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Review

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# Bone markers in craniofacial bone deformations and dysplasias

## Markery kostne w dysplazjach i wybranych deformacjach kości twarzoczaszki

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## Summary

Various forms of bony deformations and dysplasias are often present in the facial skeleton. Bone defects can be either localized or general. Quite often they are not only present in the skull but also can be found in other parts of the skeleton. In many cases the presence and levels of specific bone markers should be measured in order to fully describe their activity and presence in the skeleton. Fibrous dysplasia (FD) is the most common one in the facial skeleton; however, other bone deformations regarding bone growth and activity can also be present. Every clinician should be aware of all common, rare and uncommon bony diseases and conditions such as cherubism, Paget's disease, osteogenesis imperfecta and others related to genetic conditions. We present standard (calcium, parathyroid hormone, calcitonin, alkaline phosphatase, vitamin D) and specialized bone markers (pyridinium, deoxypyridinium, hydroxyproline, RANKL/RANK/OPG pathway, growth hormone, insulin-like growth hormone-1) that can be used to evaluate, measure or describe the processes occurring in craniofacial bones.

**Keywords:** **Facial skeleton • bone markers • dysplasia • deformations • fibrous dysplasia.**

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## Introduction

Bone, due to the dominant content of inorganic substances, is classified as mineralized tissue. Because of its constant activity it should be classified as an active tissue, which plays an important role in regulating the concentration of electrolytes in the body. Its main function is related to metabolic storage of calcium, phosphorus and magnesium. The continuous process of bone remodeling is related to adequate function of osteoblasts, osteocytes and osteoclasts, which influences normal bone mass, size and shape [15,30]. Bone remodeling is a complicated process described as replacement of bone components designed to remove small defects or adapt to the changing requirements of the construction of the bone. In an adult human about 10% of their bone mass is exchanged each year, while in children the process is much more intense and is estimated to be about 50% per year [3,4,33].

Histologically, bone tissue includes parts of the essence of intercellular cells and osteo- components such as osteoblasts, osteocytes and osteoclasts. Osteoblasts are involved in organic bone matrix synthesis and mineralization of bone tissue (bone matrix produces bubbles). Factors such as parathyroid hormone (PTH), growth hormone (GH), thyroid hormones, and cytokines (peptides responsible for bone growth and differentiation, prostaglandins, lymphokines, monokines) stimulate their activity. Corticosteroids, on the other hand, have the opposite effect. Osteocytes of bone surfaces play a major role in the rapid regulation of calcium and phosphorus, because of their sensitivity to the effects of PTH, calcitonin and calcitriol. The last group of the three main presented bone cells is that of osteoclasts (osteoclastic cells). PTH at a low concentration of calcium stimulates osteoclasts, resulting in bone resorption. Calcitonin, which is an antagonist of PTH, and estrogens, can easily inhibit the action of osteoclasts [6,7,26,29]. Many forms of bone disorders are well known. Carefully performed detailed differential diagnosis is important to evaluate the insensitivity and form of common and rare cases of bone diseases.

Fibrous dysplasia (FD) is the most common facial bone skeleton disorder. In most cases elevated levels of alkaline phosphatase (ALP) are present. Depending on age, stages and progression of FD, different therapeutic outcomes are possible [23]. Both fibrous and calcified lesions are still a diagnostic challenge. Both children and adults may suffer from various forms and intensity of bony dysplasia, but the juvenile one might even be life-threatening. Differential diagnosis should include Paget's disease, Noonan, Ramos syndromes and others.

Cherubism is a type of skeletal bilateral or symmetric fibro-osseous dysplastic lesion in both maxillary and mandibular bones. Quite often it is characterized by aggressive and expansive bone growth in children [22]. Sclerosteosis is a rare bone dysplasia in the skull and skeleton long bones. In this case sclerostin affects the osteocytes' function and activity [24]. Sclerosteosis is a progressive bone dysplasia, with recessive inheritance. Quite often it occurs in the skull, mandible, ribs and clavicles. Differential diagnosis should include van Buchem disease, cleidocranial dysplasia and others. Other rare bone disorders should also be remembered, especially fibrodysplasia ossificans progressiva (FOP) [2,35].

