Review article
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Mechanisms of musculoskeletal consequences of COVID-19

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Abstract

Introduction A coronavirus, SARS-CoV-2, called COVID-19 by the WHO has caused a pandemic of respiratory illness killed more than 6 million people. The severe infection has a significant negative impact on the entire musculoskeletal system.

The objective was to summarize literature data on the mechanisms of the condition and identify musculoskeletal symptoms of COVID-19.

Material and methods An internet search of PubMed, MedLine and eLIBRARY library databases using the search terms: COVID-19, aseptic osteonecrosis, post-COVID-19 syndrome, arthropathy, musculoskeletal system, spondylitis, osteoporosis was performed.

Results and discussion Musculoskeletal symptoms of COVID-19 are reported in 31-59% of cases. Mechanisms of musculoskeletal involvement of coronavirus infection include cytotoxic effect of the virus on osteogenesis cells, vascular inflammation and coagulopathy, "cytokine storm", side effects of drug therapy and hypoxia. According to an etiological factor, musculoskeletal manifestations of SARS-CoV-2 include autoimmune (reactive arthritis, sacroiliitis, ankylosing spondylitis, axial spondyloarthritis, psoriatic arthritis) conditions caused by impaired circulation of bone tissue (aseptic osteonecrosis), infectious (septic arthritis, spondylitis, spondylodiscitis) and metabolic (osteopenia, osteoporosis) conditions.

Conclusion It has been established that COVID-19 infection has a negative impact on the musculoskeletal, endocrine and immune systems increasing the risk of degenerative diseases of the musculoskeletal system and infectious complications in orthopaedic patients early post surgery.

Keywords: COVID-19, aseptic osteonecrosis, post-Covid syndrome, arthropathy, musculoskeletal system, spondylitis, osteoporosis

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INTRODUCTION

A coronavirus, SARS-CoV-2, called COVID-19 by the WHO has caused a pandemic of respiratory illness killed more than 6 million people [1]. Despite the general understanding of the symptoms and consequences of COVID-19, the full spectrum of the disease's impact on the human body is still unknown. In the future, patients who have suffered from COVID-19 may face long-term consequences of the disease. In December 2020, the UK National Institute for Health and Care Excellence published guidance on the long-term effects of COVID-19, and based on relapsing nature of post-COVID symptoms the following integrative classification was proposed [2]:

1) acute COVID-19: signs and symptoms of COVID-19 for up to 4 weeks;

2) ongoing symptomatic COVID-19: signs and symptoms of COVID-19 from 4 to 12 weeks;

3) post-COVID-19 syndrome: signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis.

COVID-19 can significantly impact the respiratory system. Many patients suffer the effects of lung damage during the acute phase, including shortness of breath and coughing. Long COVID-19 can affect virtually any organ in the body. SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE 2) as the receptor for entry into host cells. ACE2 is present in many cell types and tissues including the lungs, the intestine, the endothelium of small vessels, smooth muscle tissue, skeletal muscles and in synovial tissue [3, 4]. ACE2 is expressed in keratinocytes, fibroblasts, endothelial cells, osteoblasts, and osteoclasts [5]. Numerous organs are potential targets for SARS-CoV-2 infection [3]. Clinical manifestations of COVID-19 pain vary from headache, abdominal pain, arthralgia, to myalgia. CWS Hoong et al. hypothesised that viral arthralgia is an uncommon but distinct manifestation of COVID-19 infection in patients with and without respiratory symptoms. The presence of musculoskeletal complaints was not associated with the risk of developing viral pneumonia. COVID-19 arthralgia was often more severe and had variable onset, while generalised body ache and myalgia were milder and coincided with the occurrence of fever or respiratory symptoms. Viral arthralgia was reported as a novel clinical manifestation of COVID-19, and untypical of a viral prodrome or a reactive arthropathy [6]. Musculoskeletal symptoms are common COVID-19 symptoms with reported prevalence of 31-59 % but have not yet been systematically investigated [7]. A retrospective cohort study of COVID-19 patients with long-term COVID progression reported by PR Sinha, N Mallick showed a significant (27 %) increase in the incidence of orthopaedic conditions such as myalgia, arthralgia, low back pain, bone infection, AVN, and joint disease [8].

One of the most important factors in the pathogenesis of COVID-19 musculoskeletal symptoms is a cytotoxic effect of the virus on osteo- and chondrogenesis, and the negative effect of drugs on the bone and the cartilage during treatment of acute COVID-19. An increased level of pro-inflammatory cytokines (tumor necrosis factor-α, interleukin-6, interleukin-1β and chemokines) persisting in patients with asymptomatic COVID-19 for 6 months after recovery plays a role [9]. A high prevalence of musculoskeletal disorders is reported in patients who suffered from COVID-19, manifested by musculoskeletal pain and structural changes in bone tissue and tendon-capsular apparatus. The timing of the onset of a COVID-19 musculoskeletal pathology is an important issue [6, 8]. In a systematic review, O.B. Khoja et al. reported musculoskeletal pain in 62.5 % of COVID-19 survivors 16 weeks after recovery [10]. C. Fernández-de-Las-Peñas et al. reported COVID-19 patients suffering from musculoskeletal consequences 4 weeks after illness [11].

