UDC: 616-036.21:578.834]:616.72
DOI 10.17721/1728.2748.2022.89.5-9

S. Borodin, PhD stud.,
Y. Tuharov, PhD stud.,
D. Ostapchenko, stud.,
L. Kot, PhD,
O. Korotkyi, Dr. Sci.
Taras Shevchenko National University of Kyiv, Kyiv, Ukraine

VIEW OF THE PATHOGENETIC MECHANISMS OF JOINT DAMAGE IN CORONAVIRUS DISEASE 2019 (COVID-19)

The Coronavirus disease 2019 (COVID-19) pandemic has had an extremely serious impact on the livelihoods of people worldwide. Despite the mainly respiratory manifestations of SARS-CoV-2 infection, its consequences can affect the functioning of most systems of organism, including the musculoskeletal, dysfunction of which is a leading factor in disability of the population. Diseases of the joints are one of the most common pathologie of modernity, which in the last decade are increasingly found in young people and even children. The musculoskeletal symptoms can be observed as isolated clinical signs and expressed regardless of the severity of the viral disease. Chronic fatigue, myalgia, swelling and joint pain may occur during the acute phase of COVID-19 and as short-term or long-term complications, but their prevalence has not been systematically studied. Considering the wide range of clinical manifestations of SARS-CoV-2 infection and the complexity of their pathogenesis, the mechanisms underlying lesions of musculoskeletal system and rheumatological complications remain unclear. Today, the main research in this direction is focused mainly on a complete understanding of the regulatory pathways of immune dysregulation and inflammation. Excessive secretion of pro-inflammatory cytokines, disruption of signal transduction and immune response are the result of the severe impact of SARS-CoV-2 infection on most organs, including joints, as well as the use of corticosteroids for the treatment of patients with COVID-19. The presented review highlights generalized information on the main pathophysiological processes that can occur in the joints as a manifestation of the impact of SARS-CoV-2 infection, and possible key mechanisms which contribute to the progression of pathological changes.

Keywords: COVID-19, SARS-CoV-2, musculoskeletal system, joints, osteoarthritis.

Introduction. The pandemic of the Coronavirus disease COVID-19 is a relevant topic worldwide due to its extremely large impact on all aspects of the daily life of society. Researchers and clinicians are actively studying the pathogenetic mechanisms of damage caused by respiratory infection SARS-CoV-2. Recently, trends in scientific research are changing from the acute consequences of viral infection to long-term ones. Although the SARS-CoV-2 virus is mainly assiciatedwith the respiratory system, reports indicate to a widespread tissue tropism of COVID-19. There is increasing evidence of the direct and indirect effects of the coronavirus infection on dysfunctions of various organ systems [1, 2]. The presence of musculoskeletal symptoms such as joint pain or arthralgia, muscle pain or myalgia, reactive arthritis and vasculitis (inflammation of blood vessels), etc., which can be both temporary and continue for months is a concern: there is a high probability of NSAID use, especially among the middle-aged and elderly population [3]. Joint and muscle pain in endemic coronaviruses is quite rare (occurs in less than 10 % of cases), while in SARS-CoV-2 arthralgia is noted in 15 % of cases, and muscle pain and general weakness occur in one quarter or half of patients with symptoms of COVID-19. But the potential mechanisms of the viral infection impact on the musculoskeletal system have not yet been systematically studiedand are currently limited [2, 4]. Given the wide range of symptoms, it is likely that the mechanism of systemic effects of SARS-CoV-2 infection is multifactorial. Proposed mechanisms include endothelial damage and dysfunction, dysregulation and hyperactivation of the immune system, which is described as a cytokine storm and the ability of coronavirus to evade the immune system. As a result, coagulation and inflammation can significantly affect the progression of the disease and possibly lead to injury to the musculoskeletal system, in particular pathological manifestations in the joints [5]. Despite the fact that there is an increase in the number of cases of arthritis after infection with COVID-19, the potential mechanisms at the origin of arthritis in the context of SARS-CoV-2 viral infection still remain at the hypothesis stage [6, 7]. Arthritis can also occur as a result of steroid and antiviral drugs used to treat COVID-19. Rheumatoid arthritis (RA), which can occur after COVID-19, deserves special attention [8]. Today, this issue is a completely new challenge for rheumatologists and scientists, which requires study and long-term observation.

