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Imaging Diagnostics, Biomarkers, and Emerging Trends in Orthopedic Research and Treatment

Authors: Gabriela Trestka, Wiktoria Domino, Maria Przygoda, Joanna Śnieżna, Wojciech Florczak, Urszula Zelik, Karol Dzwonnik, Jagienka Włodyka, Jakub Dziewic, Kamila Stępień, Sabina Adamczyk

Abstract

With an aging population, increasing sports participation, and a rising number of obese individuals, researchers are addressing the growing prevalence of musculoskeletal diseases. Early diagnosis is crucial for effective treatment and disease prevention. Imaging techniques and biomarkers are essential tools in orthopedic diagnostics, providing critical insights into disease progression, treatment efficacy, and clinical outcomes prediction.

This paper offers an overview of key imaging modalities, including X-ray, CT, MRI, ultrasonography, scintigraphy, and fluorescence tomography (FLAIR), highlighting their strengths, limitations, and clinical applications. X-ray and CT are commonly used for bone-related issues, while MRI and ultrasonography are invaluable for evaluating soft tissues.

Scintigraphy and FLAIR, on the other hand, are particularly effective for detecting metabolic activity and soft tissue changes.

Biomarkers, such as those used in osteoarthritis, osteoporosis, joint inflammation, and bone regeneration, complement imaging techniques by enabling early diagnosis, monitoring disease progression, and predicting treatment outcomes. The integration of biomarkers with imaging provides a more comprehensive approach to patient care.

Finally, emerging technologies like artificial intelligence, smartphones, 4DCT, and 3D printing of implants are poised to revolutionize orthopedic diagnostics and treatment. These advancements promise greater precision in diagnostics, personalized treatments, and improved patient outcomes, though challenges in implementation and technology adoption remain.

Key words: orthopedics, x-ray, computed tomography, magnetic resonans imaging, biomarkers, imaging diagnostics

Introduction

In orthopedics, imaging techniques and biomarkers play a crucial role in diagnosis, monitoring treatment progress, and predicting clinical outcomes. Below, I will present details on various imaging techniques and biomarkers used in orthopedics.

Imaging Techniques in Orthopedics

a) **X-ray (Radiography)**

X-ray is the most commonly used imaging technique in both orthopedics and other medical fields. In orthopedics, its applications include:

- Assessing the type, location, and shape of fractures or potential displacements of bone fragments,
- Evaluating joint degeneration by observing changes in joint structure (e.g., joint space narrowing, presence of osteophytes, changes in bone shape),
- Identifying bone deformities, such as postural defects, congenital bone abnormalities, or limb deformities,
- Detecting pathological bone changes, such as osteoporosis, bone tumors, and osteomyelitis,
- Evaluating treatment effectiveness (e.g., effectiveness of surgical methods, outcomes of fracture healing, dislocations, and other orthopedic injuries).

The main advantages of X-ray are speed, availability, and effectiveness in imaging bones. Many studies use radiographs to confirm patient well-being following surgical treatment, adjust therapy, and determine the intensity of rehabilitation [4]. However, due to its limited ability to assess soft tissues and early pathological changes, its application does not always meet the diagnostic needs of various cases. Sometimes, limiting the diagnostic process and failing to conduct more advanced tests can result in missing significant pathologies in patients [6]. Another limitation is radiation exposure, which increases the risk of carcinogenesis. Awareness of this issue is crucial for improving the safety of the examination. Additionally, it is important to consider that, for example, overweight patients may require a higher radiation dose for penetration through adipose tissue, or that patients with congenital genetic defects may be more susceptible to radiation exposure. Identifying high-risk groups for cancer development can help in determining the appropriate diagnostic method [7].

b) **Computed Tomography (CT)**

CT is a more advanced imaging technique that provides detailed three-dimensional images, particularly useful for assessing complex bone fractures (e.g., multi-fragment fractures, joint fractures, displaced fractures, skull, facial or spinal fractures), joint pathologies, bone tumors, the presence of bone metastases, spinal injuries, metabolic bone diseases, deformities, and for planning orthopedic surgeries. Due to its high resolution and ability to obtain three-dimensional images, CT is also used for navigation during surgeries under CT control. However, like X-ray, the method is limited by radiation exposure, which is much higher in CT scans. Nevertheless, there are ways to reduce radiation doses for patients. Low-dose CT protocols with radiation exposure equivalent to regular radiographs have been developed for conditions such as spondylolysis and should be used whenever possible. Clear communication with the radiology team about the specific information being sought from the scan is necessary to minimize patient radiation doses and reduce the risk of medical errors, such as incorrect imaging localization or scanning the wrong body part. Additionally, it should be noted that whole-body scanning is reserved for exceptional cases, as this practice has not been shown to reduce in-hospital mortality compared to isolated studies of specific body parts in trauma patients [7].