COVID-19 musculoskeletal conditions are the largest contributors to the global burden of disability in younger and working aged people [1, 12]. Detection and treatment of SARS-CoV-2 infection in the early stages have a great social and economic role. Although post-Covid musculoskeletal disorders are widely discussed, there is no consensus regarding the chronology and definition of the main types of musculoskeletal conditions associated with COVID-19.

The objective was to summarize literature data on the mechanisms of the condition and identify common musculoskeletal symptoms of COVID-19.

MATERIAL AND METHODS

An internet search of PubMed, MedLine and eLIBRARY library databases using the search terms: COVID-19, aseptic osteonecrosis, post-COVID-19 syndrome, arthropathy, musculoskeletal system, spondylitis, osteoporosis was performed. Publications reporting pathogenesis of post-Covid syndrome, musculoskeletal disorders associated with COVID-19 infection and the effect of the SARS-CoV-2 virus on bone and cartilage tissue were collected.

RESULTS AND DISCUSSION

The main mechanisms of musculoskeletal disorders associated with COVID-19 infection

Cytotoxic effects on osteogenesis cells

The effect of the SARS-Cov-2 virus on osteogenesis is widely discussed. A research model of mice infected with COVID-19 demonstrated a bone mass decreased by 24.4 % (p = 0.0009), trabeculae decreased by 19.0 % (p = 0.004) and thickness of trabecular bone decreased by 6.2 % (p = 0.04). Surviving infected mice also showed osteoclasts increased by 64 %, their surface area increased by 27 %, and osteoclasts on the bone surface increased by 38 % [13]. It is hypothesized that the SARS-CoV specific protein, 3a/X1, promotes osteoclastogenesis by accelerating the differentiation of osteoclasts from monocyte/macrophage precursors, enhancing the expression of receptor activator of NF-kB ligand (RANKL) and inflammatory cytokines such as TNF-α facilitating osteoclastogenesis. SARS-CoV-2 can directly infect erythroid progenitor cells in human bone marrow [14]. Specifically, a decrease in lymphocyte count was observed when hematopoietic stem cells treated with SARS-CoV-2 S protein reduced the number of multipotent lymphoid progenitor cells (MPCs) [15]. Incubation of MPC with protein S increased the monocyte population and contributed to a marked increase in osteoclastogenesis [16]. Interestingly, the results show that SARS-CoV-2 remains in erythroid progenitor cells after 14 days of the initial infection [15]. Individuals who have had COVID-19 infection are likely to be diagnosed with osteoporosis, which is associated with a high risk of fractures and progression of degenerative changes in the musculoskeletal system [14].

«Cytokine storm»

A hyperinflammatory reaction of the immune system, which is more pronounced in patients with moderate and severe forms of COVID-19 infection, has an adverse effect on osteo- and chondrogenesis. Although the inflammatory response of the immune system can be observed in mild cases and in asymptomatic carriers, to a less pronounced extent compared to severe forms of the disease [16]. S.W.X. Ong et al. conducted a prospective multicenter cohort study and reported an elevated level of pro-inflammatory cytokines at 6 months compared with healthy controls, regardless of the severity of the coronavirus infection and persistent symptoms. Recovered COVID-19 patients had elevated levels of pro-inflammatory T cell-associated cytokines such as IL-17A, IL-12p70, IL-1β and SCF that continued to increase after recovery [9]. It is known that inflammatory cytokines such as IL-1β, IL-6, IL-17, chemokine ligand CXCL10, tumor necrosis factor (TNF-α) and vascular endothelial growth factor A (VEGF-A) are elevated in patients with infection COVID-19 having a damaging effect on osteo- and chondrogenesis. IL-1β, IL-6 and tumor necrosis factor (TNF-α) activate chondrocytes of the superficial layer of cartilage leading to increased synthesis of matrix metalloproteinases (MMPs) and, ultimately, to increased degradation of the articular cartilage. IL-1β, IL-6 increase bone resorption by stimulating osteoclast activity. Although IL-17 was originally thought to affect only immune cells, it has been shown to stimulate osteoclastogenesis in patients with rheumatoid arthritis (RA) by inducing the formation of OC-like multinucleated cells through prostaglandin E2 and expression of OC differentiation factor (ODF) [3].

Vascular inflammation and coagulopathy

Vascular inflammation plays a key role in the pathogenesis of COVID-19 [17]. SARS-CoV-2 infects vascular endothelial cells by interacting with angiotensin-converting enzyme 2 receptors [18]. The body's immune response to viral invasion leads to a disruption of homeostasis in the form of hypercoagulation. Vascular changes associated with COVID-19 include endotheliitis, vasoconstriction and rupture, thrombotic microangiopathy, capillary dysfunction accompanied by poor oxygenation of bone tissue, can cause avascular osteonecrosis [19, 20].

