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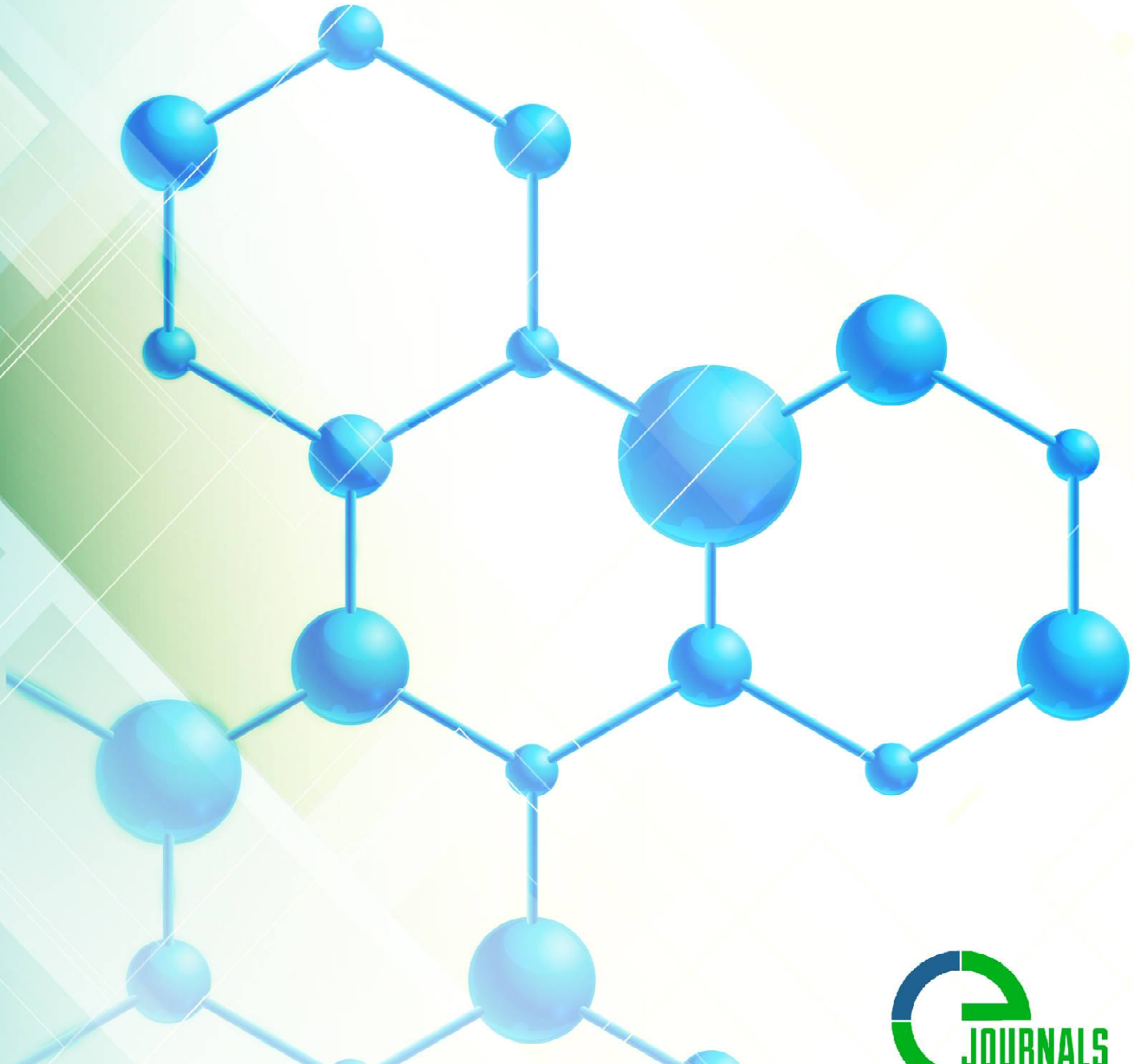

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ROLE OF BIOMARKERS OF ORGANIC MATRIX OF BONE TISSUE IN CHRONIC HEMATOGENOUS OSTEOMYELITIS IN CHILDREN

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Abstract: role of biomarkers of organic matrix of bone tissue in chronic hematogenous osteomyelitis in children bone biomarkers included arrangement, resorption and controller are discharged amid the bone remodeling forms. These bone biomarkers have pulled in much consideration within the clinical assessment of osteoporosis treatment within the past decade. Combination with the estimation of bone mineral thickness, the clinical applications of bone biomarkers have given comprehensive data for conclusion of osteoporosis. In any case, the explanatory approaches of the bone biomarkers are still the challenge for encourage clinical trials.

