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BIOCHEMICAL MEDIATORS IN OSTEOPOROSIS

Polyana Keyla Ferreira Neves
Graduated in Nursing by the institution: Centro Universitário Uninovo. Olinda, Pernambuco, Brazil
http://lattes.cnpq.br/4183937816118585

Gisely Brenda Rodrigues da Silva
Nurse by institution: Centro Universitário Uninovo. Olinda, Pernambuco, Brazil
http://lattes.cnpq.br/9835460195017329

Jéssica Andréia Pereira Barbosa
PhD in Biological Sciences from the institution: Universidade Federal de Pernambuco (UFPE). Recife, Pernambuco, Brazil
http://lattes.cnpq.br/9714576747578601

Marize Conceição Ventin Lima
Master in Nursing by the institution: Universidade de Pernambuco (UPE)/"Universidade Estadual da Paraíba" (UEPB). Recife, Pernambuco, Brazil
http://lattes.cnpq.br/2998182683790208

Marllon Alex Nascimento Santana
PhD in Biological Sciences by the institution: Universidade Federal de Pernambuco (UFPE) and Professor at the institution's Health Center: Centro Universitário Uninovo. Recife, Pernambuco, Brazil
http://lattes.cnpq.br/6480438283722441

Abstract: Introduction: Osteoporosis (OP) is a silent and multifactorial disease that causes a decrease in bone mineral density (BMD), being related to osteometabolic disorders that may be associated with some biochemical mediators, such as the reduction or shortage of minerals, vitamins and hormones. that are important in the maintenance of bones, such as calcium (Ca^2+), vitamin D, parathyroid hormone (PTH), calcitonin and collagen. Laboratory tests are essential for an early, quick and accurate diagnosis so that the individual can initiate the necessary treatment by regulating the levels of biochemical mediators, preventing the progression of the disease and, consequently, the decrease in bone mass. **Objective:** Group research in order to address the main biochemical mediators that can cause changes in bone tissue, helping to identify the development, diagnosis and treatment of OP. **Methodology:** Narrative review of the literature. Articles published in the period between 2015 and 2020, in a free and complete version, in the databases: Scientific Electronic Library Online (SCIELO), Medical Literature Analysis and Retrieval System Online (MEDLINE) via Pubmed and Virtual Health Library (BVS) were selected. **Results:** For the construction of the theoretical framework, 28 articles were used, since they addressed the definition of OP, pathophysiology, statistics, risk factors and biochemical mediators associated with the prevention of the pathology. **Final considerations:** OP is a public health problem, requiring greater interest in preventing this disease by regulating important mediators, such as minerals, vitamins and hormones.
Keywords: Osteoporosis. Biochemistry. Metabolism. Bone Tissue.

INTRODUCTION

Osteoporosis (OP) is an osteometabolic disorder caused by a decrease in bone mineral density (BMD) due to intrinsic conditions, such as the natural factors and endocrine changes, as well as extrinsic causes that are characterized by the lifestyle adopted by the individual. FANARO, 2016). The people most affected by OP, and consequently susceptible to fractures, are the elderly, postmenopausal women, excessive caffeine consumers, sedentary people and individuals who adopt hyperprotein diets and low in calcium (Ca^2+) (ANDRADE, 2015; OSELAME et al., 2016).

Bone tissue is composed of essential cells such as osteoblasts, osteoclasts and osteocytes, which are responsible for the frequent renewal of bone mass, carrying out the constitution, destruction and restructuring of the bone matrix, respectively. If there is instability during the bone repair cycle, such as an increase in osteoclast action and a decrease in osteoblast action, they lead to an increase in BMD loss, resulting in bone damage and, consequently, the development of OP (SILVA et al., 2017).

The progression of OP is associated with osteometabolic disorders, which may be linked to some biochemical mediators, such as the decrease or shortage of minerals, vitamins and hormones that are important in the maintenance of bones, such as Ca^2+, vitamin D, calcitonin, parathyroid hormone (PTH) and collagen. Therefore, it is of great importance that these mediators are regulated so that the development of the disease does not occur, aiming at prevention and even treatment (BELLAN, PIRISI, SAINAGHI, 2015; PORFÍRIO, FANARO, 2016; YAZDANI et al, 2019).