Hypoxia

Patients with pneumonia mediated by acute coronavirus infection and extensive damage to the lung tissue can develop hypoxia. H Tao et al. hypothesized that oxygen deprivation signaling impairs osteoclast differentiation and osteoblast formation [21]. Hypoxia enhances the hyperproduction of pro-osteoclastogenic cytokines, including receptor activator of nuclear factor B ligand (RANKL), vascular endothelial growth factor (VEGF), macrophage colony-stimulating factor (M-CSF) leading to activation of osteoclasts [22]. Hypoxia-inducible factor (HIF-1) increases osteoclast differentiation through overexpression of RANKL and nuclear factor, activated cytoplasmic T cell 1 (NFATc1) [23]. Hypoxia signaling appears to inactivate osteogenesis capacity of osteoblasts [24]. In recent years, the negative effects of oxidative stress on bone metabolism have received much attention. Multiple mechanisms are involved in osteoclast activation, including regulation of mitogen-activated protein kinases (MAPKs) and intracellular Ca2+ levels[25]. In addition, excess free radicals interfere with osteoblast adhesion impairing bone homeostasis. Hypoxemia can also lead to impaired Ca2+ metabolism and damage to osteocytes [21].

Iatrogenic effects on the musculoskeletal system in patients who suffered acute coronavirus infection

There is no specific therapy for COVID-19. The action of drugs recommended by health systems in various countries of Western Europe, the USA and Russia for the treatment of COVID-19 is based on blocking the hyperproduction of pro-inflammatory cytokines and preventing viral replication. They have many side effects that cause long-term complications in many organs and systems, including the musculoskeletal system.

JAK kinase inhibitors may have an adverse effect on bone tissue by inhibiting osteoclastogenesis, since selective inhibition of Janus kinase 2 leads to a decrease in RANKL-induced osteoclast differentiation [26]. A number of cohort studies and meta-analyses describe the risks of osteonecrosis from protease inhibitors. S.O. Lee et al. reported 54 % of patients taking protease inhibitors for more than a year to treat HIV infection developed aseptic osteonecrosis [27]. Glucocorticosteroids are also associated with a greater risk of metabolic disorders and blood supply to bone tissue. Their use in the treatment of COVID-19 is based on the suppressed expression of pro-inflammatory cytokines, such as IL-1, IL-2, IL-6, TNF-α and IFN-γ, and leukocytes migrated to inflammation sites, which prevents the development of a “cytokine storm” [28]. The negative effect of glucocorticosteroids is based on bone resorption by enhancing osteoclast differentiation and reducing osteoblastogenesis. They can also cause apoptosis of osteoblasts and osteocytes and reduce production of growth hormone. It is generally accepted that the risk of pathological fractures due to osteoporosis and avascular necrosis is associated with the dose and duration of use, decreasing upon cessation. Osteonecrosis can develop in 9-40 % of patients taking glucocorticosteroids for a long time with the risk of avascular necrosis increasing by 3.6 % with the dose increasing with every 10 mg/day [29]. The unfavorable effect of glucocorticosteroids

is based on lipid metabolism disorders associated with their use. Accumulation of low-density lipoproteins results in the formation of fat emboli leading to blockage of peripheral blood vessels and ischemic necrosis of bone tissue [30]. Large doses of glucocorticosteroids can cause peripheral vascular thrombosis by reducing the activity of tissue plasminogen activator (t-PA) and increasing the level of plasminogen activator inhibitor antigen-1 (PAI-1) in plasma [31].

Types of musculoskeletal disorders associated with COVID-19 infection

Based on an analysis of the available literature, musculoskeletal disorders associated with COVID-19 infection can be divided into 4 main groups: autoimmune, bone circulatory disorders, infectious, metabolic according to the leading etiological factor (Table 1).

Table 1

Types of musculoskeletal disorders associated with COVID-19 infection

Etiology	Nosology	Publications
Autoimmune	Reactive arthritis, sacroiliitis, ankylosing spondylitis, axial spondyloarthritis, psoriatic arthritis	[4, 32, 33, 34, 35, 36, 37, 38]
Bone circulatory disorders	Aseptic osteonecrosis	[17, 19, 20, 39, 40]
Infectious	Septic arthritis, spondylitis, spondylodiscitis	[41, 42, 43, 44, 45]
Metabolic	Osteopenia, osteoporosis	[46, 47, 48, 49]