c) **Magnetic Resonance Imaging (MRI)**

MRI is an essential diagnostic tool for assessing soft tissues such as muscles, tendons, ligaments, and articular cartilage, and also for diagnosing bone changes. By utilizing a strong magnetic field and radio waves, MRI does not use ionizing radiation. Its applications include:

- Assessment of tendon, ligament, joint capsule, articular cartilage, muscle, meniscus, and intervertebral disc damage,
- Detection of fatty tissue and soft tissue tumors (particularly valuable for diagnosing sarcomas) [8],
- Diagnosing fascial inflammation, synovial capsule inflammation,
- Diagnosing inflammatory diseases, such as rheumatoid arthritis (RA) or ankylosing spondylitis (AS),
- Postoperative evaluation,
- Treatment and rehabilitation planning.

MRI also helps less experienced residents or surgeons understand the complexity of hip findings, encouraging them to pursue more complicated treatment strategies similar to those employed by more experienced orthopedic surgeons. This phenomenon is called the "MRI effect," where detailed imaging results lead to the adoption of more complex treatment approaches [18].

In clinical practice, MRI has been limited in evaluating implants due to image artifacts caused by metallic materials. However, recent techniques such as MARS (Metal Artifact Reduction Sequences), SEMAC (Slice Encoding for Metal Artifact Correction), and VAT (View Angle Tilting) have been developed to reduce distortions and improve image quality, thereby enhancing MRI's diagnostic capabilities [9].

Despite its advantages, MRI has several limitations, including issues with availability, cost, and the time required for the examination. Additionally, MRI is sometimes ordered without a clear clinical indication. For example, in cases of benign bone tumors, a simple X-ray is typically sufficient for diagnosis [8].

d) **Ultrasonography (USG)**

Ultrasonography (USG) in orthopedics is a non-invasive diagnostic tool that enables real-time assessment of musculoskeletal structures. The undeniable advantages of this method include the absence of radiation, no need for contrast agents, low cost, and wide availability. Some common applications of ultrasound in orthopedics include:

- Diagnosis of soft tissue injuries (e.g., rotator cuff tears, ligament ruptures, cartilage damage),
- Diagnosis and management of joint inflammation (e.g., rheumatoid arthritis, bursitis, detection of joint effusion, intra-articular drug injections, or joint aspiration under ultrasound guidance),
- Monitoring of rehabilitation and treatment progress,
- Assessment of degenerative joint changes.

Ultrasound is an excellent screening tool for diagnosing certain musculoskeletal conditions, such as rotator cuff tears. Studies have shown that it is an effective and more cost-efficient alternative to MRI, reducing unnecessary imaging and shortening the time patients have to wait for surgery. A limitation of this method is that its accuracy depends on the operator's experience, meaning the diagnosis may not always be accurate. [19] Integrating ultrasound into orthopedic practice can enhance patient care by facilitating more precise treatment decisions and reducing unnecessary interventions. It helps confirm diagnoses, especially in cases where clinical presentation alone may not suffice to differentiate between similar lesions (e.g., ganglion cysts vs. lipomas or soft tissue tumors) [5]. Ultrasound also has the potential to become a primary tool in the diagnosis of meniscal injuries, especially in the hands of experienced operators. However, a full understanding of its limitations and the possibility of artifacts is essential to avoid diagnostic mistakes. [20]

d) **Scintigraphy**

Scintigraphy involves the injection of a radioactive isotope, most commonly technetium-99m (99mTc), which binds to various tissues in the body. In orthopedics, bone scintigraphy is often used, where the radioactive isotope accumulates in areas of increased metabolic activity, such as:

- Inflammatory changes (particularly useful when conventional imaging techniques, such as X-ray, fail to show clear changes; bone scintigraphy has high sensitivity for identifying active joint inflammation) [10],
- Fractures (e.g., microfractures, fatigue fractures, early-phase healing changes),
- Tumors,
- Joint abnormalities,
- Bone ischemia (scintigraphy is used to diagnose bone blood flow issues, such as avascular necrosis).

