69. Kim S.R., Lee K.S., Lee K.B., Lee Y.C. Recombinant IGFBP-3 inhibits allergic lung inflammation, VEGF production, and vascular leak in a mouse model of asthma. *Allergy: European Journal of Allergy and Clinical Immunology.* 2012; 67 (7): 869–877. DOI: 10.1111/j.1398-9995.2012.02837.x.
70. Han C.Z., Juncadella I.J., Kinchen J.M. et al. Macrophages redirect phagocytosis by non-professional phagocytes and influence inflammation. *Nature.* 2016; 539 (7630): 570–574. DOI: 10.1038/nature20141.
71. Haywood N.J., Slater T.A., Matthews C.J., Wheatcroft S.B. The insulin like growth factor and binding protein family: Novel therapeutic targets in obesity & diabetes. *Mol. Metab*. 2019: 19: 86–96. DOI: 10.1016/j.molmet.2018.10.008.

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The possibility of using radiology modalities in the diagnosis of crystalline arthropathy

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ABSTRACT

A review of current techniques of instrumental and laboratory diagnosis of crystalline arthropathies is presented. Advantages and disadvantages of various methods of diagnostic radiology and diagnostic radiologic criteria employed in primary and differential diagnosis of crystal deposits are discussed in relation to their etiology and clinical peculiarities. It is proven from a wide pool of published studies that the method of ultrasonic diagnosis is the most available one, has no contraindications, and demonstrates the best sensitivity and specificity in the diagnosis of crystalline arthropathy.

Key words: diagnostic ultrasound, diagnostic radiology, crystalline arthropathies, gouty arthritis, hydroxyapatite deposition disease, calcium pyrophosphate-deposition disease.

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Возможности применения лучевых методов исследования в диагностике кристаллических артропатий

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РЕЗЮМЕ

Представлен обзор современных методов инструментальной и лабораторной диагностики кристаллических артропатий. Обсуждаются достоинства и недостатки лучевых методов исследования в выявлении критериев и построении дифференциального ряда среди различных по природе кристаллических депозитов.

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Показано, что метод ультразвуковой диагностики обладает высокой чувствительностью и специфичностью в диагностике кристаллических артропатий.

Введение в диагностическую практику ультразвукового метода исследования позволит значительно повысить точность диагностики кальцификатов с последующим своевременным назначением лечебной и профилактической тактики пациентами с данным типом артрита, а новый набор диагностических критериев применительно к ультразвуковому исследованию в артрологии может способствовать дальнейшему повышению точности диагностики кристаллических артропатий.

Ключевые слова: УЗИ, радиология, кристаллические артропатии, подагрический артрит, гидроксиапатитная артропатия, пирофосфатная артропатия.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

Joint diseases are the most common pathology of the musculoskeletal system, leading to disability among all age groups of the population [1]. Rheumatic diseases with joint damage include such nosological forms as rheumatoid arthritis, psoriatic arthritis, and reactive arthritis. Lesions of the joints of the peripheral skeleton belong to a large group of spondyloarthritis. Most rheumatic diseases (RD) affect the structures of the human musculoskeletal system and, thus, significantly reduce the quality of life and limit opportunities for active social life [2].

According to the American Rheumatology Society, the distinction of up to 200 nosological units of rheumatic pathology is justified [3]. Older persons are most susceptible to metabolic and degenerative rheumatic diseases. About 40% of people over the age of 70 suffer from osteoarthritis, and 25% of them cannot tolerate daily physical activity. More than half of patients with rheumatoid arthritis are unable to work within 10 years after the onset of the disease, and 80% of them constantly experience severe pain, significantly impairing the quality of their life [1].

Timely diagnosis of early arthritis is a serious problem of modern rheumatology. Among patients with rheumatic diseases who sought medical care for the first time, 41% of cases were incorrectly diagnosed with rheumatic diseases at the outpatient stage. Only in 49% of patients, the diagnosis was confirmed after a specialist examination [2].

Another problem is high cost of managing patients with RD. This is determined by the complexity and high cost of research methods, as well as the need for long-term and sometimes lifelong treatment of many, especially young, patients using expensive conservative, surgical methods, sanatorium-resort, and social and psychological rehabilitation.

The nature of pathological changes, their localization and prevalence, and the patterns of involvement of different groups of joints provide a differential diagnosis between various rheumatic diseases.

A special place in the list of joint diseases is occupied by crystalline arthropathies due to the complexity of diagnosis and the peculiarities of the clinical presentation. Arthropathies include a group of diseases characterized by deposition of microcrystals of various chemical composition in the joints and periarticular tissues. The main nosological forms of inflammatory polyarthritis associated with the deposition of crystal structures are gout (deposition of urate crystals), pyrophosphate arthropathy (deposition of calcium pyrophosphate crystals), and hydroxyapatite arthropathy (deposition of hydroxyapatite crystals) [1, 3].

THE MAIN NOSOLOGIES OF INFLAMMATORY POLYARTHROPATHIES

Gout (gouty arthritis) is a chronic progressive joint disease characterized by disruption of purine metabolism and increased content of uric acid in the blood, followed by monosodium urate depo-

sition in the tissues and formation of gouty tophi surrounded by fibrovascular tissue. Gouty tophi are painless nodular formations ranging from 5 mm to 10 cm. The period of their formation from the onset of the disease is 5–6 years. The prevalence of gout is 3.9% in the US, 10.9% in France, 1.4–2.5% in the UK, 1.4% in Germany, and 3.2–6.1% in New Zealand [3].