Autoimmune musculoskeletal disorders associated with COVID-19 infection

Analysis of literature data shows that patients with COVID-19 may develop a wide variety of autoimmune disorders. G.G. Tardine et al. reported 25 clinical observations of reactive arthritis developed after a new coronavirus infection. More than half of the patients had a mild course of the disease, and three were treated in the intensive care unit. Four were positive for the HLA-B27 antigen, one had antinuclear antibodies (ANA), two had RF, and one had AB-CCP [4]. D. Colatutto et al. reported the natural history of reactive arthritis and sacroiliitis in two patients who developed COVID-19 infection. Blood samples showed a slight increase in the cytokine profile; the HLA-B27 antigen was negative in both patients [32]. L. Novelli et al. reported psoriatic spondyloarthritis triggered by SARS-CoV-2 infection in a 27-year-old patient [33]. There were several reports of ankylosing spondylitis and axial spondyloarthritis attributed to COVID-19 [34, 35]. Three main pathophysiologic pathways have been proposed by I.M. Omar et al. to explain the effects of COVID-19 in the musculoskeletal system, including the cytokine storm, development of a prothrombotic state, and autoimmunity [36]. Up to 45 % of COVID-19 patients exhibit at least one circulating autoantibody. Higher concentrations of autoantibodies often result in more severe symptoms, suggesting that autoimmunity plays a role in the pathogenesis of COVID-19. SARS-CoV-2 has several epitopes that cross-react with host antigens and could result in autoimmune conditions. There are also studies that describe cases of increased levels of antibodies to cyclic citrullinated peptide (ACCP) after COVID-19, which were not examined prior to involvement in some cases, and which were negative in other cases, and could suggest an association between COVID-19 infection and rheumatoid arthritis developed in the post-Covid period [37, 38].

Mechanisms leading to autoimmune disorders of the musculoskeletal system triggered by COVID-19 may include:

a) excessive synthesis of angiotensin II induced by coronavirus, which leads to synovial hyperplasia by activating its receptors located on the synovial membrane. Angiotensin II increases expression of inflammatory cytokines, chemokines and production of reactive oxygen species [38];

b) activation of pro-inflammatory subpopulations of T cells [36, 37];

c) activation of Toll-like receptor-7 synovial membranes initiating an inflammatory response [37, 38];

d) "cytokine storm" [36, 38].

Aseptic osteonecrosis

Avascular osteonecrosis occurs in 5-58 % of cases affecting the head of the femur, humerus, vertebral bodies, calcaneus and talus [39]. There is no consensus on the mechanism of osteonecrosis triggered by COVID-19. Drug therapy is essential in treatment of COVID-19 [17, 26, 40]. S.R. Agarwala et al. report a series of three cases in which patients developed AVN of the femoral head after being treated for COVID-19 infection. The mean dose of prednisolone used in these cases was 758 mg (400-1250 mg), which is less than the mean cumulative dose of around 2000 mg steroid, documented in the literature as causative for AVN. Patients were symptomatic and developed early AVN presentation at a mean of 58 days after COVID-19 diagnosis as compared with the literature which shows that it generally takes 6 months to 1 year to develop AVN post steroid exposure. The authors suggest a greater risk of osteonecrosis associated with COVID-19 viral infection, when treated with low doses of steroids [17]. Many authors report circulatory disorders due to thrombotic microangiopathy and vascular inflammation and the cytotoxic effect of the virus on osteogenesis cells as the main mechanisms of this pathology [19]. M.A. Panin et al. reported a series of clinical observations of osteonecrosis of the femoral head triggered by COVID-19 with a patient receiving no glucocorticosteroids during treatment for coronavirus infection and who was diagnosed with bilateral osteonecrosis of the femoral heads after 180 days [20].

Secondary musculoskeletal infections associated with SARS-Cov-2

According to the literature, infectious lesions of post-COVID musculoskeletal sequelae are common. V. Bagaria reported a high incidence of periprosthetic joint infections, soft tissue abscesses, and septic arthritis at 1 year in 12 of 90 patients admitted for COVID-19 [41]. M.V. Ardakani et al. reported a series of five cases in which patients developed septic arthritis concomitant with AVN after being treated for COVID-19 infection. An average time period of onset of hip symptoms from the beginning of the COVID-19 infection was 41.6 days [42]. I.V. Esin et al. described the clinical manifestations of infectious spondylitis in 4 patients who suffered from COVID-19, reporting a higher frequency of multi-level lesions and a greater risk of death after surgery due to the generalization of the infectious process and progression of multiple organ failure [43]. I.I. Ustenko et al. and G. Talamonti et al. reported cases of spinal epidural abscess purulent spondylodiscitis and epiduritis in patients who suffered a severe form of COVID-19 [44, 45]. Secondary immunodeficiency caused by a damaging effect of the SARS-CoV-2 virus on the immune system is the most likely cause of infectious damage to the musculoskeletal system [50]. It is capable of damaging lymphocytes, including B cells, T cells and Nk cells, leading to suppression of the immune system during illness. A decrease in lymphocytes and host immune function is the main reason contributing to the development of secondary bacterial infection [51]. An increase in bacterial adhesion due to viral infection; cell destruction by viral enzymes; release of planktonic bacteria from biofilms; synergy in viral-bacterial co-infections; an increased number of immature phagocytes; dysregulation of nutritional immunity; modulation of apoptosis and inflammation can be alternative mechanisms of infectious damage to the musculoskeletal system in the post-Covid period [52]. There is a high probability of developing secondary immunodeficiency mediated by the immunosuppressive effect of drugs used to treat moderate and severe forms of COVID-19 [44].

Risk factors of infectious lesions of the musculoskeletal system may include age over 60 years, long-term hospital stay and mechanical ventilation, stay in the intensive care unit (severe COVID-19), a history of chronic bacterial infections, chronic renal failure with the need for hemodialysis [43].

