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Modern Methods of Diagnosis of Osteoporosis, Advances in Treatment and Solutions to Existing Problems

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Abstract: Due to its severity, duration and progression, osteoporosis is considered a "silent" disease of the 21st century, posing a threat to public health. It mainly affects postmenopausal women and the elderly. An imbalance between resorption and bone formation is a sign of osteoporosis. It is diagnosed using densitometry and double radiography. Various aspects are taken into account in the treatment of this disease. On the other hand, pharmacological treatment approaches include the use of antiresorptive drugs, as well as new approaches to regenerative medicine, such as cell therapy and the use of bioactive hydrogels. However, non-pharmacological treatments require lifestyle changes, such as diet, physical activity, and giving up bad habits such as smoking or excessive alcohol consumption. This review examines the biology of bone tissue and existing methods of diagnosis and treatment of osteoporosis, as well as new approaches. Dual-energy X-ray absorptiometry and a fracture risk assessment tool are the most widely used methods. Since they have limitations, alternative technologies have been proposed. Here is an overview of the currently used and new approaches to the diagnosis of osteoporosis.

Keywords: Dual-energy X-ray absorptiometry, Wnt signaling pathway, antiresorptive drugs, resorption activity, cathepsin K inhibitors.

Introduction. The awns support the structure during movement, protect internal organs, accumulate calcium and phosphates and produce hormones that control mineral and energy metabolism. Although the ratio of cortical and trabecular tissues in bone mass varies depending on its strength, the total bone mass consists of about 80% of these two tissues. For example, there is more cortical tissue in long bones than in vertebrae. Spongy bone has a higher metabolic resorption activity than cortical bone, and it is less dense, flexible and brittle [1,2,3,4]. Bones are constantly being rebuilt (resorbed and regenerated), which helps the skeleton heal fractures and adapt to new loads. Osteoporosis develops as a result of excessive resorption, in which the microstructure of bones deteriorates. Osteoporosis usually does not show symptoms in the early stages and is most often diagnosed after injuries caused by the disease. To prevent fractures, technologies have been developed that can identify at-risk groups and offer them treatment. In addition to analyzing the interaction of various energy stimuli with bone tissues, statistical models were used to assess various clinical risk factors. Due to its consequences for public health, this condition has been dubbed "the silent epidemic of the 21st century." It is the most prevalent of the metabolic bone diseases and is severe, chronic, progressive, and clinically silent. Osteoporosis is divided into two main types: primary and secondary. Primary osteoporosis includes idiopathic osteoporosis in children and young adults with unknown etiopathogenesis. Involutional osteoporosis affects men and women and is more often associated with aging. Type I osteoporosis is also called postmenopausal osteoporosis [5-12]. Type II, or senile osteoporosis, occurs in people over 75 years of age and is characterized by loss of trabecular and cortical bone as a result of aging. Secondary osteoporosis, which accounts for less than 5% of osteoporosis and is caused by medications or diseases, accounts for the most common. Postmenopausal osteoporosis, which is associated with two conditions, menopause and aging, is the most common type of osteoporosis [13,14,15].

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Among the population over the age of 50, the percentage of men and women with osteoporosis is 16.0% and 29.9%, respectively, in the United States. 200 million women suffer from osteoporosis. In the European Union, this is 6.8% and 22.5%, in Australia — up to 7% and more than 23%, in China — 6.46% and 29.13%. In Latin America, the number of hip fractures in women and men aged 50 to 64 is projected to increase by 400 percent from 1990 to 2050. An increase of 700 percent is projected for the population over 65 years of age. More than 10 million people in Brazil suffer from osteoporosis, which is one in 17 people. However, only a third of patients with osteoporotic hip fracture receive a diagnosis and only a fifth receive treatment [16,17,18,19]. In 2015, more than 2 million osteoporosis-related fractures were reported among Medicare (American Health Insurance Fund) participants. Spending is expected to exceed $95 billion by 2040, with an estimated $57 billion in 2018. Such estimates take into account aging and an increase in the number of fractures in osteoporosis. In six European countries (France, Germany, Italy, Spain, Sweden and the United Kingdom), up to 3 million fractures occur annually with associated health care costs of more than $40 billion. By 2030, spending is expected to increase by more than 23% to about $52 billion [20,21,22,23].