The formation of gouty tophi in the articular and periarticular tissues is accompanied by the development of gouty arthritis (gouty arthropathy). Recurrent acute mono- or oligoarthritis of the joints of mostly the lower extremities – the metatarsophalangeal joint of the 1st finger and the interphalangeal joint of the 3rd finger, dominates in the clinical presentation of gouty arthritis. This does not exclude the involvement of other small and large joints of the peripheral (hand, knee, shoulder, elbow, ankle, and hip joints) and axial (sacroiliac joints, spine joints) skeleton in the process, with rapid development of acute pain syndrome, reaching its maximum within 6–12 hours, and subsequent chronic pain syndrome.

With a chronic course, damage to target organs, in particular, kidneys, progresses with the development of chronic renal failure. In the absence of treatment, the attack-free periods are shortened, arthritis attacks become more frequent, their intensity and duration increase, and "new" joints get involved.

During visual examination, attention is drawn to hyperemia and hyperthermia of the skin in the joint area, pain upon palpation, and formation of protruding areas at the tophus level [4]. Prolonged exposure of the underlying structures to tophi leads to damage to the soft tissue structures of the joint, articular hyaline cartilage, and the underlying bone tissue. Periarticular and intraarticular tophi affect the formation of erosions – marginal destructions, usually with clear external contours.

A standardized and fundamental method of detecting erosions is radiography, which has limitations in early diagnosis of diseases of the joints. Radiographic signs of gout appear in the late chronic period, usu ally no earlier than 6 years [5] after the onset of the disease, and are almost always present in patients with subcutaneous tophi.

Hydroxyapatite crystal deposition disease (HADD) is a disease of unknown origin, characterized by joint pain syndrome in combination with the deposition of hydroxyapatite crystals in the periarticular tissues, mainly in the tendons, joint capsules, sacs, and synovial membrane.

There are primary (idiopathic) and secondary calcium-hydroxyapatite arthritis. The latter develops in chronic renal failure, diffuse diseases of the connective tissue, and after traumatic injuries. Calcinosis of individual tumors is also hydroxyapatite crystal deposition.

The most common localization of the deposition of hydroxyapatite crystals is the shoulder joint, less often the femur (large trochanter), the elbow joint, the wrist and knee joints, as well as the joints of the hand, foot, and lumbar spine. Hydroxyapatite arthropathy can affect the tendons of other muscles, such as the gluteus medius or the thigh muscles. The deposition of crystals often occurs at a distance of 1 cm from the place where the tendons attach to the bones. Calcifications of various sizes and shapes can be deposited in articular sacs and capsules.

The disease is more common in middle age, more often in men, and proceeds according to both mono- and oligoarthritis pattern [6]. It may occur acutely or have a chronic recurrent character. It is characterized by soft tissue edema and limited mobility in the affected joints. An asymptomatic course of the disease is also possible.

Visualization or detection of calcifications is crucial in determining the cause of the pain syndrome. The most sensitive in detecting calcifications in the tendons and ligaments are radiological methods, such as plain radiography and computer tomography (CT).

Calcium pyrophosphate dihydrate crystal deposition disease (CPPD crystal deposition disease, pseudogout or pyrophosphate arthropathy) is an inflammatory joint disease of the mono-or oligoarthritis type with acute, subacute, and chronic course. It is the third most prevalent after rheumatoid arthritis and gout among inflammatory arthritis. The frequency of CPPD crystal deposition disease increases with age [7].

The development of CPPD crystal deposition disease is accompanied by the formation and deposition of calcium pyrophosphate dihydrate crystals (CPPD) in the joints and resulting inflammation [8], pseudogout forms of inflammatory arthritis, [9] and a possible asymptomatic course of the disease [10]. The most commonly affected joints are the knee joints, followed by the joints of the upper extremi-

ties, the hip joint, and the joints of the foot, as well as the pubic symphysis [11].

The clinical presentation of CPPD crystal deposition disease is often similar to that of gout (pseudogout) with a longer period of development and less pronounced pain syndrome. At the same time, hyperthermia, hyperemia, swelling, and concretion of soft tissues may occur in the area of the affected joint. An acute attack of CPPD crystal deposition disease may be accompanied by fever.

The chronic course is characterized by a less pronounced clinical picture, rare involvement of the metacarpophalangeal joints in the pathological process, the absence of extra-articular symptoms, and morning stiffness. Against the background of a chronic disease course, acute attacks may occur as well.

With a complicated course, a destructive (rheumatoid-like) form of the disease may appear, requiring differential diagnosis with all erosive arthropathies, as well as with pseudo-neuropathic arthropathy, characterized by an increased sensitivity to palpation and the absence of obvious neurological symptoms. Rheumatoid-like and pseudo-neuropathic forms present a significant diagnostic problem.

In an acute attack, especially with monoarthritis of a large joint, septic arthritis can develop in some cases. In these cases, it is important if the patient had similar attacks in the past. Besides, the absence of "septic" changes in the blood, the noticeable effect of antibiotics, and characteristic changes on X-ray images are essential. The appearance of acute synovitis should always lead to the consideration of septic arthritis as a differential diagnosis.

