovchi faktor (KSF), NF-k reptseptorining aktivlovchi ligand (RANKL) kabi stimullovchi, osteoprotergin (OPG) kabi ingibirlovchi faktorlar ta'sirida amalga oshadi. Shuningdek, bu jarayonga bir qator endogen moddalar ham ta'sir etadi, xususan androgenlar ta'sirida osteoblastlar differensiyatsiyasi kuchayadi, shuningdek, androgenlar fiziologik konsentratsiyalarda IL-6 va paratgormon ta'sirida sintezi kuchaygan PGE miqdorini kamaytirish xususiyatiga ega. Bu jarayonni molekular mexanizmlarini yaxshi tushunish, erkaklardagi osteoporozni davolash imkoniyatlarini kengaytiradi, chunki androgenlar defitsit hollarda androgenlarni qo'llash, turli xil xavfli nojo'ya ta'sirlarini keltirib chiqarishi mumkin, shuning uchun bu masala dolzarb masalalardan hisoblanadi.

Kalit so'zlar: osteoporoz, androgen defitsiti, prostaglandin E, IL–6, paratgormon.

РОЛЬ АНДРОГЕНОВ В ОСТЕОПОРОЗЕ

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Абстракт

Актуальность. Остеопороз у мужчин является одной из важнейших медицинских и социальных проблем. Согласно статистике, инвалидность и смертность из-за остеопороза у мужчин в 2 раза выше, чем у женщин.

Материалы. Поиск по базам данных проводился до 23 февраля 2019 года. Всего было проанализировано 34 статьи, включая клинические испытания и биологические эксперименты. Запланированный мета-анализ был невозможен из-за неоднородности и неполного представления результатов.

Заключение. Ремоделирование кости состоит из взаимосвязанных стадий, таких как резорбция и формирование, в которых участвуют остеобласты, остеокласты, остеоциты вместе с иммунными клетками и местными цитокинами. Начало ремоделирования начинается, как только остеоциты получают сигналы о физической нагрузке или из-за эндогенных факторов (снижение содержания кальция в крови) из-за парагормонов. В этом случае остеокластогенез стимулируется остеоцитами или остеобластами. Непрерывная последовательность процессов резорбции и формирования, а также формирование кости в рассасываемом количестве осуществляется под влиянием стимулирующих факторов, таких как колониестимулирующий фактор (KSF), активирующий лиганд рецептора NF-k (RANKL) и ингибирующих факторов, таких как остеопротергин (OPG). Метаболизм костной ткани контролируется местными факторами и гормонами. Андрогены играют важную роль в метаболизме костной ткани как у мужчин, так и у женщин. Дифференцировка остеобластов усиливается под влиянием андрогенов, а андрогены в физиологических концентрациях обладают свойством снижать количество PGE, синтез которого повышается под влиянием IL-6 и парагормона.

Ключевые слова: остеопороз, дефицит андрогенов, простагландин E, IL-6, паратиреоидный гормон.