In most people, osteoporosis is diagnosed only after a fracture due to its severe course. Such fractures cause long-term health problems. Its impact on the world is increasing due to an aging population, which requires global efforts to prevent bone fractures. Screening to identify at-risk groups who are indicated for treatment, including vitamin D and calcium intake, can reduce the social and economic burden. Bone densitometry is a common method of diagnosing osteoporosis. WHO has proposed dual-energy X-ray absorptiometry (DXA) as the gold standard of measurement. Based on these measurements, osteoporosis is diagnosed and the risk of fractures is assessed. WHO also recommends exploring other technologies for these purposes. Currently, there is no generally accepted policy in Europe aimed at identifying patients at high risk of fractures [24,25,26,27].

Therefore, there is a clear need to develop technologies that complement existing methods of diagnosing osteoporosis in order to improve results and reduce technology costs in order to ensure broad coverage. Unlike other reviews, this study focuses on modern methods of diagnosing osteoporosis, as well as technologies that have been developed to reduce the cost of examinations and improve the treatment of the disease. In this way, the reader will learn about current trends and efforts to develop technologies for bone health assessment.

The purpose of this review is to provide a theoretical overview of the biology of bone tissue, as well as existing methods for the diagnosis and treatment of osteoporosis, including new approaches.

Diagnosis of osteoporosis and assessment of the probability of fractures. Currently, the diagnosis of osteoporosis mainly depends on the assessment of bone mass using densitometry (DEXA). Despite the fact that osteoporosis is not only an indicator of densitometry, it also allows you to quantify bone tissue, which is used as a diagnostic criterion and is considered a prognostic indicator of fracture risk. This makes assessment the best strategy for assessing the rate of bone loss and for controlling the development of the disease [25,26,27]. According to the WHO expert committee, MPC values are classified as follows: The norm includes MPC above 1 standard deviation; osteopenia includes MPC from 1 standard deviation to 2.5 standard deviation; osteoporosis includes MPC less than 2.5 standard deviation; and established osteoporosis includes MPC less than 2.5 standard deviation plus fracture due tofor the fragility of the bones. For this classification, the T index, also known as the t-value, was used, which is the number of standard deviations that are higher or lower than the average MPK in healthy young people of the same sex [28,29,30]. In clinical practice, various diagnostic tests are also used to monitor the treatment of osteoporosis. Dual-energy X-ray absorptiometry is the most recommended method for diagnosing osteoporosis, as it allows you to predict the risk of fractures, prescribe therapy and monitor its effectiveness. Bidirectional X-ray absorptiometry measures the mineral density of the axial bones (spine and hip joint) by passing a beam of X-ray photons with two energy peaks through the patient's body. This allows you to estimate the calcium content in the bones. A study conducted in postmenopausal women showed a relationship between BMD and fracture risk, and the t-score was -2.5 [31,32,33,34]. In a recent study, the results of densitometry were compared with the assessment of MPC using Hounsfield units (HU) in computed tomography (CT). In this study,

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it was shown that the HU of the articular cavity and the proximal humerus can be reliably measured and compared with the results of densitometry of patients. Earp et al. (2021) found that using opportunistic Hounsfield values obtained by computed tomography of the shoulder for other purposes may help to detect abnormal bone density earlier. This provides an additional method of detecting patients who may benefit from further diagnostic examination and possible treatment. This first-of-its-kind study demonstrates the fantastic prospects of a new method for diagnosing osteoporosis using computed tomography [28,29,30,33,34,35].

Osteoporosis treatment and innovative methods. Taking prescription medications, taking calcium and vitamin D supplements, and lifestyle changes can be part of the treatment of osteoporosis. In most cases, patients are prescribed medications as a treatment for osteoporosis. They can be extremely effective in treating this disease and can significantly change people's lives, as they help strengthen bones gradually and prevent fractures. Osteoporosis can be the result of rapid bone loss as a result of decreased estrogen levels for several years after menopause. Hormone replacement therapy (HRT) is a method that some people can use to make up for estrogen deficiency [11,14,17,21,22]. Osteoporosis largely requires an integrated approach that includes both traditional and innovative treatment methods. Behaviors and environmental factors such as smoking, alcohol consumption, diet, and exercise remain important in the non-drug treatment of this disease. Calcium and vitamin D supplements are still relevant from a pharmacological point of view. Antihormonal and antiresorptive pharmacological drugs are newer treatments, and doctors should prescribe them with caution, taking into account possible side effects. Romozozumab, a monoclonal antibody targeting sclerostin, is one of the new treatments that show positive results in stimulating bone formation and reducing bone resorption [30,31,32,33,34,35].