The aim of this review paper is to discuss known bone markers and their use as prognostic and diagnostic factors indicating selected craniofacial and skull bone disorders.

## Bone markers

Various forms, types and subtypes of bone markers are used worldwide. Some factors such as the RANKL/RANK/OPG pathway, growth hormone (GH) and vitamin D have a great influence on skeletal bones, and could be important diagnostic markers. The focus of this article includes markers of bone remodeling activity which are already well known and used in routine diagnostics, but also those which are used rarely due to the lack of adequate knowledge about them.

It is believed that the receptor activator of nuclear factor-κB (RANK) and its ligand (RANKL, receptor activator of nuclear factor-κB ligand) play an important role in regulation of the bone remodeling process. The balance between osteoprotegerin (OPG) and RANK/RANKL is a key factor of differentiation, activity and survival of osteoclasts. The ratio between them may be used as a marker of bone remodeling activity and also for the evaluation of the degree of bone mineralization. RANKL is a member of the tumor necrosis factor (TNF) and TNF receptor (TNFr) superfamilies, which both respectively bind the receptor activator of NF-κB RANK. It is a protein expressed by osteoclasts [31]. The correlation between estrogen and the RANK pathway is important to correlate hormone levels, age and bone activity.

Estrogen is one of the most important hormones known which participates in bone turnover. Various studies worldwide indicate its importance. Estrogen levels and its interaction with the RANK/RANKL/OPG pathway have shown that it stimulates OPG secretion and downregulates the expression of RANKL [17].

RANK/RANKL signaling triggers osteoclast differentiation, proliferation and activation; thus it prominently affects the resorption phase during bone remodeling. On the other hand, OPG is produced by many types of tissue, including osteoblasts, endothelial cells, vascular smooth muscle, and lymphoid cells, and other cell types, raising the question of the specificity of this protein in bone mass regulation. It is a decoy receptor for RANKL, thus inhibiting the production of osteoclasts [34,28]. Up-regulation of OPG is expected to decrease the interaction of RANKL with RANK and consequently reduce osteoclastic bone resorption [20].

Factors influencing the activity and stimulation of osteoclast formation and inducing overall RANKL expression are known. Many of them are cytokines, such as interleukin-1 (IL-1), IL-6, IL-11, TNF-α, glucocorticoids, PTH, 1,25 $(OH)_2$ vitamin D3 and calcitriol. RANK expression is stimulated by vitamin $D_3$, IL-1, oncostatin M (OSM), interferon gamma (IFN-α), vasoactive intestinal peptide (VIP), macrophage inflammatory protein-1-α (MIP-1α) and RANKL [5,8]. OPG expression is stimulated with: cytokines (TNF-α, IL-1α, IL-18, TNF-β), bone morphogenic proteins, 17β-estradiol, and mechanical stress acting on the bone (called tensional forces). Nevertheless, the opposite effect on OPG is exerted by drugs (corticosteroids, immunosuppressive agents), PTH, prostaglandin E2, and basic FGF (fibroblast growth factor) [1]. The level of IGFBP-3 (insulin-like growth factor-binding protein 3) is believed to be a marker of OPG concentrations in serum [19].

OPG prevents the connection between RANKL and RANK by binding itself to RANKL. Its mechanism is focused on blocking the maturation and activation of osteoclasts and bone resorption. Regulation of metabolic processes occurring in the bones depends on the balance and proper association between OPG and RANK/RANKL. In contrast, disruption of this balance has been observed in some diseases featuring impaired bone structure, such as osteoporosis and Paget›s disease. Therefore it is concluded that the ratio of the concentration levels of RANK, RANKL and OPG indicates which process is currently present in the bone structure [14]. Evaluating levels and activity of both RANK and OPG combined with growth hormone influence may be a useful diagnostic tool.

Growth hormone (GH) is a very important hormone. It is responsible for proper bone growth and it takes part in maintaining balance of metabolic processes. GH affects bone metabolism and has multidirectional activity. First of all, it stimulates bone, cartilage and connective tissue growth. Green theory states that GH acts directly on the target cells (chondrocytes, osteoblasts) in their corresponding stimulating GH receptor (GHR), or indirectly *via* IGF-1 (insulin-like growth factor). Mitogenic action of IGF-1 selectively promotes cell multiplication in young differentiated clones. As tissue growth results from both the creation of new differentiated cells and their subsequent clonal expansion, both effectors increase tissue growth [11].