Keywords: organic matrix, bone tissue, chronic hematogenous osteomyelitis, bone biomarkers.

Several factors have to be considered in the design of a human biomonitoring programme or the use of biomonitoring data, for example whether the parent compound or a stable metabolite is the most suitable biomarker and in which matrix it should be determined. Analytical methods have to be sufficiently sensitive and selective to produce reliable data. The objective of this study was therefore i) to identify the most suitable biomarkers (parent compound vs. metabolites) for the selected substance groups and metals, ii) to describe the most suitable human matrix for their biomonitoring and iii) to discuss state-of-the-art analytical methods for the determination of this biomarker in this matrix., including the sample selection and a comprehensive quality assurance/quality control programmed to ensure precise, accurate and comparable data across the EU. Osteoporosis is a worldwide disease with reduction of bone mass and decrease of bone strength to result in bone fragility and fracture. Based on the report of World Health Organization (WHO), the disease of osteoporosis has been diagnosed by bone mineral at the hip and/or the spine at least 2.5 standard deviations below in comparison with the bone mass of young healthy adults as determined by dual-energy X-ray absorptiometry. The people with osteoporosis are steadily increased because of aging society occurring worldwide. There are about 200 million people are suffered from osteoporosis in the word and approximately 8.9 million fractures are caused by osteoporotic fracture. In the osteoporotic fractures, hip fractures have led to mortality rates up to 20-24% within

the first year and then the death rate has steadily increased for at least 5 years.After hip fractures, the survivors may lose the capability of action and independence with 40% unable to walk independently and 60% requiring assistance at least 1 year. Due to the loss of capability, around 33% patients are totally dependent or in a nursing home in the year following a hip fracture. Nowadays, osteoporosis is a major concern of public health because of its healthcare cost. Moreover, the fracture caused by osteoporosis is the most important factor for the decreases of quality of life and survival rate in aging people.

Osteomyelitis - (osteomyelitis, Greek osteon - bone, myelos - bone marrow and itis-inflammation) - an infectious inflammatory process that affects all elements of the bone - the bone marrow, the bone itself and the periosteum, i.e. panostitis, however the term panostitis has not found wide application in medical literature. Chronic hematogenous osteomyelitis is a consequence of an acute process. Its substrate is bone necrosis. Primary chronic osteomyelitis is a rare form of the disease and is characterized by a predominantly sluggish torpid course, often with minimal patient complaints.

Chronic hematogenous osteomyelitis (CHO) develops after an acute one and is characterized by a long-term course, when periods of exacerbation and remission (relative well-being) alternate. The morphological substrate for such a course of the disease, as a rule, is the site of a bone that died as a result of acute inflammation. Over time, it is rejected by the living bone, and a sequester is formed, which is usually located in the bone cavity - the sequester box. Purulent fistulas, which are pathological passages in tissues connecting the osteomyelitic cavity with the external environment, are a frequent component of CGO. Usually, a fistula opens on the skin with its external opening and is a kind of drainage that dumps excess pus into the external environment. Being an unconditional pathology, the fistula, however, allows the patient sometimes to live for many months and years with minimal manifestations of the inflammatory process. When the fistula closes or it is not able to drain the pathological intraosseous focus, conditions are created for the exacerbation of the disease. Pain appears or intensifies, the temperature rises, local signs of an acute inflammatory process (swelling, redness, etc.) are observed. In the future, paraossal phlegmon may develop, or a purulent fistula will reopen. As a rule, patients with an exacerbation of CHO urgently seek medical help. Untimely assistance in this case is fraught with the danger of spreading the purulent process to the surrounding tissues, increasing intoxication, and developing sepsis.