The gamma camera records the radiation emitted by the radioactive isotope, creating an image showing areas with increased metabolic activity, which may indicate the presence of pathology. Although it has limitations in anatomical resolution, it is a valuable tool in cases where other imaging techniques do not provide sufficient information.

e) **Fluorescence Tomography (FLAIR)**

FLAIR (Fluid-Attenuated Inversion Recovery) is an MRI imaging sequence that is particularly useful in orthopedics for diagnosing inflammatory conditions, edema, and soft tissue damage. FLAIR allows for clear imaging of tissues by suppressing signals from fluids (e.g., water, synovial fluid, hematomas), enabling more precise assessment of soft tissue changes, such as ligaments, tendons, cartilage, and inflammation or post-traumatic conditions. It can be used in imaging conditions such as RA, AS, bacterial arthritis, ligament injuries, tendinopathies, microfractures, bursitis, muscle inflammatory diseases, soft tissue infections, post-traumatic hematomas, joint edema, early-stage osteoarthritis, cartilage assessment, bone metastases (detecting edema), osteomyelitis, and stress fractures. The advantage of FLAIR is its high sensitivity to fluid detection and the absence of radiation. However, the longer examination time can be a limitation in some cases.

Biomarkers in Orthopedics

Biomarkers are substances whose presence, concentration, or activity in the body allow for the assessment of pathological processes, health status, or the body's response to treatment. In orthopedics, biomarkers can be used for diagnosis, disease progression prediction, and monitoring treatment outcomes.

a) Biomarkers in Osteoarthritis (OA)

- **CTx (Collagen Type I Crosslinks):** A biomarker associated with the degradation of collagen type I, useful in monitoring the progression of osteoarthritis.
- **MMP-3 (Matrix Metalloproteinase-3):** An enzyme that degrades extracellular matrix in joints and other cartilage components, particularly in osteoarthritis. Its increase correlates with disease progression.
- **HA (Hyaluronic Acid):** An inflammatory biomarker, with increased levels in synovial fluid indicating cartilage damage. It is released by cells to support regenerative processes in damaged joints.
- Further analysis using MiRNet 2.0 revealed that miR-203a-3p is involved in several OA-related processes, such as VEGF signaling, apoptosis, cell proliferation, and TGFβ signaling [15],
- Additionally, studies suggest other biomarkers with diagnostic potential for predicting osteoarthritis, including **MCL1**, **SIK1**, **JUND**, **NFKBIA**, and **JUN** [11].

b) Biomarkers in Osteoporosis

- **P1NP (Procollagen Type 1 N-terminal Propeptide):** A biomarker indicating bone remodeling processes, with fluctuations signaling resorptive and osteogenic activity. Its increase during teriparatide treatment is correlated with a positive response to osteoporosis therapy [12].
- **CTX (C-terminal telopeptide):** A marker for collagen degradation in bone, useful for assessing bone resorption and fracture risk. Significant increases in CTX have been observed in soccer players at the start and end of the season, which may aid in early diagnosis of athletes with excessive joint strain [13].

- **Bone Densitometry (DXA):** While an imaging technique, DXA is also considered a biomarker for diagnosing osteoporosis by assessing bone mineral density and fracture risk.

c) Biomarkers in Joint Inflammation

- **CRP (C-reactive Protein) and ESR (Erythrocyte Sedimentation Rate):** those are inflammatory markers, commonly elevated in inflammatory joint diseases (e.g., rheumatoid arthritis). However, their elevation is not specific to rheumatoid diseases, though they can assess inflammation severity, disease activity, or treatment effectiveness.
- **TNF-α (Tumor Necrosis Factor-alpha) and IL-6 (Interleukin-6):** Cytokines that play a key role in the pathogenesis of autoimmune diseases and can serve as biomarkers for disease activity in rheumatoid arthritis or other inflammatory joint conditions.

d) Biomarkers in Soft Tissue Injuries

- **Troponins:** Primarily used to diagnose myocardial infarction, troponins can also serve as biomarkers for skeletal muscle injury, intense physical exertion, or myocyte breakdown due to immunological factors.
- **Myosin:** A muscle protein whose elevated levels can indicate skeletal muscle damage.