Metabolic disorders of bone tissue associated with COVID-19

There are several mechanisms of bone metabolism disorders including the direct cytotoxic effect of the virus on bone marrow cells, hyperinflammation reaction and hypoxia enhancing osteoclastogenesis [3, 13, 22]. Side effects of drugs used to treat the condition are one of the risk factors for osteoporosis and osteopenia after COVID-19 infection [26, 46]. L. Sapra et al. report the role of various factors in the risk of developing skeletal disorders in viral diseases including COVID-19. The authors suggest that SARS-CoV-2 has direct and indirect effects on bone metabolism [47]. Experiments performed by B. Mi et al. in a mouse model demonstrated overexpression of microRNA (miR-5106) triggered by SARS-CoV-2 in fracture healing *in vitro* and *in vivo* [48]. A retrospective cohort study performed at San Raffaele University Hospital in Milan showed that thoracic vertebral fractures were detected in 36 % of COVID-19 patients with osteoporosis beng previously diagnosed in 3 % of the patients [49]. Endocrine pathology plays an important role in disturbed osteometabolism due to coronavirus infection. Cases of primary hypoparathyroidism and decompensation of hypoparathyroidism due to COVID-19 were reported in numerous studies. PTH deficiency contributes to a decreased rate of bone tissue remodeling and associated with decreased markers of the bone turnover in the blood and iliac bone biopsy [53]. In 2020, S. Elkattawy et al. reported the first case of primary hypoparathyroidism caused by SARS-CoV2 infection in a 46-year-old male patient with no history of parathyroid pathology who was hospitalized with respiratory failure and had a long-term inpatient stay [52]. S. Bossoni et al. reported a case of a 72-year-old female patient with a history of thyroidectomy who presented with mild COVID-19 infection and acute perioral paresthesia and dysarthria. Laboratory studies revealed low calcium levels, increased serum phosphorus and decreased parathyroid-stimulating hormone, suggesting that SARS-CoV-2 infection caused severe hypocalcemia in the context of subclinical postoperative hypoparathyroidism [55].

V.E. Georgakopoulou et al. reported a case of a 53-year-old patient with hypoparathyroidism that developed due to COVID-19. The patient had no symptoms associated with this condition and had a normal serum calcium level of 8.9 mg/dL [56]. In some studies, hypocalcemia was identified as a biochemical marker of the aggressive course of SARS-CoV-2 [57]. Vitamin D plays an important role in the regulation of osteogenesis and is one of the risk factors for the development of osteoporosis [58]. Much evidence suggests that vitamin D deficiency is closely associated with the incidence of COVID-19. Patients with osteoporosis were found to be more susceptible to SARS-COV-2 infection and the manifestations of the condition exacerbated after exposure to COVID-19. Some COVID-19 patients develop decreased bone density as a complication [59]. F. Liu et al identified and characterized 42 common targets for VitD on both COVID-19 and osteoporosis. Further bioinformatic analysis revealed 8 core targets in the VitD-COVID-19-osteoporosis network. These VitD targets involved in the ErbB and MAPK signaling pathways are critical for fibrotic diseases such as COVID-19 and ossification due to the bidirectional regulatory role of this pathway in profibrotic/antifibrotic disorders and bone formation/bone resorption, respectively. These results identified new mechanistic insights into the functional role and molecular network of VitD in both COVID-19 and osteoporosis [60].

CONCLUSION

The mechanism by which COVID-19 affects the musculoskeletal system include the cytotoxic effect of the virus on osteogenesis cells, hyperinflammation reaction, vascular disorders and coagulopathy, hypoxia and drug therapy for coronavirus infection. Based on an analysis

of the available literature, four most common etiological factors of the musculoskeletal consequences of COVID-19 infection have been identified to include autoimmunity, bone circulatory disorders, infection and metabolic disorders.

The SARS-CoV-2 virus causes direct damage to the immune system, to B cells, T cells and Nk cells and leads to the development of secondary immunodeficiency and infectious pathology of the musculoskeletal system. Immunodeficiency mediated by COVID-19 increases the risks of early infectious postoperative complications in patients operated on for impaired locomotion. Patients who have had coronavirus infection may develop osteopenia and osteoporosis due to a cytotoxic effect of the virus on bone marrow cells and due to endocrine disorders increasing the risk of fractures and progression of degenerative changes in the osteoarticular system. An analysis of the available literature did not establish an accurate chronology of the development of persistent musculoskeletal symptoms associated with COVID-19, which was likely due to the short observation period of this cohort of patients.