Potential cellular targets of the musculoskeletal system for SARS-CoV-2 infection. Coronaviruses are known to enter host cells in three ways: receptor-mediated plasma membrane fusion, receptor-mediated endocytosis, or antibody-dependent viral entry. Receptor proteins on the surface of host cells are critical forvirus attachment to cells. SARS-CoV-2 mediates infection by binding its spike protein (which comprises S1 and S2 subunits) to one of its main receptors, the angiotensin-converting enzyme 2 (ACE2), using the host cell surface proteases, in particular, transmembrane serine protease 2 (TMPRSS2), lysosomal cathepsins, proprotein convertase it is also known as a furin, etc., the expression of which is crucial for the fusion of membranes and the final penetration of the virus into the cell [9].

ACE2 is expressed to varying degrees in almost all human organs (lung, heart, gut, adipose tissue, thyroid, kidney, vessels, and brain) [10]. Therefore, all types of cells and tissues that express ACE2 may be potential targets for SARS-CoV-2 infection. It is believed that SARS-CoV-2 can achieve a primary infection through the respiratory tract, then enter the circulation and infect non-target tissues containing ACE2- and TMPRSS2-rich cell types.

In studies [2] showed that a part of B cells in the epithelium of the respiratory tract, mast cells, macrophages, alveolar cells and T cells express ACE2 and TMPRSS2. In human skeletal muscle tissue, multiple cell types (endothelial cells, smooth muscle cells, pericytes, muscle stem cells, macrophages, adaptive immune cells and muscle fibers) express TMPRSS2. However, only smooth muscle cells and pericytes express ACE2. Several cells in the synovium, including fibroblasts, monocytes, B cells, and T cells, express ACE2 and TMPRSS2. In articular cartilage, proliferative, hypertrophic and effector chondrocytes express ACE2, and only homeostatic chondrocytes express TMPRSS2. In the meniscus, a small proportion of cartilage progenitors and

regulatory fibrochondrocytes express ACE2, while TMPRSS2 is not detected. ACE2 was found to be expressed in samples of composite unenriched cortical and trabecular bone and in osteoblast-enriched samples, whereas TMPRSS2 was almost undetectable in composite bone tissue but was expressed in all osteoblast-enriched samples.

Similar results indicate that musculoskeletal tissues may be potential sites of direct infection by SARS-CoV-2. Despite significant research efforts to learn more about the pathogenesis of COVID-19, musculoskeletal involvement is understudied. However, there is scientific evidence [11, 12], which report that RNA of SARS-CoV-2 was not detected in any of the knee joint samples: synovial fluid, synovial membrane and bone tissue, as well as in myocytes of muscle tissue, despite a positive result in samples of other tissues (sputum, nasopharyngeal secretions, blood and feces). During the past few months there have been isolated reports [13, 14] about of cases SARS-CoV-2 RNA detection in the synovial fluid, which is associated with the development of arthritis on the background of a viral infection. The establishment of such cases raises the probability that SARS-CoV-2 RNA may be a pathological stimulus for local synovial inflammation in the joint, which deserves further consideration and investigation.

Clinical manifestations and symptoms of joint disease in COVID-19. The clinical spectrum of COVID-19 symptoms ranges from asymptomatic infection or mild respiratory symptoms (dry cough, nasal congestion, sore throat and dyspnea) to severe pneumonia with acute respiratory distress syndrome and multiorgan dysfunction. New evidence suggests that SARS-CoV-2 infection can cause musculoskeletal damage during the infectious or post-infectious stage. Patients with COVID-19 sometimes experience hypocalcemia, vitamin D deficiency, and possible immobilization due to the disease, which contributes to bone demineralization. In general, SARS-CoV-2 infection may be a trigger forclinical arthritis, through mechanisms related to immune inflammation, but most often it is associated with arthralgia, myalgia and muscle weakness [15]. Today the overwhelming number of studies on COVID-19 consider the occurrence of arthralgia and myalgia together as a single entity [3, 16]. However, researches are emerging that highlight the appearance of joint pain associated with COVID-19 as a new and clear manifestation of SARS-CoV-2 infection which was previously underrecognized by clinicians [16, 17]. Arthralgia is mentioned as one of the possible early symptoms in patients with COVID-19, which occurs independently of respiratory symptoms [18]. Also, systematic reviews confirm that approximately 4 % to 12 % of patients still suffer from arthralgia during the first year after infection [19, 20]. The causes of joint pain can be varied: from degenerative and destructive processes to inflammation of the periarticular tissues. It can also be caused by other conditions, such as an infection or vaccination [21].