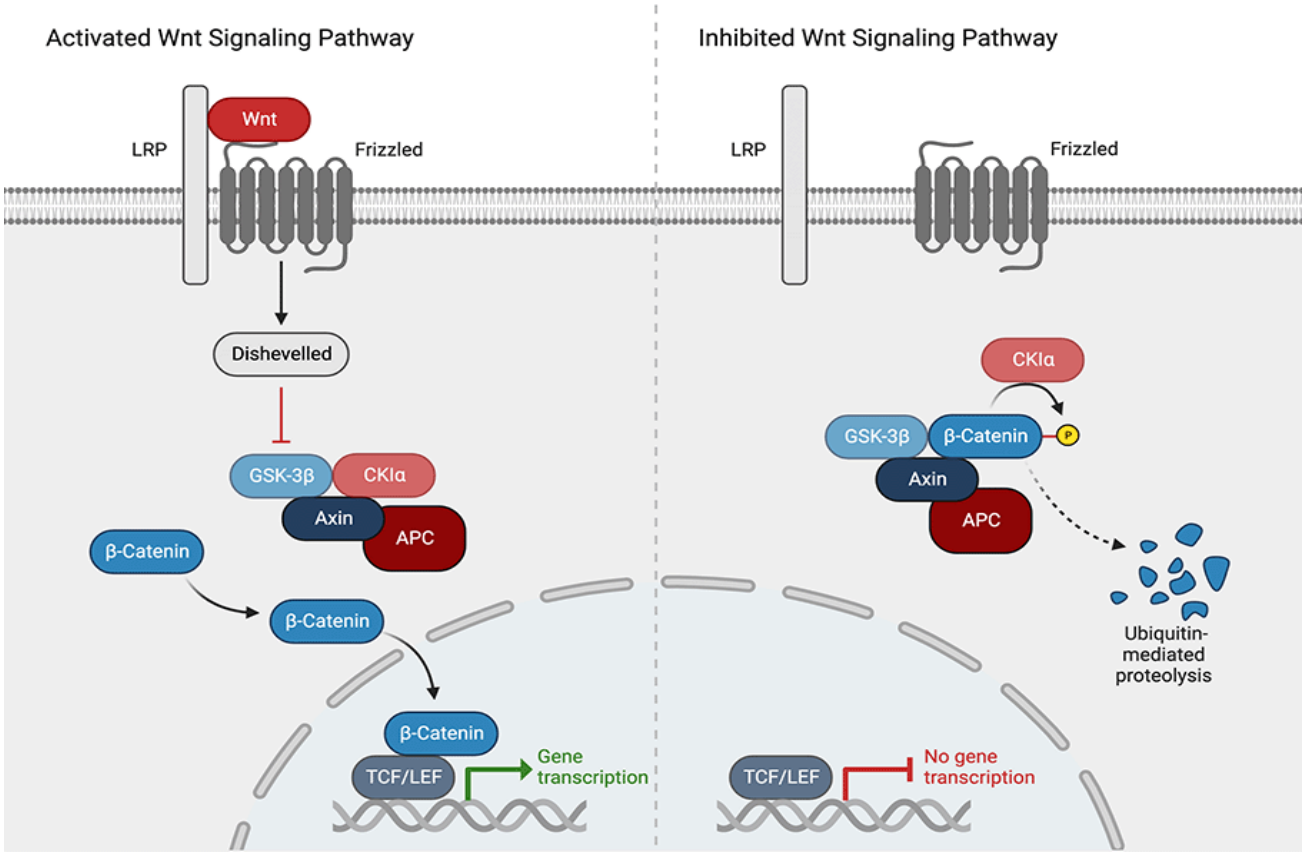

Figure 1. Wnt signaling pathway, potential agents and targets.

Secreted glycoproteins modified by lipids activate the Wnt signaling pathway of the BHT. They can take effect through canonical or non-canonical pathways when they bind to receptors on the cell surface. The canonical path prevails in bone formation. A protein associated with low-density lipoprotein receptors (LDPE), single-pass transmembrane receptors 5/6 and the seven-membrane Frizzled signaling receptor (FZD) make up the receptors of various Wnt in the canonical pathway.