Insulin-like growth factor (IGF-1), also called somatomedin C, is produced by the liver and cartilage under the influence of GH. Only 1% of IGF-1 is biologically active; the rest is bound to IGF binding protein (IGFBP-3 – insulin-like growth factor binding protein-3) and acid-labile glycoprotein (acid-labile subunit – ALS). IGFBP-3 is used as a metabolic reservoir for IGF-I and prolongs its half-life [10].

It is known that the metabolic effect of GH stimulation depends on its receptor activity in tissues, while growth promoting factors are influenced by IGF-1. Physiologically, GH increases bone turnover, promoting metabolic processes of the bone, and is responsible for the increase of bone mineral density (BMD) and bone mineral content (BMC). GH also stimulates the skeletal muscle mass and strength and increases myocardial performance, leading to a rise in physical activity and augmentation of bone mass by stimulation of osteoblasts' activity. GH, by acting on the kidney tissue, activates hydroxylase α-1, thus increasing the synthesis of 1,25 $(OH)_2$ vitamin D3, as well as, indirectly through IGF-I, increasing phosphate reabsorption in the renal tubules, which ultimately leads to a positive calcium balance [25,36].

It is believed that GH and IGF-1 influence the balance between OPG, RANKL and RANK. Presence and activity of OPG play a key role in the metabolic processes in the bone tissue initiated by the GH. Flint et al. suggest that the increased concentration of OPG may be due to the lack of response of anabolic alignment of IGF-1 and GH in children with growth hormone deficiency (GHD) [7].

Growth hormone deficiency during the most intensive stage of bone mass growth and formation, which occurs in untreated GHD, may result in low bone mass and osteoporosis in adulthood. Alignment of growth hormone deficiency with RHGH treatment should therefore also positively affect bone metabolism processes. It is however possible that the improperly functioning mechanisms of bone turnover affect the therapeutic effect (understood as the change in growth velocity) of RHGH treatment in GHD.

Some vitamins and microelements are important in bone growth and metabolism. Vitamin D along with phosphates is closely related to bony metabolism and function. Vitamin D is a group of fat-soluble secosteroids responsible for enhancing intestinal absorption of calcium and phosphate. In humans, the most important compounds are 25-hydroxyvitamin D (25 $(OH)D_3$, calcidiol) and 1,25-dihydroxyvitamin D (1,25(OH)2D3, calcitriol). In medicine, a $25(OH)D_3$ blood test is used to determine how much vitamin D is in the body [7,18]. Vitamin D is produced naturally by the skin when exposed to ultraviolet light, and its concentration is also directly related to diet and supplementation. Recently it is believed that the concentration of vitamin D can be determined on adipose tissue. A higher concentration of vitamin D is observed in obese patients than those who have a correct body mass index (BMI). Vitamin D has a pleiotropic effect on our body. The amount of $1,25(OH)D_3$ is directly involved in absorption of calcium and phosphate and ensures proper bone mineralization. Research shows that the concentration of $25(OH)D_3$ below 20 ng/ml is associated with an increased risk of cardiovascular diseases, autoimmune diseases or the development of certain cancers [12]. Vitamin D is the only accessible hormone affecting the expression of calbindin, which is responsible for active calcium absorption from the intestine. Vitamin D deficiency is directly associated

with a reduction of muscle strength and increased risk of falls with bone fractures [13]. Also evaluation of certain levels of vitamin D, phosphatases and GH might be valuable in various forms of cranial bone dysplasias and malformation and might indicate the nature and stage of the process.