Viral arthritis usually manifests as a polyarticular arthritis that coincides with other viral symptoms, the pathological mechanism of which may be mediated by local destruction after viral infiltration of tissue or an immune-mediated response triggered by molecular mimicry. Some identified cases of arthritis in patients with COVID-19 were clinically more consistent with reactive arthritis, although often the patient was not diagnosed extra-articular symptoms, as it is usually triggered by bacterial infections, but it can also be caused by viruses. Reactive arthritis is usually mono- or oligoarticular and asymmetric in distribution, may occur sometime after the initial viral symptoms and in most cases, it disappears within three to six months without causing long-term problems [6, 13]. Arthritis may be a response to a masked pulmonary or gastrointestinal infection as a consequence of COVID [6, 22] or it may be a nonspecific consequence of the "cytokine storm" that accompanies symptomatic forms of the disease [23].

In addition, it is important to understand the effects on the musculoskeletal system of modern drugs: the use of antibiotics to eliminate any factors associated with reactive arthritis, analgesics for pain relief, nonsteroidal anti-inflammatory and specific antiviral agents, steroids or antirheumatic drugs, given that the side effects profile of many of these drugs coincides with the symptoms that are characteristic of COVID-19 and may mask the presence of SARS-CoV-2 infection.

Therefore, clinical signs of damage to the musculoskeletal system, in particular the joints, against the background of both acute infection and long-term COVID-19 must be carefully analyzed in combination with the results of laboratory tests, including parameters associated with inflammation and infection (Interleukin 6, procalcitonin, C-reactive protein, etc.). Monitoring symptoms is of paramount importance to minimizing any progressive and long-term disability.

Pathophysiological mechanisms of joint damage in SARS-CoV-2 infection. It has been established that the pathophysiological mechanisms of COVID-19 are related to direct viral invasion via ACE2 receptors, dysregulation of the renin-angiotensin-aldosterone system (RAAS), hypoxia, hyperinflammation, endotheliopathy and thrombosis [24]. The potential mechanisms underlying the occurrence of joint pathologies or complications of their course caused by SARS-CoV-2 infection remain at the hypothesis stage. However, their main evaluation is focused mainly on immunopathological features, which include the hyperactivation of immune cells, prolonged inflammatory response, release of a large number of pro-inflammatory cytokines and chemokines, insufficient interferon response and possible production of autoantibodies [8]. An inflammatory reaction (both innate and adaptive immune response) in the airways caused by SARS-CoV-2 infection can lead to systemic inflammation. In severe cases, COVID-19 can excessively stimulate the immune response, leading to uncontrolled release of cytokines, a so-called "cytokine storm," T-cell depletion and lymphopenia [25]. The systemic inflammatory response together with other concomitant pathological factors, causes disruption or deregulation of many organ systems, exacerbation of existing pathologies and can be a trigger for pathological changes in the joints [26].

Studies have shown that SARS-CoV-2 infection induces an increase in important pro-inflammatory molecules which impact on musculoskeletal tissues: interleukin 1 beta (IL-1β), IL-6, IL-8, IL-17 and tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), interferon-gamma inducible protein 10 (IP-10 or CXCL10), monocyte chemoattractant protein 1 (MCP1), C-reactive protein (CRP), soluble receptor for advanced glycation end products (sRAGE), receptor activator of nuclear factor-B ligand (RANKL), vascular endothelial growth factor (VEGF) and macrophage colony stimulating factor (M-CSF), et al. [27]. These inflammatory mediators can promote phenotypic stability of joint cartilage, catabolic cascades and tissue destruction, leukocyte infiltration or tissue repair [2, 28]. IL-1β, IL-6 and TNF-α are key inflammatory factors in the pathogenesis of osteoarthritis (OA), induce chondrolysis, that may result in the occurrence of arthralgias, and are involved in joint degeneration and synovial cell activation in RA [29]. CXCL10, IL-17 and TNF-α are known to play an important role in

osteoclastogenesis [30, 31]. It is believed that IL-1β, IL-17 and TNF-α involved in inflammatory processes in tendinopathy and degenerative tendon disorders [32].