METHODS OF INSTRUMENTAL AND LABORATORY DIAGNOSTICS

The leading place in the diagnosis of crystalline arthropathies is occupied by radiation methods of investigation, which include radiography, tomographic methods (CT and magnetic resonance imaging (MRI)), and ultrasound. The features of visual manifestations of certain forms of crystalline arthropathies are determined by the chemical composition of the crystals.

Computed tomography. Urate crystals, which lead to the formation of gouty tophi, are non-radiopaque in *gouty arthritis*, so in radiography and CT, bone changes at the site of tophus deposition have the form of erosion – marginal lytic destruction with clear contours. In gouty arthropathy, erosions have a rounded or oval shape are of various sizes and are accompanied by a periosteal reaction in the form of a thin rim of bone density surrounding the soft-tissue structure of the tophus completely or partially.

Large expansion and severity of intra-articular tophi, as well as long duration of the process lead to widespread extensive destruction of the adjoining articular surfaces. With para-articular localization of the tophus, the usual width of the articular fissure is maintained for a long time, since its deposition at the level of the hyaline cartilage does not occur simultaneously over its entire surface. In case of violation of calcium metabolism, calcified inclusions can be visualized in the tophi.

Small bone defects may resemble erosions in rheumatoid arthritis, psoriatic arthritis, calcium pyrophosphate arthropathy, or cysts that do not have specific manifestations. When using single-energy CT, gouty tophi look like low-density bone defects with more accurate (compared to radiography) determination of the prevalence, localization, nature of the periosteal reaction, and calcified inclusions in disrupted calcium metabolism in tophi.

In the last decade, dual-energy CT (DECT), a modified computed tomography based on the use of low- and high-energy X-rays (80 and 140 kV) to obtain images of various types of tissues, has been used in clinical practice.

Registration of the difference in the attenuation of the X-ray beam by urates and trabeculae, supplemented by color coding of urates and calcium in the joints and surrounding tissues, allows for the identification of urate salts *in vivo* with high accuracy, regardless of their size and localization.

DECT provides a qualitative and quantitative assessment of monosodium urate crystals and shows good sensitivity and specificity in predicting gout compared to the synovial fluid analysis. The sensitivity of the method is 85–100% and the specificity is 83–92% [12, 13].

Deposits of hydroxyapatite crystals and calcium-pyrophosphate crystals in *hydroxyapatite arthritis and calcium-pyrophosphate arthritis* are accompanied by the formation of chondrocalcinosis, so X-ray methods are highly sensitive in their detection. In radiography, chondrocalcinosis (CC)

manifests itself in the form of point and linear areas of calcification in the projection of hyaline and fibrocartilage. Typical sites of calcification include the fibrous tissue of the the knee joint meniscus, the triangular fibrocartilage disc of the wrist joint, the temporomandibular joint disc, and the intervertebral disc.

Radiography is still a popular method in detection of chondrocalcinosis. At the same time, the prevalence and localization of chondrocalcinosis are being discussed in publications. Therefore, A. Abhishek et al. (2012) conducted an X-ray study of the knee, hip, and hand joints among a representative group of 3,170 volunteers [14]. Signs of CC were detected in 428 (13.7%) people. The most frequent localization of CC was the knee joint (8%). At the same time, its fibrocartilage was affected more often (88.5%) than hyaline cartilage (55%). It was more often affected in lateral (89.1%) than medial (74%) aspects.

The prevalence of CC in the wrist joint was 6.9%, in the hip joint – 5%, in the pubic symphysis – 3.6%, and in the meta carpophalangeal joint – 1.5%. The age of the patient did not correlate with the localization of CC in the hyaline cartilage compared to the fibrocartilage.

Radiologically, crystalline deposits are visualized as structureless areas of induration, varying in size and density. Periarticular calcifications have a linear, triangular, rounded, or oval shape and are localized according to the place of tendon attachment. Large tumor-like areas of calcification occur in patients with chronic renal failure or diffuse connective tissue diseases.

In *osteoarthritis*, the prevalence of calcification deposits in the tissues of the ankle joint is 51.3% [15], in the shoulder join – 98.9% [16], in the hip joint – 96.6% [17], and in the knee joint – 4.3–100% [17, 18]. Computed tomography has high sensitivity and specificity in the diagnosis of joint tissue calcification. In the work of M. Devyani et al. (2014) using single- and dual-energy CT, the presence of CPPD crystals in several structures of the knee joint was demonstrated [19].

In 2013, S. Touraine et al. performed a high-resolution CT on 68 knee joints (34 pairs of joints) from postmortem donors with an average age of 84 years. The results showed calcified fibrocartilage in 34% and calcified hyaline cartilage in 21% of the knee joints [20]. This study also revealed a high prevalence of CPPD deposits in the periarticular tissues of the tibia.

A broader CT study of the knee joints in a group of 608 patients conducted in Japan demonstrated a clear correlation between the presence of CPPD crystals and the depth of cartilage degeneration in the knee joint, confirming the opinion that crystal deposition is associated with cartilage thinning [21]. However, the reasonability of using this modality due to the presence of radiation exposure, its cost, and the issues of CT accuracy requires additional research aimed at justifying the availability of this method in the diagnosis of crystalline arthropathies (or in the CC detection) [22].