e) Biomarkers in Bone Regeneration

- **BMPs (Bone Morphogenetic Proteins):** Proteins that stimulate the formation of new bone tissue and can be used to assess regenerative processes after fractures or orthopedic surgeries. BMP levels are also elevated in cartilage regeneration, which may be utilized in therapies involving stem cells [14].
- **OPG (Osteoprotegerin) and RANKL (Receptor Activator of Nuclear Factor κB Ligand):** Biomarkers involved in osteogenesis and bone resorption processes. OPG and RANKL are also therapeutic targets in osteoporosis treatment by inhibiting osteoclast activity.

f) Application of Biomarkers in Orthopedic Practice

- **Early Disease Diagnosis:** Biomarkers enable early detection of diseases such as osteoporosis and osteoarthritis before structural changes are visible in imaging.

- **Disease Progression Monitoring:** Biomarkers help track disease progression and treatment efficacy, especially in inflammatory joint diseases or osteoporosis.
- **Treatment Outcome Prediction:** Biomarkers can predict treatment response, such as in the case of inflammatory joint diseases or post-surgical regeneration in orthopedic patients.

  In combination with imaging, biomarkers represent a vital diagnostic tool that allows for a more precise and comprehensive approach to orthopedic patient care.

Future Directions in Orthopedic Diagnostics

Artificial intelligence is an exciting and growing field in medicine to assist in the proper diagnosis of patients. Although the use of artificial intelligence in orthopedics is currently limited, its utility in other fields has been extremely valuable and could be useful in orthopedics, especially spine care. Automated systems have the ability to analyze complex patterns and images, which will allow for enhanced analysis of imaging. Although the potential impact of artificial intelligence integration is promising, there are several limitations that must be overcome. [1] While this represents an important step in the advancement of this specialty, the concept of AI is rich with statistical jargon and techniques unfamiliar to many clinicians. This knowledge gap may limit the impact and potential of these novel techniques. [2] Smartphones represent a valuable tool in medical practice, offering unique support in various clinical settings. The majority of orthopedic surgeons possess smartphones, which are nearly always readily accessible. Their portability, coupled with internet connectivity, renders them an advantageous resource when advanced diagnostic methods are not readily available. Modern smartphones are capable of storing substantial amounts of data, are easily updatable, and support a wide range of applications on both iOS and Android platforms, which can aid in routine clinical practice. [3] Furthermore, ultrasound probes that interface with smartphones are now commercially available. This innovation has the potential to significantly enhance trauma surgery by facilitating the transmission of critical information between paramedics, emergency medical teams at the scene, and the surgical teams responsible for performing the operation. The real-time sharing of diagnostic images would streamline on-site assessments, improve the efficiency of emergency interventions, and better prepare hospital teams for the imminent arrival of the patient. Furthermore, in the era of epigenetics, I believe that to enhance the comfort of genetically predisposed patients, efforts should be made to identify the factors regulating the expression of genes responsible for synthesizing molecules involved in cartilage formation or the regeneration of damaged joints, with the goal of developing new therapeutic options for the chronically ill patient population.

Four-dimensional computed tomography (4DCT), or dynamic CT, is an advanced imaging technique increasingly used in orthopedics for both clinical and research purposes. Unlike traditional CT, 4DCT captures moving structures over time, allowing real-time visualization of dynamic processes. With improvements in technology and reduced radiation exposure, it has become a safe and effective method for evaluating joint movement. Initially focused on wrist motion, 4DCT is now applied to other joints such as the shoulder, elbow, hip, knee, and ankle. This technology enhances understanding of joint dynamics, including instability, impingement, and kinematics, offering valuable insights into joint function throughout its full range of motion. [18]

3D printing of metal implants is an emerging innovation in orthopedics, offering several advantages, including personalization, improved osseointegration, faster production times, and efficient material usage. By utilizing CT or MRI data, implants can be precisely tailored to meet the individual needs of patients, thereby enhancing their functionality. This process also allows for the creation of implants with micropores that promote bone integration, as well as the customization of mechanical properties to match the patient’s natural bone. However, challenges remain, including a lack of familiarity with the technology among surgeons, high equipment costs, limited material options, and the need to meet rigorous sterilization and safety standards. [16]