Initial verification is required through levels of calciuria, Ca^2+, serum vitamin D, thyroid function, alkaline phosphatase and phosphorus, as they are essential for an early, rapid and accurate diagnosis, allowing the individual to initiate treatment, preventing the progression of the disease. OP and the decrease

in bone mineral density (RADOMINSKI et al, 2017).

In Brazil, the estimate of the development of OP varies with age, being 0.1% (between 18 and 24 years old), evolving to 27.7% (from 80 years old) (CAMARGOS, BOMFIM, 2017). In mid-2010, the Unified Health System (SUS) spent around BRL 81 million due to examinations and treatments performed by patients with OP, including serious situations of falls and bone ruptures. It is estimated that per year, hip fractures must reach 160,000 by 2050, which is a worrying situation, since it results in a major public health problem (STOLNICKI, OLIVEIRA, 2016).

The aim of this study is to bring together research from the literature in order to address the main biochemical mediators that can cause changes in bone tissue, helping to identify the development of OP. In addition, the investigation of these biochemical mediators is relevant in the diagnosis and treatment of the disease, allowing a prior and effective result to establish the appropriate therapeutic method through the regulation of minerals, vitamins and hormones.

METHODOLOGY

This is a narrative literature review, based on searches carried out from April 2020 in the databases of available electronic libraries: Scientific Electronic Library Online (SCIELO); Medical Literature Analysis and Retrieval System Online (MEDLINE) via Pubmed and Virtual Health Library (VHL), where 28 articles were selected for the construction and foundation of the theoretical framework, using the following descriptors: Osteoporosis. Biochemistry. Metabolism. Bone Tissue.

The inclusion criteria used were: articles that addressed the development process of Osteoporosis, concept, statistics, risk factors and biochemical mediators associated with the prevention of the pathology, in a free and complete version, published in the period between 2015 and 2020, with no language restriction. As for the exclusion criteria, the following methods were adopted: disregarded articles whose theme was not associated with the objectives proposed in the study, incomplete and non-free texts, published prior to the year 2015, as well as those that were not presented as articles.

DEVELOPMENT

Bone connective tissue, produced from mesenchyme, consists of blood and lymphatic vessels, nerves, osteogenic cells (osteoblasts, osteoclasts and osteocytes) and bone matrix. The formation of bone tissue takes place through three stages that take place at the same intensity and in a respective manner. Initially, the synthesis of demineralized collagen occurs, with the aim of originating an osteoid matrix (previously demineralized bone mass), later the matrix undergoes differentiation, where it becomes mature. Finally, there is a reduction in collagen production, helping in the process of constant mineralization until the matrix becomes intact. However, for the last stage of the cycle of formation of bone tissue to occur, it is necessary that there is an association of phosphate(PO_4^{-3}) and calcium (Ca^{2+}), since it allows the development of hydroxyapatite crystals that later join collagen in order to provide resistance to the bone (MOREIRA, DEMPSTER, BARON, 2019).

Osteoblasts are responsible for remodeling the bone matrix, while osteoclasts are responsible for absorbing the destroyed tissue through the excretion of proteolytic enzymes, which are made possible by lysosomes and acids such as citric and lactic (FARIAS, LAGO, ANDRADE, 2015). Osteocytes are another cell type that participate in bone remodeling, having microfilaments that allow interaction with other bone cells, manipulating osteoclasts to regions where bone tissue

restructuring is required (MOREIRA, DEMPSTER, BARON, 2019). During life, the bone matrix is continuously renewed through the harmonic action of osteoblasts, osteoclasts and osteocytes that enable the maintenance and consolidation of the skeleton. Osteoblasts are capable of synthesizing specific cytokines (M-CSF, osteoprotegerin (OPG) and RANKL) that help in the formation and differentiation of osteoclasts. Thus, when there is a decrease in these components, there is consequently an attenuation in the amount of osteoclasts, making it impossible to destroy the aged tissue, leading the individual to develop OP (CHEN et al, 2018).

To carry out reabsorption, osteoclasts move and attach to the bone matrix through podosomes, which are structures that facilitate their mobility and stability during activity. With the presence of hydroxyapatite crystals, osteoclasts absorb tissue through processes such as proteolysis and acidification. After the digestion that occurs in the extracellular environment, the remnants of metabolism are stored intracellularly or taken to the basolateral region, where they are discarded (MOREIRA, DEMPSTER, BARON, 2019).