Magnetic resonance imaging. Among crystalline arthropathies, MRI is highly informative in the diagnosis of gout based on the visualization of both heterogeneous, mainly the hypo-intensive T2 WI and FSat tophus, and fibrovascular tissue surrounding tophus, clearly visualized after contrast enhancement. However, MRI is rarely used to visualize crystals in other crystalline arthropathies (hydroxyapatite and calcium-pyrophosophate arthropathies) due to the fact that the crystal structures do not generate a signal.

The use of MRI as an imaging method in conditions associated with the deposition of CPPD crystals often leads to misdiagnosis [23]. The insensitivity of MRI to the detection of calcified crystals in the cartilage tissue was confirmed by the study of B. Dirim et al. (2012). It showed that 75% of CPPD crystal deposits were missed when using MRI with a field strength of 1.5 T in the study of the cadaveric knee joint [24]. In this regard, it is justified to conduct a greater number of studies to determine the possibilities of MRI diagnostic methods in crystalline arthropathies for using the techniques in routine diagnostic practice.

Light methods of investigation (light microscopy, polarized light microscopy, phase-contrast microscopy) are currently the standard in the detection of CPPD crystals in the synovial fluid in the diagnosis of patients with CPPD [25]. In CPPD, crystals can be detected in the synovial fluid even in a previously non-inflamed joint, which is also a characteristic feature of gout. On the one hand, the phenomenon of the formation and persistence of crystals in the joints is extremely stable and does

not depend on the stage and period of the disease. On the other hand, CPPD crystals have weak refraction or do not refract the light at all [26]. This means that they are poorly visualized and require more experience and time (looking at a minimum of 30 fields of view), and sometimes special calcium coloring. A prerequisite for the visualization of CPPD crystals is their high concentration in the synovial fluid. A low concentration of CPPD crystals in the synovial fluid can lead to a negative result, due to the difficulty of detecting them in a single sample of synovial fluid.

Ultrasound diagnostics. To date, there is no doubt about the relevance of ultrasound in arthrology as a non-invasive and safe method, which hashigh informative value and is a valuable diagnostic tool for the accurate assessment of intra-articular and para-articular structures involved in a wide range of rheumatic diseases in adults and children [27]. In the modern literature, the issues of ultrasound diagnostics in the study of RA patients are widely covered and include assessment of the thickness and nature of synovial vascularization, the state of the state of synovial tissue in chronic arthropathies, and the activity of the inflammatory process [7, 23, 28–32].

Along with the indicated field of ultrasound use in arthrology, the literature data of the last decade indicate the increasing role of ultrasound in the diagnosis of crystalline arthropathies and high diagnostic effectiveness of the method in detecting small crystal deposits [7, 23, 28–32]. Ultrasound imaging of tissues is based on acoustic resistance of tissues with their reflection of ultrasound and formation of an image of the object under study as acoustic reflections. This makes it possible to better differentiate the crystalline bodies from the surrounding tissues (hyaline cartilage, synovial fluid, etc.) due to the greater number of acoustic signals reflected from them [32].

In *gouty arthropathy*, ultrasound is used not only to determine intra-articular exudate, which is noted in various phases of the disease, but also to visualize the tophi and clarify the condition of the hyaline cartilage. Tophi in ultrasound imaging are characterized as heterogeneous, mainly hyperechoic formations, which may be surrounded by a more hypoechoic surface rim. Additionally, the signs of gout include a hyperechoic surface of the hyaline cartilage, in contrast to the localization of the hyperechoic line in the thickness of the articular cartilage, which occurs in calcium-pyrophosphate arthropathy [33].

Ultrasound can visualize hyperechoic point and linear areas in the projection of soft tissues, the snowstorm sign in the synovial fluid due to the presence of small, rounded particles of different echogenicity, as well as bone erosion [33]. The fibrovascular tissue surrounding the inflammatory process results in the presence of color loci when using Doppler color flow mapping.

High accuracy of ultrasound in the detection of gouty tophi is described in the work of M. Gruber et al. (2013) [31]. A study of 21 patients with clinical suspicion of chronic or acute gout in 37 joints showed a comparable sensitivity of DECT (67.6%) and ultrasound (64.7%).

Different variants of the visual pattern of calcified intraarticular and para-articular structures according to ultrasound data in hydroxyapatite and calcium-pyrophosphate arthropathies were described [7, 28, 34–36].

Thus, in patients with *hydroxyapatite arthropathy*, four morphological forms of tendon calcification were identified: arc-shaped (a hyperechoic arc with clear acoustic shadowing), nodular (a single hyperechoic focus without an acoustic shadow), fragmentary (two or more hyperechoic foci with or without acoustic shadowing), fragmented and cystic (hyperechoic band with anechoic or low-echogenic content) [36]. The nodular, fragmented, and cystic forms are associated with the acute symptomatic phase of calcific tendinitis, while the arc-shaped form is more consistent with the chronic or asymptomatic phase [36].

For visualization of CPPD deposits in the study of patients with calcium-pyrophosphate arthropathy, A. S. Ellabban et al. (2011) proposed the following ultrasound criteria. Criterion I: thin hyperechoic bands parallel to the surface of the hyaline cartilage; criterion II: a “point pattern” consisting of several thin, glittering hyperechoic areas; criterion III: homogeneous hyperechoic nodular or oval deposits, often mobile, localized in the articular sacs and recesses [37].