It should be noted that the increased level of inflammatory mediators promotes vasodilation and induces dysfunction of endothelial cell, which can result in impaired blood circulation in the synovial membrane and subchondral bone, degenerative changes in articular cartilage, stimulation of osteocyte apoptosis and osteoclast formation, and affects bone metabolism. Endothelial cells are rich in ACE2, so the virus itself can directly cause dysfunction by simply infecting the cells [33].

The inflammatory effects of key cytokines such as IL-1, IL-6, IFN-γ and TNF-α are realized through the appropriate intracellular signaling pathways resulting in the activation of nuclear factor kappa-light-chain-enhancer of activated B cells' (NF-κB), JAK/STAT and MAPK pathways [34, 35]. Through various combinations of cytokine receptors and signal transduction pathways, a one signaling molecule may not only participate in one pathway, but also affect the transduction of other pathways.

S. Ong, et al. reported that abnormally elevated levels of pro-inflammatory cytokines (particularly IL-1β) persisted 6 months after contracting COVID-19, even in patients who remained asymptomatic during the acute phase of the disease [36].

The relationship between COVID-19 and RA. The consequences of COVID-19, in particular rheumatological manifestations that occur during the course of a coronavirus infection or after an acute illness, have been investigated since 2019. In the literature sources it is mentioned that respiratory viruses can be associated with the development of RA – an autoimmune disease which results in joint destruction, is characterized by chronic inflammation, progresses cumulatively and has a wide range of extra-articular (systemic) manifestations [37, 38]. In terms of the severity of joint damage, RA is unparalleled among other diseases of the musculoskeletal system. For the treatment of this pathological condition, a "treat to target" strategy is often used, which aims to achieve a state of remission or a low disease activity, and needs the use of immunosuppressive drugs, which requires increased attention to their immune status to minimize infectious risks, especially during the COVID-19 pandemic [39].

As you know, any infectious pathology is closely related to autoimmune, since both pathogenetic mechanisms interact with each other, jointly causing the response of the immune system. The mechanisms of the development of autoimmune reactions include the induction of costimulators of antigen-presenting cells (primarily macrophages that first encounter an infection); molecular mimicry (when a foreign antigen has a common sequence or structural similarity with its own antigens); the influence of viruses that cause polyclonal activation of B-lymphocytes, provoking the synthesis of a significant number of antibodies, some of which are autoreactive, etc. Because most patients with an autoimmune disease the symptoms appear long before the onset of abnormal immune reactions, it is often difficult to pinpoint the factors responsible for the onset of the disease.

The mechanisms of the autoimmune reactions caused by the SARS-CoV-2 virus have not been sufficiently studied, and it is still too early to predict a direct relationship between the coronavirus infection and the development of RA [40]. Immunologists and rheumatologists suggest that SARS-CoV-2 may indeed be the virus that causes acute autoimmune diseases in genetically predisposed patients. In the modern scientific literature, the question is even raised: is COVID-19 an infection or an autoimmune disease? [41]. Although several cases of RA after COVID-19 have been reported [42, 43], more research is still needed to understand whether the manifestation of RA is related to SARS-CoV-2 infection or is a coincidence. Both COVID-19 and RA have similar pathogenesis mechanisms mediated by aberrant ACE/ACE2 activity, and driven by the activities of analogous macrophage clusters [8, 44]. ACE activation promotes the accumulation of angiotensin II, which may be pathologically involved in both COVID-19 and RA. In the inflammatory environment, angiotensin II is known to induce inflammatory responses and vascular permeability by enhancing the production of prostaglandins and VEGF. These inflammatory mediators further contribute to the activation of nuclear factor NF-κB, which enhances inflammatory reactions and promotes the infiltration of inflammatory cells into damaged tissues [8, 35]. Therefore, the hyperactivation immune inflammatory response provoked by COVID-19 may serve as a potential causative factor in the development of autoimmune and rheumatic manifestations.