Diagnosis of CHO in most cases is not difficult, since usually patients with such a diagnosis have long been in the field of view of a specialist who is familiar with the features of the course of the disease. However, it is possible to judge structural changes in the bone: their nature, severity and prevalence only on the basis of an instrumental examination of the patient. The examination begins with a survey radiography, which makes it possible to identify the main pathological changes in the bone tissue. At the same time, many details of the bone lesion may be inaccessible even to an experienced eye. At the same time, their assessment is extremely important when planning a surgical intervention, which is the main method of treating patients suffering from CGO. The possibilities of multispiral X-ray computed tomography allow objectifying and visualizing in detail changes in bone structures, which is especially important in case of damage to massive bones, such as, for example, pelvic bones, sternum, etc. Moreover, modern instrumental diagnostics of osteomyelitis in a significant number of cases provides for the mandatory performance of computed tomography (CT). In HGO, it is absolutely necessary. The presence of a purulent fistula is considered the basis for fistulography. The study involves the introduction of a radiopaque substance into the fistulous tract, followed by a series of x-rays. Fistulography is primarily necessary for planning surgical intervention,

since all purulent fistulas must be removed. Magnetic resonance imaging in the diagnosis of chronic hematogenous osteomyelitis is of auxiliary importance, helping in some cases to identify the prevalence of damage to the soft tissues surrounding the bone, including purulent streaks in complex anatomical areas, for example, in pelvic osteomyelitis.

With the development of acute hematogenous osteomyelitis, a number of successive changes are observed. The process begins acutely with the bone marrow. In the development zone infection develops serous inflammation, manifested by hyperemia and edema, following a short-term stage of serous inflammation, a limited abscess, phlegmon of the bone marrow, then necrosis. Already by the 3rd day of the disease, the bone marrow, periosteum, medullary canals and surrounding soft tissues are infiltrated with exudate. The process spreads through the medullary canal quickly from the metaphysis to the diaphysis, etc., then pus through the Haversian canals comes out under the periosteum. A developing subperiosteal abscess is not only a consequence of the release of pus under the periosteum, but also the result of inflammation of the periosteum itself. In children, the periosteum is loosely soldered to the bone and therefore often exfoliates over a considerable distance, in adults - in a limited area. Detachment of the periosteum, as well as vascular thrombosis in the Haversian canals sharply disrupts bone nutrition, which, along with hyperedges inflammation and toxic exposure leads to necrosis of large areas of bone and periosteum. The periosteum becomes necrotic, pus penetrates into the surrounding tissues and intermuscular phlegmon develops, necrosis and fusion of muscles, and pus penetrates into the subcutaneous tissue fiber - subcutaneous phlegmon, skin necrosis and fistulas open.

Osteomyelitis is a significant cause of morbidity in children throughout the world. Multiple imaging modalities can be used to evaluate for suspected osteomyelitis, however magnetic resonance imaging has distinct advantages over other modalities given its ability to detect early changes related to osteomyelitis, evaluate the true extent of disease, depict extraosseous spread of infection, and help guide surgical management. MRI has assumed a greater role in the evaluation of osteomyelitis with the increase in musculoskeletal infections caused by methicillin-resistant Staphylococcus aureus which have unique imaging features that are well-demonstrated with MRI. This review focuses primarily on the use of MRI in the evaluation of osteomyelitis in children and will include a discussion of the clinically important and characteristic findings on MRI of acute bacterial osteomyelitis and related conditions.

Hematogenous osteomyelitis is the most common type of osteomyelitis in children. This occurs when an infection elsewhere in the body spreads to the bone via the bloodstream. Risk factors for development of hematogenous osteomyelitis include trauma, prematurity, urinary tract infections, vascular catheters and immunodeficiencies. The blood vessels in the metaphyses have sluggish flow and discontinuous endothelium, which predispose to infection. The most common bones to be affected are the fastest growing bones that have highly vascularized long bone metaphyses and metaphyseal equivalents. Common sites include the distal femur, proximal tibia, proximal humerus and distal radius. Most cases start with a focal infection in the metaphyseal marrow which progresses to local decalcification and bony destruction.Occasionally, multiple foci may be infected which eventually coalesce. This infection can spread within the marrow cavity and as the pressure increases within the marrow cavity, the infection can spread through Haversian canals in the cortex into the subperiosteal space, giving rise to a subperiosteal abscess. Similarly, the infection can traverse the periosteum and infect the adjacent soft tissues leading to pyomyositis.Infection may also spread across the physis into the epiphysis and joint space.