In the same study, the results of ultrasound of 60 patients with exudate in the knee joint showed the following. Criterion II was detected in 30 pa-

tients (criterion II alone – in 21 patients, and in combination with criterion I and/or criterion III – in 9 patients), criterion III alone was detected separately in 2 patients. Criterion II was identified in all 18 patients with signs of CC of the wrist joint, which makes it the most common one. On ultrasound, CPPD deposits are represented by hyperechoic inclusions with clear acoustic shadowing with a diameter of >10 mm. However, the appearance of acoustic shadowing is possible at the early stage of the disease with a crystal diameter of up to 2–3 mm.

When visualizing CPPD deposits, criterion II is most often found inside the cartilage tissue or tendons of the joint [38]. Moreover, ultrasound has demonstrated successful detection of CPPD crystals in periarticular tissues that were not radiologically visualized [39].

In the course of the conducted studies, the ultrasound method showed fairly high sensitivity and specificity (from 60–85% to 90.6–100%, respectively [29, 30, 34, 37, 40], as well as successful identification of the criteria for CPPD deposit occurrence [34, 37]. However, the sensitivity of ultrasound to detect CPPD varied depending on the structure under study, ranging from 34% (tendon) to 80% (hyaline cartilage).

Low sensitivity in detecting calcifications at the tendon level is probably determined by late involvement of these structures in the pathological process. [35]. In addition, low sensitivity of ultrasound to the visualization of calcinates in tendon tissues may be associated with their high echogenicity or late involvement in the pathological process [35].

The sensitivity indicators for detecting chondrocalcinosis ranged from 55–81% for hyaline cartilage and up to 68–100% for fibrocartilage. The best diagnostic results were achieved when the cartilage tissue itself was visualized in more than one joint.

CPPD deposits on the surface of the hyaline cartilage can imitate the "double contour" (in the form of an additional band of increased echogenicity) of uric acid deposits in gout [41, 42]. Since this pattern is considered the most specific sign of gout, it is necessary to conduct more studies to improve the accuracy of ultrasound diagnostics in the visualization of crystal structures in gout in order to establish a specific nosological form of joint damage [43].

The values of sensitivity and specificity of ultrasound also depend on the reference method used in the study. Thus, the use of knee cartilage biopsy as a reference method resulted in lower sensitivity and specificity of ultrasound results, which may be explained by the presence of too small CPPD crystals in the tissue. [7].

In the last decade, **ultrasound elastography** has been introduced into clinical practice, particularly for cirrhotic liver lesions.

Quasi-static ultrasound elastography is based on the assessment of the elasticity of tissues by comparing images before and after their compression. The possibilities of the method vary depending on how the mechanical stress in the tissues is created (by static or dynamic compression), and on the method of result evaluation. The method shows high efficiency in the study of superficially located organs, especially the mammary and thyroid glands [44].

Shear wave elastography (dynamic elastography*)* is based on the use of transverse waves, as opposed to longitudinal waves emitted by sensors in traditional ultrasound diagnostics. The method is used in the diagnosis of cirrhosis and pronounced fibrotic changes in the liver, although it cannot be considered reliable for detecting the onset of the pathological process. A serious disadvantage of the method is the inability to obtain a two-dimensional picture with sufficient resolution [44].

Indications for elastography are gradually expanding, and in recent years, publications have begun to appear that provide data on the use of elastometry in the study of soft tissue structures of the peripheral and axial skeleton [45–47]. The findings of the studies by E.E Drakonaki et al.(2012) showed that this method may be even more sensitive than MRI or B-mode imaging with detection of subclinical changes in the muscles and tendons [40].

A common problem of most of the conducted studies is insufficient correctness of the methodological aspects of the research: a small number of studied patients, incorrect material selection for comparative characteristics of the obtained results, and a relatively small number of studies performed in general [7].

CONCLUSION

The literature data indicate a current indicate the current demand for ultrasound examination for the identification of crystal structures in joint diseases,

in particular, in crystalline arthropathies. This is determined by the physical capabilities of the method, which provides visualization of the echogenicity of crystal structures, the presence of acoustic shadowing typical of calcified structures, as well as determination of the exact localization of calcinates. All of the above-mentioned justifies the use of ultrasound as a valuable tool in assessing the state of joint structures in various types of joint dam- age, including crystalline arthropathies.

However, to date, contradictory data on the results of ultrasound in the study of patients with crystalline arthropathies have been published. Thus, there is relatively high variability in the sensitivity of the method, depending on the structure under study: cartilage or tendon. There is no definite clarity in the differentiation of hyperechoic deposits, similar in structure (urate crystals, pyrophosphate and calcium hydroxyapatite, crystals of other etiologies).

At the same time, the possibilities of ultrasound are not fully applied. Currently, the B-mode is mainly used in diagnostics, while additional introduction of shear wave elastography can significantly expand the diagnostic potential of this modality. There is no clarity on ultimate possibil- ities of ultrasound in the diagnosis of crystal- line arthropathies due to the insufficient number of studies on this topic with the use of the same criteria and the same groups of joints.

Radiography, computed tomography, and polar- ized light microscopy continue to provide important information in the diagnosis of CPPD crystals. In combination with ultrasound, these methods emphasize the polyarticular and systemic nature of CPPD crystals, high rate of calcification of not only cartilage, but also ligaments and tendons, as well as inflammation and destruction of tissues associated with the crystal deposition. Introduction of ultrasound into diagnostic practice will significantly improve the accuracy of calcification diagnosis, followed by the timely administration of therapeutic and preventive tactics in patients with this type of arthritis.