Analyzing the results of scientific research, several possible specific mechanisms can be identified, such as the polyclonal activation of B-lymphocytes; immunosuppression, which occurs in most patients with COVID-19 in the early phases of the disease; inadequate syndrome of recovery of the immune system after the acute phase and immunosuppression with a breakthrough of autotolerance; the results of polypharmacotherapy, glucocorticoids, immunoglobulins and other immunoactive drugs [45].

A critical view at the crosstalk between COVID-19 and OA. Osteoarthritis is one of the most common diseases in the elderly, which ischaracterized by inflammation of all articular structures, muscle atrophy, bone remodeling and sclerosis, cartilage destruction, meniscus damage, synovial membrane hypertrophy, osteophyte development and ligament dysfunction. Often of this pathology is present simultaneously with other chronic diseases such as cardiovascular disease, diabetes and obesity. These comorbidities are risk factors for infection with COVID-19 and its high severity. Currently, there is not enough evidence that COVID-19 provokes the development of OA. Scientific sources suggest [5] that the inflammatory reaction in the organism caused by the SARS-CoV-2 virus, even of a low degree, can generate a large number of pro-inflammatory cytokines, which contributes to the destruction of cartilage, thus inducing of OA or worsening its course. Studies of the biochemical mechanisms of the potential effects of SARS-CoV-2 infection on cartilage degeneration or synovial inflammation in the joints are still at the initial stage [46].

Conclusions. Pathological changes in the organism caused by COVID-19 are mainly related to the expression of ACE2 in the appropriate cells of various tissues, impaired functioning of the renin-angiotensin system and inflammation. An excessive inflammatory reaction can cause serious damage to the musculoskeletal system, more than the coronavirus infection itself. Muscle fatigue, myalgia, joint pain and arthritis are the most common extrapulmonary manifestations of SARS-CoV-2 infection, which can have severe short-term or long-term consequences, the elimination of which sometimes require the use of steroids, nonsteroidal anti-inflammatory drugs, or physiotherapy. It is believed that these symptoms mainly arise as a result of inflammatory and immune reactions, in the development of which pro-inflammatory effector cytokines are involved in combination with factors related to concomitant therapy. Studies emphasize

that laboratory indicators (increased levels of C-reactive protein, creatinine, D-dimer, cytokines, lymphopenia, leukocytosis, etc.) and imaging methods (computed tomography, magnetic resonance imaging, ultrasound, radiography) play a crucial role in the diagnosis and assessment of manifestations of COVID-19. However, most of these methods focus mainly on the respiratory, cardiovascular and digestive systems, only a few results are related to the musculoskeletal system. Clinical features and mechanisms of musculoskeletal manifestations of COVID-19 require study and in-depth analysis.

