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Peculiarities of Reparative Osteogenesis in Fractures of the Proximal Femur in Patients with Concomitant Arterial Hypertension

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Treatment of patients with fractures of the proximal femur is an important problem in modern traumatology. Hip fractures are more commonly associated with osteoporosis. Elderly and senile people make up a significant proportion of patients with fractures. Arterial hypertension (AH) in the elderly population is a disease with a high prevalence. When treating fractures of the proximal femur, it is necessary to take into account the features of reparative osteogenesis characteristics of patients with concomitant arterial hypertension. Medicines used to treat hypertension have a beneficial effect on bone tissue. Pharmacological correction of hypertension in these patients is essential to optimize fracture healing.

Keywords: Arterial Hypertension; Angiotensin Converting Enzyme Inhibitors (ACEI); Fractures of the Proximal Femur.

Relevance

Treatment of patients with fractures of the proximal femur is an urgent problem of modern traumatology. These fractures result in significant morbidity and mortality, along with a large socioeconomic burden[1,2]. As life expectancy and geriatric populations increase, the number of hip fractures worldwide to increase from 1.26 million in 1990 to 4.5 million by 2050[3]. Fractures of the proximal femur occur, as a rule, in young patients through high-energy trauma and in elderly patients as a result of low-energy osteoporotic disorders[4]. A significant part of these fractures are fractures of persons of the elderly and senile age.

The relationship between fractures and osteoporosis

Hip fractures are more likely to be associated with osteoporosis[5]. According to the World Health Organization, osteoporosis is a progressive systemic skeletal disease characterized by low bone mass and disruption of bone histoarchitecture with a subsequent increase in

bone fragility and increased risk of fracture[6]. He is considered a "silent thief" who usually does not show up clinically until a fracture occurs. In the USA, osteoporosis is responsible for 1.3 million fractures, including 250000 hip fractures[7]. The prevalence of osteoporosis in Europe is 27.6 million, and one in three women and one in five men over the age of 50 suffer from osteoporotic fractures[8]. Patients with a lower bone mineral density (BMD) with hip fractures are more likely to fracture in the intertrochanteric region than the femoral neck[9]. Another study found no correlation between the type of fracture and the severity of osteoporosis[10].

FRAX algorithm

Bone regeneration is a genetically programmed physiological process. However, about 10% of fractures do not heal normally[11]. Therefore, the identification of risk factors that disrupt reparative osteogenesis is an important area of research. Algorithmized models are used to assess the risk of fracture based on special questionnaires. These models make it possible to predict the likelihood of fractures in men and women, taking into account the patient's existing pathology, lifestyle, hereditary factors, history of fractures, etc. The FRAX (Fracture Risk Assessment Tool) algorithm is widely used to identify individuals at high risk of fractures. It was developed in the UK by a group of WHO experts led by Professor John Kanis and supported by various international organizations working on the problem of osteoporosis[12]. Using this program can calculate the 10-year probability of a femoral neck fracture and other typical fractures (vertebral bodies, radius, and humerus) associated with osteoporosis in people aged 40 to 90 years. The value of the FRAX algorithm lies in the fact that bone densitometry (BMD of the femoral neck) can be used to determine the risk of fracture, or risk assessment can be performed without this indicator. However, the FRAX program is in its present form does not capture specific aspects of fracture history that are required to differ individuals at high risk from those at very high risk of fracture. The occurrence of a recent major fragility fracture, particularly of the spine or hip, indicates the need for prompt assessment and early intervention in such patients[13].

Bone metabolic disorders

Bone regeneration restores bone tissue lost due to injuries, fractures, etc. Bone tissue is biologically very active and is constantly regenerated due to the balanced activity of bone-resorbing osteoclasts and bone-forming osteoblasts[14]. An imbalance in the functioning of these cells ultimately disrupts bone metabolism and leads to metabolic bone disease, most often to osteoporosis[15]. Based on bone metabolism, osteoporosis can be divided into two forms: osteoporosis with a low and high metabolism. The condition with low metabolism is characterized by a decrease in both bone-forming and bone-resorption activity. Conversely, a state with a high degree of turnover is characterized by increased activity of these processes. High-turnover osteoporosis is the most common form and occurs in postmenopausal women (called primary type I osteoporosis) or in patients with hyperparathyroidism[16]. Low-turnover osteoporosis occurs in the elderly (called age-related osteoporosis or primary type II osteoporosis) or after medication[17]. In elderly and senile patients against the background of osteoporosis, a violation of the mechanisms of remodeling is noted, which is expressed in the dominance of resorption over bone formation. Bone loss can also be associated with chronic medical conditions[18]. Regeneration research aims to understand the molecular mechanisms that control regeneration, potentially providing attractive therapeutic targets for reactivating latent regenerative responses in adulthood or with aging[19].