Further research is required to determine the possible potential of the method. A new set of diagnostic criteria applied to ultrasound in arthrology may further improve the accuracy of examination. It is also necessary to study the reliability of the method and bring the research results to a consensus.

REFERENCES

1. Marianovskiy A.A. Rheumatic diseases of the musculoskeletal system: biotherapeutic concept of complex treatment.. *Lechaschi Vrach Journal* . 2003; (3): 10–14 (in Russ.).
2. Galushko E.A. Medical and social importance of rheumatic diseases: extended abstract of Doc. Sci. (Med.). M.; 2011: 48 (in Russ.).
3. Neogi T., Jansen T.L., Dalbeth N., Fransen J., Schumacher H.R., Berendsen D., Brown M., Choi H., Edwards N.L., Janssens H.J., Lioté F., Naden R.P., Nuki G., Ogdie A., Perez-Ruiz F., Saag K., Singh J.A., Sundy J.S., Tausche A.K., Vazquez-Mellado J., Yarows S.A., Taylor W.J. Gout classification criteria: an American College of Rheumatology European League Against Rheumatism collaborative initiative. *Arthritis & Rheumatology*. 2015; 67 (10): 2557–2568. DOI: 10.1002/art.39254.
4. Mirmiran R., Bush T., Cerra M.M., Grambart S., Kauschinger E., Younger M., Zychowicz M. Joint Clinical Consensus Statement of the American College of Foot and Ankle Surgeons® and the American Association of Nurse Practitioners®: Etiology, Diagnosis, and Treatment Consensus for Gouty Arthritis of the Foot and Ankle. *J. Foot Ankle Surg*. 2018; 57 (6): 1207–1217. DOI: 10.1053/j.jfas.2018.08.018.
5. Barskova V.G. Gout diagnosis (lecture). *Rheumatology Science and Practice*. 2012; 50 (4): 62–66 (in Russ.). DOI: 10.14412/1995-4484-2012-1114.
6. Saber M., Mudgal P. Hydroxyapatite deposition disease. URL: https://radiopaedia.org/articles/hydroxyapatite-deposition-disease?lang=gb.
7. Adinolfi F., Iagnocco A., Filippucci E., Cimmino M.A., Bertoldi I.,
8. Di Sabatino V., Picerno V., Delle Sedie A., Sconfienza L.M., Frediani B., Scir C.A. Ultrasound in the diagnosis of calcium pyrophosphate dihydrate deposition disease. A systematic literature review and a meta-analysis. *Osteoarthritis Cartilage.* 2016; 24 (6): 973–981. DOI: 10.1016/j.joca.2016.01.136.
9. Rutsch F., Terkeltaub R. Parallels between arterial and cartilage calcification: what understanding artery calcification can teach us about chondrocalcinosis. *Curr. Opin. Rheumatol*. 2003; 15 (3): 302–310. DOI: 10.1097/00002281-200305000-00019.
10. Tedeschi S.K., Stone R.M., Helfgott S.M. Calcium pyrophosphate crystal inflammatory arthritis (pseudogout) with myelodysplastic syndrome: A new paraneoplastic syndrome? *J. Rheumatol.* 2017; 44 (7): 1101–1102. DOI: 10.3899/jrheum.170106.
11. Abhishek A., Doherty M. Update on calcium pyrophosphate deposition. *Clin. Exp. Rheumatol*. 2016; 34 (4 Suppl. 98): 32–38.
12. Wada N., Yamashita K., Hiwatashi A., Togao O., Kamei R., Momosaka D., Maeda Y., Matsushita T., Yamasaki R., Iida K., Yamada Y., Kira J.I., Honda H. Calcium pyrophosphate dihydrate crystal deposition disease of the spinal dura mater: a case report. *BJR Case Rep.* 2017; 4 (1): 20170049. DOI: 10.1259/bjrcr.20170049.
13. Smelser C.D., Stoffey R.D., Gentili A., Steinbach L.S., Chew F.S., Guglielmi G. Gout Imaging *Medscape*. 2017. URL: https://emedicine.medscape.com/article/389965-overview.