References

1. Lopez M, Bell K, Annaswamy T, Juengst S, Ifejika N. COVID-19 guide for the rehabilitation clinician: a review of non-pulmonary manifestations and complications. Am J Phys Med Rehabil. 2020;99(8):669-73. PubMed PMID: 32467492; PubMed Central PMCID: PMC7299122.
2. Disser NP, De Micheli AJ, Schonk MM, Konnaris MA, Piacentini AN, et al. Musculoskeletal consequences of COVID-19. J Bone Joint Surg Am. 2020;102(14):1197-204. PubMed PMID: 32675661.
3. Cipollaro L, Giordano L, Padulo J, Oliva F, Maffulli N. Musculoskeletal symptoms in SARS-CoV-2 (COVID-19) patients. J Orthop Surg Res.2020;178. https://doi.org/10.1186/s13018-020-01702-w.
4. Schett G, Manger B, Simon D, Caporali R. COVID-19 revisiting inflammatory pathways of arthritis. Nat Rev Rheumatol.2020;16:465-70.
5. Lauwers M, Au M, Yuan S, Wen C. COVID-19 in joint ageing and osteoarthritis: current status and perspectives. Int J Mol Sci. 2022;23(2):720. doi:10.3390/ijms23020720.
6. Wendling D, Verhoeven F, Chouk M, Prati C. Can SARS-CoV-2 trigger reactive arthritis? Joint Bone Spine. 2021;88(1):105086. doi:10.1016/j.jbspin.2020.105086.
7. Gasparotto M, Framba V, Piovella C,Doria A, Iaccarino L. Post-COVID-19 arthritis: a case report and literature review. Clin Rheumatol.2021;40:3357-62.
8. Dewanjee S, Kandimalla R, Kalra RS, Valupadas C, Vallamkondu J, et al. COVID-19 and rheumatoid arthritis crosstalk: emerging association, therapeutic options and challenges. Cells. 2021;10(12):3291. doi:10.3390/cells10123291.
9. Zhang Q, Xiang R, Huo S, Zhou Y, Jiang S, Wang Q, Yu F. Molecular mechanism of interaction between SARS-CoV-2 and host cells and interventional therapy. Sig Transduct Target Ther.2021;6:233. https://doi.org/10.1038/s41392-021-00653-w.
10. Angeli F, Zappa M, Reboldi G, Trapasso M, Cavallini C, Spanevello A, Verdecchia P. The pivotal link between ACE2 deficiency and SARS-CoV-2 infection: one year later. Eur J Intern Med. 2021;93:28-34.PubMed PMID: 34588140.
11. Grassi M, Giorgi V, Nebuloni M, Zerbi P, Gismondo MR, et al. SARS-CoV-2 in the knee joint: a cadaver study. Clin Exp Rheumatol. 2022;40(3):608-12. PubMed PMID: 34665699.
12. White-Dzuro G, Gibson LE, Zazzeron L, White-Dzuro C, Sullivan Z, et al. Multisystem effects of COVID-19: a concise review for practitioners. Postgrad Med. 2021;133(1):20-7. PubMed PMID: 32921198.
13. Kuschner Z, Ortega A, Mukherji P. A case of SARS-CoV-2-associated arthritis with detection of viral RNA in synovial fluid. J Am Coll Emerg Physicians Open. 2021;2(4):e12452. doi:10.1002/emp2.12452.
14. Yokogawa N, Minematsu N, Katano H. Case of acute arthritis following SARS-CoV-2 infection. Ann Rheum Dis. 2020;80(6):e101. doi: 10.1136/annrheumdis-2020-218281.
15. Hasan LK, Deadwiler B, Haratian A, Bolia IK, Weber AE, Petrigliano FA. Effects of COVID-19 on the musculoskeletal system: clinician's guide. Orthop Res Rev. 2021;13:141-50. PubMed PMID: 34584465.
16. Hoong CWS, Amin MNME, Tan TC, Lee JE. Viral arthralgia a new manifestation of COVID-19 infection? A cohort study of COVID-19-associated musculoskeletal symptoms. Int J Infect Dis. 2021;104:363-9. PubMed PMID: 33476761; PubMed Central PMCID: PMC7813485.
17. Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS. Extrapulmonary manifestations of COVID-19. Nat Med. 2020;26(7):1017-32.
18. Joob B, Wiwanitkit V. Arthralgia as an initial presentation of COVID-19: observation. Rheumatol Int. 2020;40:823.doi: 10.1007/s00296-020-04561-0.
19. Sapkota HR, Nune A. Long COVID from rheumatology perspective – a narrative review. Clin Rheumatol. 2022;41(2):337-48.
20. Fernández-de-las-Peñas C, Navarro-Santana M, Plaza-Manzano G, Palacios-Ceña D, Arendt-Nielsen L. Time course prevalence of post-COVID pain symptoms of musculoskeletal origin in patients who had survived to SARS-CoV-2 infection. Pain. 2022;163(7):1220-31. PubMed PMID: 34561390.
21. Motaqi M, Hatef B, Askari Ashtiani A, Ghanjal A. Musculoskeletal problems in patients with COVID-19: a review study. Asian J Sports Med. 2021;12(3):e111040. doi: 10.5812/asjsm.111040.
22. Ono K, Kishimoto M, Shimasaki T. Reactive arthritis after COVID-19 infection. RMD Open. 2020;6:e001350.doi: 10.1136/rmdopen-2020-001350.
23. Quartuccio L, Semerano L, Benucci M, Boissier MC, De Vita S. Urgent avenues in the treatment of COVID-19: targeting downstream inflammation to prevent catastrophic syndrome. Joint Bone Spine. 2020;87(3):191-3. PubMed PMID: 32321634; PubMed Central PMCID: PMC7167227.