Bone structure

It is known that in morphofunctional terms, bone is one of the most complex and biologically active tissues. In many respects it is superior to other body systems and is the most massive, multifunctional, has a high metabolic and reparative activity. There are three main types of cells involved in the repair and regeneration of bones: osteoblasts, osteoclasts, and osteocytes. They interact via signaling molecules to regulate the differentiation of progenitor cells for skeletal modeling and remodeling[20].

Osteoblasts, derived from mesenchymal stem cells (MSC) of bone marrow, blood, and pericytes, are involved in bone formation and repair bone tissue removed by osteoclasts[21]. Biochemical

and cytochemical studies have shown that osteoblasts contain a high content of RNA, which reflects their activity and constant biosynthetic function[22].

Each osteoblast synthesizes and builds up a new bone matrix around it, mineralizes it, and turns into an osteocyte with processes in the tubular system that connects it to neighboring cells. Changes in the overall rate of tubular network formation increase osteoblast activity and bone formation[23].

Osteocytes are definitively differentiated cells immobilized in the bone matrix. Osteocytes are able to recognize old or damaged areas of bone and attract osteoclast precursors to sites that require restructuring[24].

Osteoclasts provide bone resorption. They are multinucleated cells formed by fusion and differentiation of monocytes / macrophages. Osteoclast formation and activity are regulated by macrophage colony-stimulating factor (M-CSF) and receptor activator of nuclear factor–êB ligand (RANKL), produced by osteoblasts[25].

The most important component of bone tissue is the intercellular substance – a unique complex of organic and inorganic components that fill the space between cells. The extracellular matrix (ECM) is a complex dynamic bio environment with exactly regulated physical and biochemical properties[26]. Moreover, its components depends on gender, age, and health status. The bone matrix consists of inorganic compounds (60%) and organic (40%). The composition of inorganic components mainly includes ECM, calcium-deficient apatite and trace elements. In contrast, organic the ECM is much more complex and consists of collagen type I (90%) and non-collagenous proteins (10%). Its synthesis is mainly performed by osteoblasts prior the mineralization process takes place[27]. Non-collagen proteins can be divided into four groups: proteoglycans, proteins containing ã-carboxyglutamate, glycoproteins, and small integrin-binding ligands, N-linked glycoproteins (SIBLIN)[28].

Key signaling pathways that control bone resorption by osteoclasts and bone formation by osteoblasts are receptor activator of nuclear factor–êB (RANK)/RANKL/osteoprotegerin and canonical Wnt signaling. Cytokines, growth factors, and prostaglandins act as paracrine regulators of the cycle[29]. Systemic neuroendocrine regulation is carried out by hormones and substances with hormone-like action. The most studied are parathyroid hormone, sex hormones, vitamin D metabolites, calcitonin, glucocorticoids, thyroid hormones[30,31].

Fracture healing process

The process of fracture healing often consists of three intersecting phases: inflammatory, reparative and remodeling, where each phase is a complex spatio-temporal distribution of cells, extracellular matrix, and bioactive signals. Fracture healing begins with trauma-induced hematoma and inflammation. Further, the short phase of endochondral formation of the external callus changes to a long phase of bone restructuring (remodeling)[32].

In terms of tissue repair, bone is unique as it is able to heal without scarring[33]. Bone fractures can heal in two forms: primary and secondary. Primary healing, or osteonal, occurs without intermediate or significant callus in the cartilage. When rigid fixation is achieved after an almost ideal reduction, the fracture heals due to the fact that osteoclasts create tunnels through the fracture site, which are subsequently filled with new[34]. Secondary bone healing, the most common form of healing, occurs with slight interfragmentary movement at the fracture site. Interfragmentary movement causes the formation of soft callus and leads to the formation of secondary bone through intramembranous and endochondral ossification[35]. This form of bone healing begins in the anabolic phase and overlaps with the catabolic phase when the callus is reduced. After these processes, the bone remodeling phase begins with the coordinated activity of osteoblasts and osteoclasts for several months. Callus tissue (soft bone marrow) is reabsorbed and lamellar bone is formed[36].

During the healing of fractures, it takes a long time from the moment of alteration to the formation of morphologically mature bone tissue filling the bone defect and restoration of bone function. In this case, the staging of the reparative process and the time duration of each stage depend on many conditions: the volume and mechanism of damage, functional disorders of individual regulatory systems and their combined dysfunctions, the degree of damage to transport systems, and the severity of edema and hypoxia.

With the accurate reduction and good fixation of bone fragments, preservation of the area of blood supply to the damaged bone in patients with an uncomplicated history, the reparative process has a favorable course and result. Advanced age, large bone defects, violation of the fracture blood supply zone, hereditary diseases, etc., reduce the body's ability to osteogenesis[37].