## Discussion

Major organs are related to bone turnover and bone administrations. This function is reserved for the thyroid and parathyroid glands, adrenal cortex and pituitary gland. The most common bone disease is Recklinghausen's disease (neurofibromatosis type 1) where healthy bone is replaced with fibrous tissues and forms giant cellular tumors, brown tumors and changes in the alveolar arches. Brown skin spots, called café-au-lait spots, are also quite common in this disease. Also Cushing disease can be diagnosed as an osteoporosis of the cranial bones but without enlargement of the Turkish saddle (the sphenoid bone corpus), which on the other hand is present in acromegaly. Hypothyroidism and hyperthyroidism are also common, but only hyperthyroidism causes osteoporosis of the mandible. Another disease manifesting in the cranial bones is Paget's disease (osteitis fibrosa). It causes cranial bone calvarium deformation and also causes increased bold cover volume. It is essential to remember that around 10% of all bony defects in Paget's disease might cause secondary bony osteosarcoma. Despite all factors mentioned above, fibrous dysplasia (FD) and cherubism are more common in children and young adults. Genetic counseling might be important to diagnose and evaluate any potential genetic disease, such as Noonan syndrome, Ramon syndrome, fragile X syndrome, McCune-Albright syndrome, neurofibromatosis type 2 and others.

Approximately 90% of the organic matrix of bone is built from type 1 collagen, which is cross-linked with specific molecules that provide rigidity and strength of bones [1]. Degradation products of collagen such as hydroxylysylpyridinoline (HP) and lysylpyridinoline (LP), pyridinoline and deoxypyridinoline, and C-terminal telopeptide of type I collagen, can be used as a marker of bone resorption [32]. Monitoring urine and blood markers is the most common diagnostic method. One advantage of bone marker examination in urine is its easy accessibility and the possibility to gain fast results. Bone turnover might be evaluated after measuring deoxypyridinoline, which is present in the urine and is present only from bone resorption (it is not metabolized or absorbed from food). This marker can also be useful for monitoring the effectiveness of antiresorptive agents, e.g. in osteoporosis treatment.

Adequate diagnosis should consist of careful examination of blood and urine. Also additional diagnostic tools, such as computed tomography, scintigraphy or SPECT should be performed, for example to investigate the growth potential activity and size of bone disorders in the skull and/or other skeletal parts [4].

In cherubism, levels of blood markers such as calcium, parathyroid hormone (PTH), calcitonin, and alkaline phosphatase (ALP) are in normal ranges. Urine examination reveals that markers such as pyridinium, deoxypyridinium and hydroxyproline are often elevated [27]. Quite important are osteocalcin and alkaline phosphatase, which are very useful diagnostic tools.

Children suffering from various bone disorders quite often require early orthodontic treatment to improve chewing, speech and proper muscle function. Orthodontic therapy can be carried out simultaneously with modeling surgery (eye socket decompression, dental arches modeling) or only with appliance of mobile braces and musculoskeletal function improvement exercises. Performing an orthodontic treatment also requires, in some special cases, evaluation of bone density and thickness. Even bone marker changes are seen in orthodontic therapy. Kopczyński performed a study to measure levels of osteocalcin (BGP), the bone resorption C-terminal telopeptide type I collagen (CTx) before and after use of a palatal appliance. The results showed no significant turnover rate of the bone either before or after treatment and also in the control group [16]. Similar studies in patients suffering from bone dysplasias or cherubism have not been reported so far.

It seems that many bone markers are used to evaluate and describe different types of bone diseases. In the facial bone skeleton quite often various manifesting conditions can be easily diagnosed while monitoring calcitonin, alkaline phosphatase and calcium levels. In selected cases, further advanced diagnostic approaches are performed after consulting an endocrinologist. Dysplastic changes in the facial skeleton could be fibrous, bony or mixed, combined with fibro-osseous lesions.

A basic diagnostic tool is still a routine radiograph, which can easily be supported with computed tomography imaging (CT, CBCT), and even magnetic resonance (MRI). Scintigraphy is routinely performed in any facial skeleton asymmetries. Nowadays SPECT imaging allows evaluation of bone growth potential and is more accurate. Scintigraphy is also very useful in order to distinguish condylar head hyperplasia (HH) and bony dysplastic lesions from other bone malformations or dysplasias. Especially children and young adults who have not yet finished their growth in any case of asymmetrical bone growth should be carefully diagnosed [21].

## Conclusions

Bone marker turnover estimation can be a very effective tool in diagnosis of skeletal disease. It is also useful in predicting results of treatment or monitoring the course of the disease. Both urine and blood examination followed by direct radiographic approaches are good diagnostic tools. There is no doubt that medical development contributes to the research for more and more new, better and less invasive possibilities for assessment of bone metabolism.

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