24. Siam HB, Abedin SM, Ahmed A, Nishat NH, Hossain MS. Pathophysiological mechanisms of disease severity in COVID-19: an update. J Adv Biotechnol Exp Ther. 2020;3(4):68-78.
25. Henderson LA, Canna SW, Schulert GS, Volpi S, Lee PY, et al. On the alert for cytokine storm: immunopathology in COVID -19. Arthritis Rheumatol. 2020;72:1059-63.
26. Ramani SL, SametJ, Franz CK, Hsieh C, Nguyen CV, Horbinski C, DeshmukhS. Musculoskeletal involvement of COVID-19: review of imaging. Skeletal Radiol.2021;50:1763-73.
27. Dos Santos PK, Sigoli E, Bragança LJG, Cornachione AS. The Musculoskeletal Involvement after mild to moderate COVID-19 infection. Front Physiol. 2022;13:813924. doi:10.3389/fphys.2022.813924.
28. Korotkyi OH, Vovk AA, Halenova TI, Vovk TB, Dvorshchenko KO, Falalyeyeva TM, Ostapchenko LI. Cytokines profile in knee cartilage of rats during monoiodoacetate-induced osteoarthritis and administration of probiotic.Biopolym Cell.2020;36(1):23-35. https://doi.org/10.7124/bc.000A1E.
29. Su C-H, Lin C-Y, Tsai C-H, Lee H-P, Lo L-C, et al. Betulin suppresses TNF-α and IL-1β production in osteoarthritis synovial fibroblasts by inhibiting the MEK/ERK/NF-κB pathway. J. of Functional Foods.2021;86:104729. https://doi.org/10.1016/j.jff.2021.104729.
30. Liu P, Lee S, Knoll J, Rauch A, Ostermay S, et al. Loss of menin in osteoblast lineage affects osteocyte-osteoclast crosstalk causing osteoporosis. Cell Death Differ. 2017;24(4):672-82. PubMed PMID: 28106886; PubMed Central PMCID: PMC5384024.
31. Kotake S, Udagawa N, Takahashi N, Matsuzaki K, ItohK,et al. IL-17 in synovial fluids from patients with rheumatoid arthritis is a potent stimulator of osteoclastogenesis. J Clin Invest. 1999;103(9):1345-52. PubMed PMID: 10225978; PubMed Central PMCID: PMC408356.
32. D'Addona A, Maffulli N, Formisano S, Rosa D. Inflammation in tendinopathy. Surgeon. 2017;15(5):297-302. PubMed PMID: 28596062.
33. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet. 2020;395:1417-8. PubMed PMID: 32325026; PubMed Central PMCID: PMC7172722.
34. Chen P, Tang Y, He W, Yang R, Lan Z, Chen R, Zhang P. Potential pathophysiological mechanisms underlying multiple organ dysfunction in cytokine release syndrome. Mediators of Inflammation. 2022;2022:7137900.https://doi.org/10.1155/2022/7137900.
35. Wong MCS, Wong S, Huang J, Yan B. Relating angiotensin-converting enzyme inhibitors or angiotensin receptor blockers with incidence or mortality of COVID-19. ESC Heart Fail. 2020;7:3119-23. PubMed PMID: 33121220; PubMed Central PMCID: PMC7524232.
36. Ong SWX, Fong S-W, Young BE, Chan Y-H, Lee B, et al. Persistent symptoms and association with inflammatory cytokine signatures in recovered coronavirus disease 2019 patients. Open forum infectious diseases. 2021;8(6):156. https://doi.org/10.1093/ofid/ofab156.
37. Favalli EG, Ingegnoli F, De Lucia O, Cincinelli G, Cimaz R, Caporali R. COVID-19 infection and rheumatoid arthritis: faraway, so close! Autoimmun Rev. 2020;19:102523. doi: 10.1016/j.autrev.2020.102523.
38. Eyupoglu OE, Ates I. The relationship between rheumatoid arthritis and COVID-19. Biomed J Sci Tech Res.2021;38(4):30501-6.
39. Hock ES, James M-MS, WailooA,Scott DL, Stevensonet M, et al. Treat-to-target strategies in rheumatoid arthritis: a systematic review and cost-effectiveness analysis. SN Compr Clin Med. 2021;3:838-54.
40. D'Silva KM, Wallace ZS. COVID-19 and rheumatoid arthritis. Curr Opin Rheumatol. 2021;33:255-61. PubMed PMID: 33625043; PubMed Central PMCID: PMC8784188.
41. Icenogle T. COVID-19: Infection or autoimmunity. Front Immunol. 2020;11:2055. doi:10.3389/fimmu.2020.02055.
42. Roongta R, Chattopadhyay A, Ghosh A. Correspondence on Onset of rheumatoid arthritis after COVID-19: coincidence or connected? Ann Rheum Dis. 2021. doi:10.1136/annrheumdis-2021-220479.
43. Özcan E, Özcan S. The new onset seropozitive rheumatoid arthritis after COVID-19 infection: coincidental or related. Kastamonu Med J. 2022;2(1):24-6.
44. Zhu Z, Cai T, Fan L, Lou K, Hua X, Huang Z, Gao G. The potential role of serum angiotensin-converting enzyme in coronavirus disease 2019. BMC Infect Dis. 2020;20:883. doi:10.1186/s12879-020-05619-x.
45. Kudryavtsev I, RubinsteinA, GolovkinA, Kalinina O, Vasilyev K, Rudenko L, Isakova-Sivak I. Dysregulated immune responses in SARS-CoV-2-infected patients: a comprehensive overview. Viruses. 2022;14:1082. https://doi.org/ 10.3390/v14051082.
46. Alhassan E, Siaton BC, Hochberg MC. Did COVID-19 impact osteoarthritis – clinical perspective? Curr Opin Rheumatol. 2022;34(1):68-72. PubMed PMID: 34698678; PubMed Central PMCID: PMC8635080.