Conclusion

In an era with so many available technologies, physicians face the challenge of avoiding unnecessary tests and instead focusing on selecting those that are most relevant to the patient's condition to initiate the diagnostic process. Continuing education on imaging techniques and new biomarkers has become the standard. However, despite the advancements in available tools, it is essential not to overlook the importance of patient communication and physical examination, which undeniably remain the cornerstone of the entire diagnostic process. In conclusion:

a) **Application of Imaging Techniques in Orthopedics**: Imaging techniques in orthopedics are essential for diagnosis and treatment planning, each with strengths and limitations. X-ray is fast and effective for bone imaging but limited in soft tissue assessment and involves radiation. CT provides detailed 3D images for complex fractures and surgery planning but carries high radiation exposure. MRI excels in soft tissue analysis and diagnosing inflammatory diseases without radiation, though it's costly and time-consuming. Ultrasonography offers non-invasive, real-time imaging with no radiation, ideal for soft tissue injuries and joint inflammation, though its accuracy depends on the operator. Scintigraphy is sensitive for detecting bone inflammation, fractures, and tumors but has limited anatomical resolution. Each technique requires careful selection based on clinical needs.

b) **The Role of Biomarkers in Orthopedic Diagnostics**: Biomarkers are an important supplement in diagnosis, monitoring disease progression, and predicting treatment outcomes in orthopedics. Laboratory parameters can anticipate changes in imaging or clinical examination. In diseases such as osteoarthritis, osteoporosis, joint inflammatory conditions, or soft tissue injuries, biomarkers can assist in early detection of the problem, assess disease progression, and monitor the body's response to therapy. Examples of biomarkers such as CTx, MMP-3, HA, P1NP, CRP, or TNF-α show high diagnostic value. Additionally, research is ongoing into further markers to facilitate the diagnostic process.

c) **Integration of Biomarkers with Imaging Techniques**: The combination of biomarkers and imaging techniques provides a comprehensive approach to orthopedic diagnostics. When used together, these methods allow for a more accurate assessment of the patient's health and enable more precise treatment planning and monitoring of therapeutic outcomes. Biomarkers help detect diseases at an early stage, before structural changes become visible in imaging.

d) **The Future of Orthopedic Diagnostics**: Emerging technologies, such as artificial intelligence (AI) and mobile applications, offer significant potential for orthopedic diagnostics. AI helps facilitate faster and more accurate image analysis, while mobile devices, like ultrasound-connected smartphones, could transform field diagnostics and emergency interventions. Additionally, 4DCT enhances our understanding of joint dynamics, and 3D-printed implants offer personalized solutions that lead to better patient outcomes. However, challenges such as knowledge gaps, high costs, and technical limitations must be addressed through continued research and innovation. The integration of these technologies, along with advancements in epigenetics, could significantly improve treatment for chronically ill and genetically predisposed patients.

e) **The Potential of Epigenetics in Orthopedics**: With advancements in epigenetics research, it is becoming possible to develop new therapies targeted at individuals genetically predisposed to joint and soft tissue diseases. Understanding the mechanisms regulating the expression of genes related to cartilage or bone regeneration opens up new therapeutic possibilities, especially in treating patients with chronic orthopedic conditions.

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Author's contribution:

Conceptualization: Gabriela Trestka, Maria Przygoda, Wiktoria Domino

Methodology: Gabriela Trestka, Urszula Zelik

Investigation: Wojciech Florczak, Joanna Śnieżna

Software: Wojciech Florczak, Joanna Śnieżna

Check: Karol Dzwonnik, Jakub Dziewic, Jagienka Włodyka

Formal analysis: Sabina Adamczyk, Kamila Stępień

Writing – rough preparation: Gabriela Trestka, Maria Przygoda, Wiktoria Domino

Writing – review and editing: Maria Przygoda, Wiktoria Domino, Urszula Zelik

Resources: Jagienka Włodyka, Sabina Adamczyk, Kamila Stępień

Data curation: Urszula Zelik, Karol Dzwonnik, Jakub Dziewic

Supervision: Gabriela Trestka, Wiktoria Domino, Wojciech Florczak

Project administration: Gabriela Trestka, Joanna Śnieżna, Jakub Dziewic

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