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REFERENCES

1. Polozhikhina M.A. Mortality during the Covid-19 pandemic and risk reduction directions: preliminary results for 2020. *Economic and social problems of Russia*. 2021;(2):50-73. (In Russ.) doi: 10.31249/espr/2021.02.03
2. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Care Services. *Long COVID: Examining Long-Term Health Effects of COVID-19 and Implications for the Social Security Administration: Proceedings of a Workshop*. Forstag EH, Denning LA, editors. Washington (DC): National Academies Press (US); 2022. doi: 10.17226/26619
3. Zheng KI, Feng G, Liu WY, et al. Extrapulmonary complications of COVID-19: A multisystem disease? *J Med Virol*. 2021;93(1):323-335. doi: 10.1002/jmv.26294
4. Taradin GG, Kugler TE, Malovichko IS, Kononenko LV. Acute arthritis associated with COVID-19. *Almanac of Clinical Medicine*. 2022; 50 (2): 139–148. doi: 10.18786/2072-0505-2022-50-015
5. Shchegolev AI, Tumanova UN. Persistenciya koronavirusa SARS-CoV-2 v telah umershih i mery zashchity ot inficirovaniya. *Bulletin of Russian State Medical University*. 2021;(3):5-12. doi: 10.24075/vrgmu.2021.029
6. 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;104:363-369. doi: 10.1016/j.ijid.2021.01.031
7. Cipollaro L, Giordano L, Padulo J, et al. Musculoskeletal symptoms in SARS-CoV-2 (COVID-19) patients. *J Orthop Surg Res*. 2020;15(1):178. doi: 10.1186/s13018-020-01702-w
8. Sinha PR, Mallick N, Sahu RL. Orthopedic Manifestations and Post-COVID-19 Infection. *J Pharm Bioallied Sci*. 2023 Jul;15(Suppl 1):S665-S668. doi: 10.4103/jpbs.jpbs_88_23
9. Ong SWX, Fong SW, Young BE, et al. Persistent Symptoms and Association With Inflammatory Cytokine Signatures in Recovered Coronavirus Disease 2019 Patients. *Open Forum Infect Dis*. 2021;8(6):ofab156. doi: 10.1093/ofid/ofab156
10. Khoja O, Silva Passadouro B, Mulvey M, et al. Clinical Characteristics and Mechanisms of Musculoskeletal Pain in Long COVID. *J Pain Res*. 2022;15:1729-1748. doi: 10.2147/JPR.S365026
11. Fernández-de-Las-Peñas C, Palacios-Ceña D, Gómez-Mayordomo V, et al. Defining Post-COVID Symptoms (Post-Acute COVID, Long COVID, Persistent Post-COVID): An Integrative Classification. *Int J Environ Res Public Health*. 2021;18(5):2621. doi: 10.3390/ijerph18052621
12. Gasparotto M, Framba V, Piovella C, et al. Post-COVID-19 arthritis: a case report and literature review. *Clin Rheumatol*. 2021;40(8):3357-3362. doi: 10.1007/s10067-020-05550-1
13. Awosanya OD, Dalloul CE, Blosser RJ, et al. Osteoclast-mediated bone loss observed in a COVID-19 mouse model. *Bone*. 2022;154:116227. doi: 10.1016/j.bone.2021.116227
14. Minasov TB, Baikov DE, Khafizov MM, Yakupova ER, The features of bone metabolism in COVID-19. *Journal of Family Medicine*. 2021;(5). (In Russ.) doi: 10.33920/med-10-2105-04
15. Huerga Encabo H, Grey W, Garcia-Albornoz M, et al. Human Erythroid Progenitors Are Directly Infected by SARS-CoV-2: Implications for Emerging Erythropoiesis in Severe COVID-19 Patients. *Stem Cell Reports*. 2021;16(3):428-436. doi: 10.1016/j.stemcr.2021.02.001
16. Ropa J, Cooper S, Capitano ML, et al. Human Hematopoietic Stem, Progenitor, and Immune Cells Respond Ex Vivo to SARS-CoV-2 Spike Protein. *Stem Cell Rev Rep*. 2021;17(1):253-265. doi: 10.1007/s12015-020-10056-z
17. Agarwala SR, Vijayvargiya M, Pandey P. Avascular necrosis as a part of 'long COVID-19'. *BMJ Case Rep*. 2021;14(7):e242101. doi: 10.1136/bcr-2021-242101
18. Murkamilov IT, Aitbaev KA, Kudaibergenova IO, et al. Damage of the Muscle System in Covid-19. *The Russian Archives of Internal Medicine*. 2021;11(2):146-153. doi: 10.20514/2226-6704-2021-11-2-146-153
19. Kingma TJ, Hoch V, Johnson C, Chaudhry B. Avascular Necrosis of the Hip: A Post COVID-19 Sequela. *Cureus*. 2022;14(10):e29976. doi: 10.7759/cureus.29976