Through cytoplasmic filaments, osteocytes are located in the bone cavity and perform interactions with osteoblasts and osteoclasts that are located in the superficial layer, forming a network that allows the reception of oxygen and essential nutrients for their survival. If there is damage to the bone tissue due to small ruptures, osteocytes undergo apoptosis near the region and signal osteoclasts through the release of characteristic signals, such as insulin-like growth factor (IGF-1) 1 and 2, osteocalcin, sclerostin, c-fos, prostaglandins, prostanoids and nitric oxide, which stimulate the process of reabsorption of damaged tissue (SAAVEDRA et al, 2016; KOMORI, 2016).

Instability in the activity of osteoblasts and osteoclasts during bone formation and remodeling processes can promote a decrease in BMD, which results in bone fragility, making the individual vulnerable to ruptures (MOTYL et al, 2017).

The bone matrix is a mass composed of organic and inorganic elements, with the organic components represented by collagen, and the inorganic elements constituted by water (H_2O), phosphate (PO_4^{-3}), Ca^{2+} and the carbonate (CO_3^{-2}). Together these components are responsible for maintaining the bone structure, and thus the support of the body (ANDRADE, 2015).

Characterized as a silent disease that directly affects the skeleton, osteoporosis (OP) results from the inconstancy that occurs during bone tissue restructuring, causing changes in the microarchitecture through matrix demineralization. The progression of OP is associated with hormonal, nutritional and spontaneous risk factors that result in a decrease in bone mass, and consequently in skeletal functional disability (RADOMINSKI et al, 2017; UKON et al, 2019).

Vitamin D's main function is to stabilize the metabolism of Ca^2+ and phosphorus (P), inducing the absorption of these minerals in the intestine and resulting in an increase in Ca^2+ and P in the plasma. Endogenous synthesis begins when there is activation of 7-dehydrocholesterol, which, through ultraviolet B radiation, is converted into vitamin D3. Vitamins D2 and D3 are synthesized through solar radiation and follow the same route of metabolism in the liver through food intake, originating 25-hydroxyvitamin D, which is the main conformation circulating in the blood. 25(OH)D is converted by 1a-hydroxylase in the kidney, resulting in 1,25(OH)2D which is the active form of the vitamin. Coming from food consumption or endogenous synthesis, the influence of vitamin D on the bones is associated with the activity of the parathyroid

hormone (HTP), as it is necessary for vitamin D to perform its function and regulate the synthesis of HPT, through the increase on Ca2+ concentration and activation of ERVD (vitamin D responsive element) in the HPT gene promoter. In addition, vitamin D prevents the multiplication of parathyroid cells, modulating sensitivity to Ca2+ and increasing the transcription of CasR (receptor susceptible to Ca2+). Therefore, the low level of vitamin D makes it impossible to regulate the synthesis of HPT, making it difficult to inhibit the proliferation of parathyroid cells and decreasing the concentration of Ca^2+, and may develop secondary hyperparathyroidism, which results in increased bone demineralization (BELLAN, PIRISI, SAINAGHI, 2015; JORGE et al, 2018).

Having as an exclusive source diets that have milk, dairy products and dark green leafy vegetables, Ca^2+ is deposited especially in teeth and bones. When ingested, Ca^2+ is absorbed in the intestinal tract and divided into two phases: active saturable, which occurs through Ca^2+ binding protein and vitamin D, since 1,25(OH)2D stimulates Ca^2 absorption + and reinforces bone mineralization. When there is hypocalcemia, the parathyroid gland produces PTH, which binds to osteoblasts that secrete osteoprotegerin, which activates pre-osteoclastic cells, and finally converts them into osteoclasts, which will carry out bone resorption by depositing Ca^2+ in the blood. When there is a low intake of Ca^2+ and vitamin D, it can lead to a deficiency of the mediators that promote bone remodeling, as it directly affects the constitution, mineralization and reabsorption of bones, thus causing the development of OP. Therefore, Ca^2+ intake is extremely important for the strength and integrity of the bone matrix (OSELAME et al, 2016; FARIAS, LAGO, ANDRADE, 2015; SAAVEDRA et al, 2016).