14. Newberry S.J., FitzGerald J., Maglione M.A. et al. Diagnosis of gout. Rockville (MD): Agency for Healthcare Research and Quality (US); 2016 Feb. (Comparative Effectiveness Reviews, No. 158). URL: https://www.ncbi.nlm.nih.gov/books/NBK350137/.
15. Abhishek A., Doherty S., Maciewicz R., Muir K., Zhang W., Doherty M. Chondrocalcinosis is common in the absence of knee involvement. *Arthritis Res. Ther.* 2012; 14 (5): R205. DOI: 10.1186/ar4043.
16. Hubert J., Weiser L., Hischke S., Uhlig A., Rolvien T., Schmidt T., Butscheidt S.K., Püschel K., Lehmann W., Beil F.T., Hawellek T. Cartilage calcification of the ankle joint is associated with osteoarthritis in the general population. BMC. *Musculoskelet Disord.* 2018; 19 (1): 169. DOI: 10.1186/s12891-018-2094-7.
17. Hawellek T., Hubert J., Hischke S., Vettorazzi E., Wegscheider K., Bertrand J., Pap T., Krause M., Püschel K., Rüther W., Niemeier A. Articular cartilage calcification of the humeral head is highly prevalent and associated with osteoarthritis in the general population. *J. Orthop Res.* 2016; 34 (11): 1984–1990. DOI: 10.1002/jor.23227.
18. Hawellek T., Hubert J., Hischke S., Krause M., Bertrand J., Pap T., Püschel K., Rüther W., Niemeier A. Articular cartilage calcification of the hip and knee is highly prevalent, independent of age but associated with histological osteoarthritis: evidence for a systemic disorder. *Osteoarthr. Cartil.* 2016; 24 (12): 2092–2099. DOI: 10.1016/j.joca.2016.06.020.
19. Mitsuyama H., Healey R.M., Terkeltaub R.A., Coutts R.D., Amiel D. Calcification of human articular knee cartilage is primarily an effect of aging rather than osteoarthritis. *Osteoarthr. Cartil.* 2007; 15 (5): 559–565. DOI: 10.1016/j.joca.2006.10.017.
20. Misra D., Guermazi A., Sieren J.P., Lynch J., Torner J., Neogi T., Felson D.T. CT imaging for evaluation of calcium crystal deposition in the knee: initial experience from the Multicenter Osteoarthritis (MOST) study. *Osteoarthritis Cartilage.* 2015; 23 (2): 244–248. DOI: 10.1016/j.joca.2014.10.009.
21. Touraine S., Ea H.K., Bousson V., Cohen-Solal M., Laouisset L., Chappard C., Lioté F., Laredo J.D. Chondrocalcinosis of femoro-tibial and proximal tibio-fibular joints in cadaveric specimens: a high-resolution CT imaging study of the calcification distribution. *PLoS One.* 2013; 8 (1): e54955. DOI: 10.1371/journal.pone.0054955.
22. Ryu K., Iriuchishima T., Oshida M., Kato Y., Saito A., Imada M., Aizawa S., Tokuhashi Y., Ryu J. The prevalence of and factors related to calcium pyrophosphate dihydrate crystal deposition in the knee joint. *Osteoarthritis Cartilage*. 2014; 22 (7): 975–979. DOI: 10.1016/j.joca.2014.04.022.
23. Miksanek J., Rosenthal A.K. Imaging of calcium pyrophosphate deposition disease. *Curr. Rheumatol.* 2015; 17 (3): 20. DOI: 10.1007/s11926-015-0496-1/.
24. Rettenbacher T., Ennemoser S., Weirich H., Hartig F., Klotz W., Herold M. Diagnostic image of gout: comparison of high-resolution US versus conventional X-ray. *Eur. Radiol*. 2008; 18 (3): 621–630. DOI: 10.1007/s00330-007-0802-z.
25. Dirim B., Resnick D., Abreu M., Wangwinyuvirat M., Trudell D.J., Haghighi P. Relationship between the degeneration of the cruciate ligaments and calcium pyrophosphate dihydrate crystal deposition: anatomic, radiologic study with histologic correlation. *Clin. Imaging.* 2013; 37 (2): 342–347. DOI: 10.1016/j.clinimag.2012.03.002.
26. Zhang W., Doherty M., Bardin T., Barskova V., Guerne P.A., Jansen T.L., Leeb B.F., Perez-Ruiz F., Pimentao J., Punzi L., Richette P., Sivera F., Uhlig T., Watt I., Pascual E. European League Against Rheumatism recommendations for calcium pyrophosphate deposition. Part I: terminology and diagnosis. *Ann. Rheum. Dis.* 2011; 70 (4): 563–570. DOI: 10.1136/ard.2010.139105.
27. Martinez Sanchis A., Pascual E. Intracellular and extracellular CPPD crystals are a regular feature in synovial fluid from uninflamed joints of patients with CPPD related arthropathy. *Ann. Rheum. Dis.* 2005; 64 (12): 1769–1772. DOI: 10.1136/ard.2005.035386.
28. Ogdie A., Taylor W.J., Weatherall M., Fransen J., Jansen T.L., Neogi T., Schumacher H.R., Dalbeth N. Imaging modalities for the classification of gout: systematic literature review and meta-analysis. *Ann. Rheum. Dis.* 2015; 74 (10):1868–74. DOI: 10.1136/annrheumdis-2014-205431.
29. Filippucci E., Gutierrez Riveros M., Georgescu D., Salaffi F., Grassi W. Hyaline cartilage involvement in patients with gout and calcium pyrophosphate deposition disease. An ultrasound study. *Osteoarthritis Cartilage*. 2009; 17 (2):178–181. DOI: 10.1016/j.joca.2008.06.003.
30. Barskova V.G., Kudaeva F.M., Bozhieva L.A., Smirnov A.V., Volkov A.V., Nasonov E.L. Comparison of three imaging techniques in diagnosis of chondrocalcinosis of the knees in calcium pyrophosphate deposition disease. *Rheumatology.* 2013; 52 (6): 1090–1094. DOI: 10.1093/rheumatology/kes433.
31. Forien M., Combier A., Gardette A., Palazzo E., Dieudé P., Ottaviani S. Comparison of ultrasonography and radiography of the wrist for diagnosis of calcium pyrophosphate deposition. *Joint Bone Spine.* 2018; 85 (5): 615–618. DOI: 10.1016/j.jbspin.2017.09.006.
32. Gruber M., Bodner G., Rath E., Supp G., Weber M., Schueller-Weidekamm C. Dual-energy computed tomography compared with ultrasound in the diagnosis of gout. *Rheumatology (Oxford).* 2014; 53 (1): 173–179. DOI: 10.1093/rheumatology/ket341.
33. Gaber W., Ezzat Y., Abd El Rahman S.F. Role of diagnostic ultrasonography in detecting gouty arthritis *The Egyptian Rheumatologist*. 2013; 35 (2): 71–75. DOI: 10.1016/j.ejr.2012.12.003.
34. Lai K.-L., Chiu Y.-M. Role of ultrasonography in diagnosing gouty arthritis. *Journal of Medical Ultrasound*. 2011; 19 (1): 7–13. DOI: 10.1016/j.jmu.2011.01.003.
35. Ruta S., Catay E., Marin J., Rosa J., García-Monaco R., Soriano E.R. Knee effusion: ultrasound as a useful tool for the detection of calcium pyrophosphate crystals. *Clin. Rheumatol*. 2016; 35 (4):1087–1091. DOI: 10.1007/s10067-015-3100-1.
36. Filippou G., Filippucci E., Tardella M., Bertoldi I., Di Carlo M., Adinolfi A., Grassi W., Frediani B. Extent and distribution of CPP deposits in patients affected by calcium pyrophosphate dihydrate deposition disease: an ultrasonographic study. *Ann. Rheum. Dis*. 2013; 72 (11): 1836–1839. DOI: 10.1136/annrheumdis-2012-202748.