20. Panin MA, Petrosyan AS, Hadjicharalambous KK, Boiko AV. Avascular Necrosis of the Femoral Head After COVID-19: A Case Series. *Traumatology and Orthopedics of Russia*. 2022;28(1):110-117. doi: 10.17816/2311-2905-1687
21. Tao H, Ge G, Li W, et al. Dysimmunity and inflammatory storm: Watch out for bone lesions in COVID-19 infection. *Med Hypotheses*. 2020;145:110332. doi: 10.1016/j.mehy.2020.110332
22. Hiraga T. Hypoxic Microenvironment and Metastatic Bone Disease. *Int J Mol Sci*. 2018;19(11):3523. doi: 10.3390/ijms19113523
23. Samarpita S, Doss HM, Ganesan R, Rasool M. Interleukin 17 under hypoxia mimetic condition augments osteoclast mediated bone erosion and expression of HIF-1α and MMP-9. *Cell Immunol*. 2018;332:39-50. doi: 10.1016/j.cellimm.2018.07.005
24. Utting JC, Robins SP, Brandao-Burch A, et al. Hypoxia inhibits the growth, differentiation and bone-forming capacity of rat osteoblasts. *Exp Cell Res*. 2006;312(10):1693-1702. doi: 10.1016/j.yexcr.2006.02.007
25. Callaway DA, Jiang JX. Reactive oxygen species and oxidative stress in osteoclastogenesis, skeletal aging and bone diseases. *J Bone Miner Metab*. 2015;33(4):359-370. doi: 10.1007/s00774-015-0656-4
26. Tsed AN, Mushtin NE, Dulaev AK, Shmelev AV. Pathological changes in the osteoarticular system during COVID-19 drug therapy (review of literature). *Grekov's Bulletin of Surgery*. 2022;181(2):85-91. (In Russ.) doi: 10.24884/0042-4625-2022-181-2-85-91
27. Lee SO, Lee JE, Lee S, et al. Osteonecrosis of the Femoral Head in Korean Patients with Human Immunodeficiency Virus Infection. *Infect Chemother*. 2020;52(4):592-599. doi: 10.3947/ic.2020.52.4.592
28. Strehl C, Ehlers L, Gaber T, Buttgereit F. Glucocorticoids-All-Rounders Tackling the Versatile Players of the Immune System. *Front Immunol*. 2019;10:1744. doi: 10.3389/fimmu.2019.01744
29. Bialik V.E., Makarov M.A., Byalik E.I., et al. Avascular necrosis of bone tissue: Definition, epidemiology, types, risk factors, pathogenesis of the disease. Analytical review of the literature. *Rheumatology Science and Practice*. 2023;61(2):220-235. (In Russ.) doi: 10.47360/1995-4484-2023-220-235
30. Koo KH, Kim R, Kim YS, et al. Risk period for developing osteonecrosis of the femoral head in patients on steroid treatment. *Clin Rheumatol*. 2002;21(4):299-303. doi: 10.1007/s100670200078
31. Kerachian MA, Séguin C, Harvey EJ. Glucocorticoids in osteonecrosis of the femoral head: a new understanding of the mechanisms of action. *J Steroid Biochem Mol Biol*. 2009;114(3-5):121-128. doi: 10.1016/j.jsbmb.2009.02.007
32. Colatutto D, Sonaglia A, Zabotti A, et sl. Post-COVID-19 Arthritis and Sacroiliitis: Natural History with Longitudinal Magnetic Resonance Imaging Study in Two Cases and Review of the Literature. *Viruses*. 2021;13(8):1558. doi: 10.3390/v13081558
33. Novelli L, Motta F, Ceribelli A, et al. A case of psoriatic arthritis triggered by SARS-CoV-2 infection. *Rheumatology* (Oxford). 2021;60(1):e21-e23. doi: 10.1093/rheumatology/keaa691
34. Sagitova ER, Kravcova ON. Coronavirus is a trigger for ankylosing spondylitis? *Practical medicine*. 2022;20(3);133-135. doi: 10.32000/2072-1757-2022-3-133-135
35. Coath FL, Mackay J, Gaffney JK. Axial presentation of reactive arthritis secondary to COVID-19 infection. *Rheumatology* (Oxford). 2021;60(7):e232-e233. doi: 10.1093/rheumatology/keab009
36. Omar IM, Weaver JS, Samet JD, et al. Musculoskeletal Manifestations of COVID-19: Currently Described Clinical Symptoms and Multimodality Imaging Findings. *Radiographics*. 2022;42(5):1415-1432. doi: 10.1148/rg.220036
37. Aronova ES, Belov BS, Gridneva GI. Rheumatological manifestations of post-COVID syndrome (literature review). *Medical alphabet*. 2022;(15):20-25. (In Russ.) doi: 10.33667/2078-5631-2022-15-20-25
38. Kamyshnikova LA, Pisankina DS, Payudis AN, et al. Post-COVID musculo-articular syndrome and COVID-19 association with rheumatoid arthritis. *Ural Medical Journal*. 2023;22(1):104-110. (In Russ.) doi: 10.52420/2071-5943-2023-22-1-104-110
39. Beketova TV, Levina NO, Ladygina DO, et al. Avascular necrosis as a part of post-COVID syndrome. Case reports. *Rheumatology Science and Practice*. 2022;60(4):420-426 (In Russ.) doi: 10.47360/1995-4484-2022-420-426
40. Torgashin A.N., Rodionova S.S. Osteonecrosis in Patients Recovering from COVID-19: Mechanisms, Diagnosis, and Treatment at Early-Stage Disease (Review). *Traumatology and Orthopedics of Russia*. 2022;28(1):128-137. doi: 10.17816/2311-2905-1707
41. Bagaria V. Usual and Unusual Musculoskeletal Sequalae of COVID 19! *Indian J Orthop*. 2021;55(Suppl 2):518-519. doi: 10.1007/s43465-021-00412-7
42. Ardakani MV, Parviz S, Ghadimi E, et al. Concomitant septic arthritis of the hip joint and femoral head avascular necrosis in patients with recent COVID-19 infection: a cautionary report. *J Orthop Surg Res*. 2022;17(1):302. doi: 10.1186/s13018-022-03192-4
43. Yesin IV, Perecmanas EO, Tulkova TE. Clinical features of infectious spondylitis in patients with COVID-19. *Russian Journal of Spine Surgery*. 2023;20(1):85-92. doi: 10.14531/ss2023.1.85-92
44. Ustenko II, Kushnir YB, Amelin AV, et al. Case reports: spondylodiscitis and epiduritis after suffering COVID-19. *Journal of Clinical Practice*. 2023;20(1):85-92. doi: 10.14531/ss2023.1.85-92
45. Talamonti G, Colistra D, Crisà F, et al. Spinal epidural abscess in COVID-19 patients. *J Neurol*. 2021;268(7):2320-2326. doi: 10.1007/s00415-020-10211-z
46. Evcik D. Musculoskeletal involvement: COVID-19 and post COVID 19. *Turk J Phys Med Rehabil*. 2023;69(1):1-7. doi: 10.5606/tftrd.2023.12521
47. Sapra L, Saini C, Garg B, et al. Long-term implications of COVID-19 on bone health: pathophysiology and therapeutics. *Inflamm Res*. 2022;71(9):1025-1040. doi: 10.1007/s00011-022-01616-9
48. Mi B, Xiong Y, Zhang C, et al. SARS-CoV-2-induced Overexpression of miR-4485 Suppresses Osteogenic Differentiation and Impairs Fracture Healing. *Int J Biol Sci*. 2021;17(5):1277-1288. doi: 10.7150/ijbs.56657
49. di Filippo L, Formenti AM, Doga M, et al. Radiological Thoracic Vertebral Fractures are Highly Prevalent in COVID-19 and Predict Disease Outcomes. *J Clin Endocrinol Metab*. 2021;106(2):e602-e614. doi: 10.1210/clinem/dgaa738
50. Komarov VT, Khichina NS, Filatova MA. Features of the course of post-infectious arthritis after a new coronavirus infection COVID-19. *Modern Rheumatology Journal*. 2022;16(S1):10. (In Russ.)
51. Bavykin AS. Cell and molecular level of strategy of COVID-19 to induce immunodeficiency. Possible therapeutic solution. *Journal of microbiology, epidemiology and immunobiology*. 2021;98(4):450-467. doi: 10.36233/0372-9311-119