In randomized trials of osteoporosis therapies with different mechanisms of action, the treatment altered the BMD of the hip, which significantly reduced fractures (44-67%)[38].

Two types of drugs are used to treat osteoporosis: those that slow bone resorption (estrogens, calcitonin, and bisphosphonates) and those that stimulate bone formation (teriparatide and strontium ranelate)[39].

Homeostatic Fracture Disorders

For the successful treatment of fractures, it is necessary not only to create optimal local conditions for osteogenesis but also to normalize homeostatic disorders, which significantly affect the metabolism of bone tissue.

An important link in the pathogenesis of osteoporotic disorders is a decrease in the blood supply to bone tissue, which causes an imbalance in the processes of remodeling and reparative regeneration of bone tissue[40]. One of the reasons for the violation of the regional blood supply to the bone tissue is endothelial dysfunction, which, with the help of a negative effect on microcirculation, can lead to disturbances in the processes of osteogenesis and osteoreparation, thereby contributing to the occurrence of osteoporosis. The structure of the microvasculature of bone tissue differs significantly from the morphology of the vascular bed of other tissues. Bone microvessels have only endothelium and do not have connective tissue and muscle layers. Therefore, it is the endothelial cells that mediate the entire humoral regulation of exchange between osteocytes, osteoblasts, osteoclasts, and blood[41].

Clinical evidence links low bone mass to cardiovascular disease and endothelial dysfunction[42,43], as well as the risk of mortality. Decreased total BMD of the femur is a preliminary predictor of overall mortality in the elderly[44].

Effect of pharmaceutical treatment of arterial hypertension on bone tissue repair

Arterial hypertension (AH) in the elderly population is a disease with a high prevalence (about 60%)[45]. Hypertension can significantly reduce BMD[46]. Disorders of bone structure and mechanics, in turn, can lead to a higher incidence of fractures[47]. Drugs used to treat hypertension have a positive effect on bone tissue. Blood pressure-lowering drugs such as â-blockers and thiazides have been shown to reduce the risk of fractures[48].

In addition, the renin-angiotensin system (RAS) also acts on bone. RAS is a hormonal cascade thought to act as a major regulator of fluid balance in the body and thus blood pressure[49]. RAS is an important target for antihypertensive drugs[50]. Szekanecz et al. are noting the commonality of the pathogenesis of arterial hypertension and osteoporosis[51]. The activity of RAS, on the one hand, by affecting the local blood flow and blood supply to the bones, causes vasoconstriction of the microvasculature, and on the other hand, it directly affects the production of angiotensin II. Angiotensin II is a growth factor that directly stimulates osteoclast proliferation and increases endothelin-1 levels. The content of endothelin-1 upon activation of RAS increases not only in the endothelium but also in osteoclasts[52,53,54].

RAS activation causes high-turnover osteoporosis with accelerated bone tissue resorption. Also, angiotensin II, by reducing ionized calcium and increasing the level of parathyroid hormone, can regulate calcium metabolism[55]. RAS components such as renin, the angiotensin-converting enzyme (ACE) receptors, and angiotensin II are expressed in the local bone[53]. The results of the study showed a significant increase in renin and angiotensinogen mRNA expression in the femur of aging mice[56].

It has been suggested that angiotensin II receptor blockers (ARBs) and ACE inhibitors (ACEIs), which are widely used drugs that inhibit RAS, have beneficial effects on bone tissue and are associated with a reduced risk of hip fractures[54]. Shown association of ACEIs with beneficial changes in bone mass, suggesting a possible negative effect of angiotensin II on bone[57]. Another study reports an increase in BMD in patients treated with ACEIs while reducing the risk of fractures[58]. There is also evidence of a positive effect of RAS blockers on the risk of femoral neck fracture[59]. However, there is little evidence of an increased risk of hip fractures at the start of treatment with

ACEIs in older people with hypertension[60], or studies showing that the use of RAS inhibitors is not associated with the long-term risk of composite fractures[61,62].

Because ARBs show effects similar to those of ACEIs, they are often used as an alternative in patients who cannot tolerate ACEIs. However, ACEIs and ARBs have different effects on angiotensin II, and therefore, their effects on the level and function of ACE may be different[61]. In a pilot study by Bayar A. et al., it was shown that an ACEI has a positive effect on fracture healing, while ARB losartan, does not show any positive effects[63].

Thus, when treating fractures of the proximal femur, it is important to take into account the features of reparative osteogenesis characteristic of patients with concomitant arterial hypertension. Pharmacological correction of hypertension in these patients is essential to optimize fracture healing.

Conflict of Interest

The authors declare that have no conflicts of interest.

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