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Neutralization of Wnt ligands or blocking their binding to the LRP/FZD receptor can be used by Wnt antagonists to block the canonical Wnt signaling pathway. Inhibitory factor Wnt 1 (WIFI-1) and sftp, for example, Wnt antagonists, prevent ligands from binding to their respective receptors. WIW1 has an extracellular portion of Wnt transmembrane receptors of the Derailed/Ruk class. It has the ability to restrain Wnt activity during OB differentiation and maturation. However, overexpression of IGF-1 causes canonical Wnt signaling and reduces the ability of resident hematopoietic stem cells to self-renew, which means that it is not suitable for controlling bone formation [18,19,24,31,32,33,35].

Discussion. Due to the imbalance between resorption and bone formation, osteoporosis is a severe, chronic, progressive and clinically asymptomatic disease. Despite the fact that osteoporosis has no obvious clinical signs, patients begin to show certain symptoms and signs, such as pain, deformity or reduced growth. The most common consequences of osteoporosis are fractures due to bone fragility, which most often occur in the vertebrae, hip joints and forearms. Although the diagnosis using methods such as bone densitometry and double radiography has been successful, more in-depth studies are needed [1,4,5,6,11]. The treatment of osteoporosis approved by the FDA mainly involves the use of drugs aimed at reducing bone resorption. The latest drugs have been developed through improved understanding of markers, cellular events, and genetic targets of osteoporosis. Thus, new targets for the treatment of osteoporosis, such as cathepsin K inhibitors or antisclerostin therapy, are being studied. However, ideal treatments for osteoporosis have not yet been developed due to their serious side effects, which limit their long-term use. Regenerative medicine is currently at the center of intensive research to address these issues [11,12,13,15,16]. Due to their ability to stimulate the immune system and their involvement in bone repair, MSCs are expected to be one of the new therapeutic approaches. MSCs can contribute to bone formation after transplantation for two reasons: either due to their ability to penetrate into tissues and differentiate into osteogenic cells, or due to the secretion of specific growth factors that accelerate bone remodeling processes and prevent bone loss. In addition, MSC is used as the main treatment method in clinical trials. Further evaluation of the results of these studies will give us information about the safety, tolerability and effectiveness of transplanted cells and will allow us to study their therapeutic effect in osteoporosis [17,18,19,20].

Antiresorptive drugs, especially bisphosphonates, are currently the main treatment for OP in most developing countries. However, the limitations and side effects of these drugs have to some extent contributed to the development of anabolic drugs such as romozomumab and teriparatide. It is possible to consider the possibility of sequential or combined treatment, in which anabolic agents are used as the first drugs, in patients with a high or very high risk of fractures. Significant efforts have been made to develop next-generation drugs with maximum efficacy and minimal toxicity; a deeper understanding of the interaction of various signaling pathways in the pathogenesis of osteoporosis may help achieve this goal [16,17,18,19,20]. Maintaining the health of the musculoskeletal system is becoming increasingly important as the population ages. Doctors of all specialties who provide medical care to adults can help their patients continue to live healthy and independently by applying recommended fracture risk assessment methods, pharmacological treatment, risk reduction counseling and long-term follow-up. At the same time, other approaches are being explored to enhance stem cell activity; these methods include gene modification, the use of extracellular vesicles, and a combination of cells and hydrogels. In the future, these may be new therapeutic approaches in clinical practice. In addition, there are non-pharmacological treatments for osteoporosis associated with lifestyle factors to prevent further fractures in osteoporosis. Eating habits, such as maintaining adequate levels of vitamin D and calcium in the body, regular physical activity with a load on bones, and quitting smoking and alcohol, are important elements of a lifestyle [21,2,23,24,25].

Conclusions. Despite significant advances in recent years, the prevention and treatment of osteoporosis and related fractures continue to be an unresolved medical problem. Understanding the molecular processes underlying the pathogenesis of osteoporosis, including the epigenetic regulation of the Wnt signaling pathway, can help in the development of new drugs with higher levels of efficacy and fewer side effects.

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The aging of the population requires the development of new technologies to improve the treatment of concomitant diseases in order to reduce health care costs and ensure quality of life. Since osteoporosis begins at an earlier age, new treatments will have a significant impact in this situation. The main challenge is to develop low-cost technology for accurate diagnosis so that low-income countries can use it.

It is also required that this technology can be integrated into portable devices to help remote populations. The reliability of quantitative indicators to support diagnosis is also crucial. Thus, the technology becomes independent of the availability of diagnostic experts.

In addition, there are non-pharmacological treatments for osteoporosis related to lifestyle factors to prevent further fractures in osteoporosis. Eating habits such as maintaining adequate levels of vitamin D and calcium in the body, regular physical activity with a load on bones, and quitting smoking and alcohol are important components of a lifestyle.

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