The first stage of osteomyelitis occurs with vascular congestion, intravascular thrombosis

and increased intraosseous pressure. Next is the suppurative stage where pus traverses the Haversian canals and forms a subperiosteal abscess. Subsequently a sequestrum may form when the periosteal and endosteal blood supply is compromised from increased pressure and vascular obstruction. This may lead to formation of an involucrum: new bone growing from the periosteum. Depending on medical or surgical treatment at this point the infection may resolve or progress with complications.

The site of osteomyelitis varies with patient age and is related to the blood supply. In early infancy osteomyelitis occurs in epiphyses and metaphyses and epiphyseal-equivalent regions. Transphyseal vessels are present in infants younger than 18-24 mo of age, which allow easier spread of infection across the physis from the metaphysis to the epiphysis[4,6]. This is the reason that infantile osteomyelitis frequently involves the epiphysis and joint space. It is important to note that this is not the most common cause of septic arthritis, which more often results from direct hematogenous synovial seeding[4]. During early infancy, isolated involvement of the epiphyseal growth plate can occur.Infection of the epiphyseal growth plate during infancy can result in growth disturbance. In the 2-16 years age group, osteomyelitis is most often located in the metaphysis.

Triple-phase bone scintigraphy using 99mTc-methylene diphosphonate (99mTc-MDP) can demonstrate evidence of infection as soon as 24 h after onset and also has the advantage of being able to depict multiple sites of infection.Osteomyelitis typically manifests as increased radiotracer uptake on all phases (angiographic, blood pool, and delayed) of the triple-phase examination.However, 99mTc-MDP scintigraphy is limited by poor anatomic detail and is insensitive for the detection of abscesses and extraosseous involvement. Furthermore, the sensitivity of 99mTc-MDP scintigraphy for the diagnosis of osteomyelitis, which in the past has been reported to be as high as 80%, may be decreasing with the increasing incidence of MRSA infections that tend to have significant soft-tissue involvement. Positron emission tomography with 18-fluorodeoxyglucose appears to be sensitive (95%) and specific (87%) for the diagnosis of osteomyelitis, however it has limited availability and involves a significant amount of radiation exposure. Scintigraphy studies using white blood cells labeled with indium-111 or 99mTc hexamethyl propylene mine oxime require relatively large volumes of blood and are not used frequently in younger children.

In contrast to the modalities listed above, MRI is both sensitive for the detection of early osteomyelitis and can also accurately depict the extent of disease as well as any associated abscess or soft-tissue extension without the risks associated with radiation exposure. MRI combines high-resolution anatomic delineation of the medullary space, cortex, and periosteum with high soft tissue contrast for detection of edema and fluid. Pre-operative MRI has been shown to reduce operative time and extent of surgical exposure in cases requiring surgical debridement. MRI does have distinct disadvantages in children including long scan times and susceptibility to motion artifacts which necessitate sedation or anesthesia in young children Additionally, MRI is contraindicated in some patients with metallic foreign bodies and certain types of implanted hardware. However, the overall superiority of MRI in evaluating osteomyelitis is reflected in recent clinical practice guidelines which indicate that MRI is the imaging modality of choice for the detection of osteomyelitis and associated infection of the extraosseous soft tissues. As such, the current best imaging approach for suspected osteomyelitis is radiography followed by MRI.

Osteomyelitis in children demonstrates abnormalities on nearly all imaging modalities, including radiography, ultrasound, computed tomography, radionuclide bone scintigraphy, and magnetic resonance imaging (MRI). The conventional approach to the imaging evaluation of suspected AHO in the past has been radiography followed by bone

scintigraphy if the radiographs were negative. In this algorithm, MRI was typically been reserved for cases of poor treatment response or suspected vertebral diskitis-osteomyelitis. However, due to multiple factors, including the rise of rapidly aggressive and invasive musculoskeletal infections with CA-MRSA, this approach may no longer be ideal.

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