37. Chiou H.-J., Chou Y.-H., Wu J.-J., Huang T.F., Ma H.L., Hsu C.C., Chang C.Y. The role of high-resolution ultrasonography in management of calcific tendonitis of the rotator cuff. Ultrasound in Medicine and Biology. *Ultrasound Med. Biol.* 2001; 27 (6):735–743. DOI: 10.1016/S0301-5629(01)00353-2.
38. Ellabban A.S., Kamel S.R., Omar H.A., El-Sherif A.M., Abdel-Magied R.A. Ultrasonographic diagnosis of articular chondrocalcinosis *Rheumatol Int.* 2012; 32 (12): 3863–3868. DOI: 10.1007/s00296-011-2320-1.
39. Wu Y., Chen K., Terkeltaub R. Systematic review and quality analysis of emerging diagnostic measures for calcium pyrophosphate crystal deposition disease. *RMD Open*. 2016; 2 (2): e000339. DOI: 10.1136/rmdopen-2016-000339.
40. Falsetti P., Frediani B., Acciai C., Baldi F., Filippou G., Prada E.P., Sabadini L., Marcolongo R. Ultrasonographic study of Achilles tendon and plantar fascia in chondrocalcinosis. *J. Rheumatol.* 2004; 31: 2242–2250.
41. Di Matteo A., Filippucci E., Salaffi F., Carotti M., Carboni D., Di Donato E., Grassi W. Diagnostic accuracy of musculoskeletal ultrasound and conventional radiography in the assessment of the wrist triangular fibrocartilage complex in patients with definite diagnosis of calcium pyrophosphate dihydrate deposition disease. *Clin. Exp. Rheumatol.* 2017; 35 (4): 647–652.
42. Adinolfi A., Picerno V., Di Sabatino V., Bertoldi I., Galeazzi M., Frediani B., Filippou G. Inquiry is fatal to certainty – is the ultrasonography double contour sign specific for uric acid-induced arthritis*? Arthritis Rheum.* 2013; 65 (7): 1952. DOI: 10.1002/art.37952.
43. Dejaco C. SP0018 The practical case: Is it really easy to distinguish gout from CPPD by ultrasound? Live case with patient. *Ann. Rheum. Dis.* 2013; 72: A5. DOI: 10.1136/annrheumdis-2013-eular.18.
44. Chowalloor P.V., Keen H.I. A systematic review of ultrasonography in gout and asymptomatic hyperuricaemia. *Ann. Rheum. Dis*. 2013; 72 (5): 638–645. DOI: 10.1136/annrheumdis-2012-202301.
45. Osipov L.V. Ultrasound elastography technology. *Medical alphabet.* 2013; 3–4 (23): 5–21 (in Russ.).
46. Alauraih A.M., O'Connor P., Tan A.L., Hensor E.M.A., Ladas A., Emery P., Wakefield R.J. Muscle shear wave elastography in idiopathic inflammatory myopathies: a case-control study with MRI correlation *Skeletal. Radiol.* 2019; 48 (8): 1209–1219. DOI: 10.1007/s00256-019-03175-3.
47. Zardi E.M., Franceschetti E., Giorgi C., Palumbo A., Franceschi F. Reliability of quantitative point shear-wave ultrasound elastography on vastus medialis muscle and quadriceps and patellar tendons. *Med. Ultrason*. 2019; 21 (1): 50–55. DOI: 10.11152/mu-1712.
48. Wadugodapitiya S., Sakamoto M., Sugita K., Morise Y., Tanaka M., Kobayashi K. Ultrasound elastographic assessment of the stiffness of the anteromedial knee joint capsule at varying knee angles. *Biomed. Mater. Eng*. 2019; 30 (2): 219–230. DOI: 10.3233/BME-191046.
49. Drakonaki E.E., Allen G.M., Wilson D.J. Ultrasound elastography for musculoskeletal applications. *Br. J. Radiol*. 2012; 85 (1019): 1435–1445. DOI: 10.1259/bjr/93042867.

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