52. Karoli NA, Rebrov AP. The Frequency and the character of bacterial infection in patients with COVID-19. *South Russian Journal of Therapeutic Practice*. 2023;4(1):28-39. (In Russ.) doi: 10.21886/2712-8156-2023-4-1-28-39
53. Grebennikova TA, Belaya ZE, Melnichenko GA. Hypoparathyroidism: disease update and new methods of treatment. *Endocrine Surgery*. 2017;11(2):70-80. (In Russ.) doi: 10.14341/serg2017270-80
54. Elkattawy S, Alyacoub R, Ayad S, et al. A Novel Case of Hypoparathyroidism Secondary to SARS-CoV-2 Infection. *Cureus*. 2020;12(8):e10097. doi: 10.7759/cureus.10097
55. Bossoni S, Chiesa L, Giustina A. Severe hypocalcemia in a thyroidectomized woman with Covid-19 infection. *Endocrine*. 2020;68(2):253-254. doi: 10.1007/s12020-020-02326-0
56. Georgakopoulou VE, Avramopoulos P, Papalexis P, et al. COVID-19 induced hypoparathyroidism: A case report. *Exp Ther Med*. 2022;23(5):346. doi: 10.3892/etm.2022.11276
57. di Filippo L, Formenti AM, Doga M, et al. Hypocalcemia is a distinctive biochemical feature of hospitalized COVID-19 patients. *Endocrine*. 2021;71(1):9-13. doi: 10.1007/s12020-020-02541-9
58. Capozzi A, Scambia G, Lello S. Calcium, vitamin D, vitamin K2, and magnesium supplementation and skeletal health. *Maturitas*. 2020;140:55-63. doi: 10.1016/j.maturitas.2020.05.020
59. Zhang JY, Wang XM, Xing X, et al. Single-cell landscape of immunological responses in patients with COVID-19. *Nat Immunol*. 2020;21(9):1107-1118. doi: 10.1038/s41590-020-0762-x
60. Liu F, Song C, Cai W, et al. Shared mechanisms and crosstalk of COVID-19 and osteoporosis via vitamin D. *Sci Rep*. 2022;12(1):18147. doi: 10.1038/s41598-022-23143-7

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