Calcitonin is a polypeptide hormone secreted by the thyroid gland, where it helps maintain the bone matrix through its binding to osteoclasts, resulting in bone strengthening and preventing excessive resorption action. After being secreted by the thyroid gland, calcitonin is metabolized and subsequently acts directly to inhibit the activity of PTH and vitamin D, influencing the increase in the absorption of Ca^2+ and phosphorus (P) through the kidneys. The low level of calcitonin in the body can cause an imbalance between the levels of minerals that are important for the preservation of bone tissue, in addition to reinforcing bone resorption and, consequently, the development of OP (GIRALDO, NOVOA, RAMOS, 2015).

Being released by the same gland and in charge of maintaining the balance of essential minerals in the extracellular region, parathyroid hormone (PTH) prevents the reabsorption of P by the renal tubules and promotes the absorption of Ca^2+ by the intestine. However, if there is an increase in its excretion, hypercalcemia and hypercalciuria are possible, which are characterized by the high level of Ca2+ in the blood and its elimination through the urine, leading to decalcification of the bone matrix. PTH also performs anabolic and catabolic functions through its interaction with bone cells. The activity of osteoblasts, osteoclasts and osteocytes are associated with the control of Ca^2+ in the body through PTH, since both enable the maintenance of the skeleton. The synthesis and release of PTH is monitored by the CasR Ca^2+ receptor, but its production is also related to a decrease in Ca^2+ levels or an increase in P in the body. Thus, catabolism occurs when there is an increase in PTH, leading to an increase in the action of osteoclasts, which results in greater destruction of bone tissue, causing damage to its structure. Anabolism is associated with the ingestion of PTH (1–34) and PTH (1–84) based on a therapeutic

method for the treatment of OP, that is, when there is demineralization of the bone matrix. Its performance results in the elevation of the constitution of the bone tissue through osteoblasts, which work constantly with the objective of recovering the conformation of the bone so that later, the osteoclasts return to carry out their function in a balanced way (GIRALDO, NOVOA, RAMOS, 2015; SILVA, BILEZIKIAN, 2015).

Configured as a fibrous protein, collagen has the function of strengthening the joint cartilage, in addition to assisting in the maturation of osteoblasts, and thus in increasing their activity, as well as decreasing the action of osteoclasts, with the objective of maintaining the regulation between the modulation and mineralization of the bone matrix. This protein is composed of 3 primordial amino acids that are expressed in a Gly-X-Y sequence, where Gly appears as glycine, X indicates proline, and Y that can appear as hydroxylysine or hydroxyproline. Most of collagen digestion takes place in the duodenum and jejunum through the action of pancreatic juice, while the smaller part passes in the stomach, due to hydrochloric acid and pepsin. Proteins and polypeptides undergo luminal hydrolysis in the intestine, through the action of enteropeptidase, and are transformed into free amino acids and short peptides. This execution occurs at a neutral pH, activating trypsinogen and trypsin, providing the activation of propeptidases in pancreatic acid. Free amino acids and small peptides are hydrolyzed into free amino acids, dipeptides and tripeptides, which undergo simple diffusion, facilitated diffusion and active transfer by co-transport, being absorbed essentially in the intestine. Type 1 collagen improves bone mineral density, influencing osteoblastic differentiation and increasing its quantity in the bone matrix. Therefore, the decrease of collagen in the body can lead to demineralization and, consequently, increase the probability of developing OP (PORFÍRIO, FANARO, 2016).

Resulting from osteometabolic alterations that affect the bone matrix, the natural, nutritional and hormonal factors that contribute to the progression of OP and result in susceptibility to bone ruptures are senility, diets rich in proteins and devoid of $Ca^{2}+$, excessive consumption of caffeine, postmenopausal women, and sedentary lifestyle (CAMARGOS, BOMFIM, 2017; OSELAME et al, 2016).

Due to the lifestyle adopted by the elderly, the high consumption of foods with low levels of $Ca^{2}+$ and vitamin D, in addition to low exposure to the sun, can cause serious repercussions, since both are fundamental components for bone health, making it impossible to produce of vitamin D and absorption of $Ca^{2}+$ by the intestine. Due to the non-absorption of $Ca^{2}+$ by the intestine, since vitamin D levels are reduced, chronic secondary hyperparathyroidism develops, which results in instability between the action of osteoblasts and osteoclasts, enabling increased maintenance of the bone matrix, causing a decrease in BMD, evolution of OP and skeletal fragility (RIZZOLI, 2018).