Надійшла до редколегії 02.05.22
Отримано виправлений варіант 01.06.22
Підписано до друку 01.06.22

Received in the editorial 02.05.22
Received version on 01.06.22
Signed in the press on 01.06.22

С. Бородін, асп.,
Ю. Тугаров, асп.,
Д. Остапченко, студ.,
Л. Кот, канд. біол. наук,
О. Короткий, д-р біол. наук
Київський національний університет імені Тараса Шевченка, Київ, Україна

ПОГЛЯД НА ПАТОГЕНЕТИЧНІ МЕХАНІЗМИ УРАЖЕННЯ СУГЛОБІВ ПРИ КОРОНАВІРУСНІЙ ХВОРОБІ 2019 (COVID-19)

Пандемія коронавірусної хвороби 2019 (COVID-19) надзвичайно серйозно вплинула на життєдіяльність людей в усьому світі. Незважаючи на переважно респіраторні вияви інфекції SARS-CoV-2, її наслідки можуть негативно впливати на функціонування більшості систем організму, зокрема й кістково-м'язової, дисфункція якої є провідним фактором інвалідизації населення. Захворювання суглобів є одними з найпоширеніших патологій сучасності, які в останнє десятиліття все частіше виявляються у молоді й навіть дітей. Симптоми ушкоджень опорно-рухового апарату можуть спостерігатися у вигляді ізольованих клінічних ознак та виражатися незалежно від важкості вірусного захворювання. Хронічна втома, міалгія, набряк і біль у суглобах можуть виникати під час гострої фази COVID-19, а також як короткочасні або тривалі ускладнення, проте їхня поширеність систематично не вивчалася. Ураховуючи широкий спектр клінічних виявів інфекції SARS-CoV-2 і складність її патогенезу, механізми, що лежать в основі уражень опорно-рухової системи та ревматологічних ускладнень, залишаються нез'ясованими. Сьогодні основні дослідження в цьому напрямі зосереджено переважно на повному розумінні регуляторних шляхів імунної дисрегуляції і запалення. Надмірна секреція прозапальних цитокінів, порушення сигнальної трансдукції та імунної відповіді є наслідком важкого впливу інфекції SARS-CoV-2 на більшість органів, включаючи суглоби, а також застосування кортикостероїдів для лікування хворих на COVID-19. У представленому огляді висвітлено узагальнену інформацію щодо основних патофізіологічних процесів, які можуть відбуватися у суглобах, як виявів впливу інфекції SARS-CoV-2, і можливих ключових механізмів, які сприяють прогресуванню патологічних змін.

Ключові слова:COVID-19, SARS-CoV-2, опорно-руховий апарат, суглоби, остеоартрит.