The preference for consuming foods with a high protein content is worrisome, due to the possibility of increasing the reabsorption of the bone matrix, since the action of osteoclasts becomes imminent. Similarly, the ingestion of diets devoid of or reduced in $Ca^{2}+$ together with hyperproteic nutrition directly affects the matrix, since the accumulation of proteins in the body makes it possible to eliminate approximately 50% of $Ca^{2}+$ through the urine, causing bone demineralization (OSELAME et al, 2016).

$Ca^{2}+$ is the most abundant constituent in bone formation. When intake and evasion of this mineral are out of harmony due to

insufficient intake, Ca^{2}+ is removed from the bones, being taken into the feces and urine. For this reason, it is essential to follow a diet abundant in vitamins and Ca^{2}+ through the intake of milk and yogurt, wholemeal bread, cereals, fruits and vegetables, avoiding the consumption of sugary, processed and fatty foods and drinks, in order to prevent the OP (VICTORIA, 2016; WARD et al, 2016).

As a result of the high consumption of caffeinated beverages, caffeine acts on the body by encouraging increased excretion of Ca^{2}+ through the urine, causing a decrease in bone mineral density (LO, KUO, CHEN, 2017), in addition to acting on osteoclasts, causing the increase in cell differentiation. In osteoblasts and osteocytes, it acts by directly affecting the stages of proliferation, distinction, formation and mineralization of bone mass, being capable of causing the death of these two cells. In addition, the mechanisms of caffeine action can occur through changes in the balance of essential minerals for bone health, such as Ca^{2}+ and phosphorus, or through the deregulation of hormones and regulators of absorption and elimination of minerals (MACEDO, BRENTEGANI, LACERDA, 2015).

Postmenopausal women are also at risk, since estrogen is considered one of the key hormones in bone maintenance, as in addition to preventing the programmed cell death of osteocytes and osteoblasts from occurring, estrogen acts on the release of the cytokine osteoprotegerin (OPG) that prevents osteoclastogenesis, that is, the distinction in mature osteoclasts, preventing the exorbitant reabsorption of bone tissue. Due to the decrease in estrogen released by the ovaries in postmenopause, the activity of osteoclasts is high, resulting in attenuation of bone mass, in addition to the impairment of lower phosphate absorption(PO_4^{-3}) and Ca^{2+} (SILVA et al, 2017; FARIAS, LAGO, ANDRADE, 2015).

Physical exercises are essential for proper bone formation and reabsorption, as the mechanical loads of fluid compression, formation and shearing stimulate the differentiation and mineralization of osteoblasts, as well as attenuating the loss of BMD. In addition, physical activities increase the vascularization of the periosteum and the regional bone area, where angiogenesis-osteogenesis is regulated by mechanical stimuli that reduce the formation of osteoclasts. In the absence of these stimuli due to a sedentary lifestyle, there is a loss of bone mass and even the evolution of OP (TONG et al, 2019).

The diagnosis of OP begins based on routine exams by requesting basic laboratory analysis that include measurements of vitamin D, Ca^{2}+, phosphorus, parathyroid hormone level, 24-hour calciuria and alkaline phosphatase, since they are essential in the assessment of the individual's health associated with the investigation of possible osteometabolic diseases. In addition, the results of these tests help in the medical opinion regarding the treatment, preventing the contraindicated therapeutic method from being applied to the patient (NEUERBURG et al, 2017; RADOMINSKI et al, 2017; WOOL et al, 2017)

There are several classes of drugs for the treatment of OP, however, the treatment preference must be evaluated individually, analyzing the effectiveness, safety and cost for each patient (SAAVEDRA et al, 2016). However, it is necessary to regulate the levels of minerals, vitamins and hormones associated with the maintenance of bone tissue (VANDENBROUCKE et al, 2017).

FINAL CONSIDERATIONS

Osteoporosis (OP) has been highlighted as a public health problem, due to its high mortality and morbidity rate, due to the limitations acquired by the patient, in addition

to high hospital and outpatient costs focused on the diagnosis and treatment of the disease.

Through this study, it is possible to validate information associated with the disease, helping in the prevention linked to biochemical factors, such as the consumption of foods that are rich in calcium (Ca^2+) and vitamin D, regulation of protein diets and beverages containing caffeine, exposure daily exposure to the sun and hormone maintenance. In addition, the analysis of biochemical mediators (vitamin D, Ca^2+, calcitonin, parathyroid hormone and collagen) enables the detection of an accurate and early diagnosis, being fundamental in the investigation of possible osteometabolic diseases.

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