Review Article
https://doi.org/10.17816/2311-2905-1707

Osteonecrosis in Patients Recovering from COVID-19: Mechanisms, Diagnosis, and Treatment at Early-Stage Disease (Review)

Alexander N. Torgashin, Svetlana S. Rodionova

National Medical Research Center for Traumatology and Orthopedics named after N.N. Priorov, Moscow, Russia

Background. Aseptic bone necrosis (osteonecrosis), as a consequence of the ongoing coronavirus disease-2019 (COVID-19) pandemic, is increasingly becoming the cause of severe pain syndrome in the hip, knee, and shoulder joints with disruption of their function. The discussion of the pathogenesis of post-COVID-19 osteonecrosis, possibility of its diagnosis, and treatment at early stages continue. As COVID-19 affects young and able-bodied people, the diagnosis and treatment of this form of aseptic necrosis at early stages have great social and economic importance.

Methods. The literature search was conducted in the databases of eLIBRARY, PubMed, and Scopus. The search depth was 10 years. Selected publications were related to the early diagnosis and treatment of aseptic necrosis following COVID-19.

Results. The form of osteonecrosis that developed after COVID-19 should now be classified according to ICD-10 as M87.3 (another secondary osteonecrosis). The review provides data on the possible mechanisms of osteonecrosis development in patients who had COVID-19, explains the role of MRI for the early detection of the pathology, provides the results of treatment that can influence both pathogenesis mechanisms, and leads to disease regression if treatment was initiated at an early stage.

Conclusions. Improving the doctors' awareness about the pathogenesis, diagnostic methods, and treatment of early disease stages will reduce the risk of developing an advanced stage of aseptic necrosis post-COVID-19, slow down the progression of the pathology, and delay or even prevent the need for joint replacement. Our concern is based on the continuation of the pandemic, the observed fact of the dramatic increase in the frequency of aseptic necrosis post-COVID-19, and the number of total arthroplasties in young and middle-aged people for aseptic necrosis of the femoral head.

Keywords: aseptic necrosis after COVID-19, osteonecrosis, COVID-19, glucocorticoids.

Cite as: Torgashin A.N., Rodionova S.S. [Osteonecrosis in Patients Recovering from COVID-19: Mechanisms, Diagnosis, and Treatment at Early-Stage Disease (Review)]. *Travmatologiya i ortopediya Rossii* [Traumatology and Orthopedics of Russia]. 2022;28(1):128-137. (In Russian). https://doi.org/10.17816/2311-2905-1707.

Alexander N. Torgashin; e-mail: alexander.torgashin@gmail.com
Submitted: 23.11.2021. Accepted: 15.02.2022. Published Online: 22.02.2022.

Обзорная статья
УДК 616.71-002.4:616.98
https://doi.org/10.17816/2311-2905-1707

Остеонекроз у пациентов, перенесших COVID-19: механизмы развития, диагностика, лечение на ранних стадиях (обзор литературы)

А.Н. Торгашин, С.С. Родионова

ФГБУ «Национальный медицинский исследовательский центр травматологии и ортопедии им. Н.Н. Приорова» Минздрава России, г. Москва, Россия

Актуальность. Асептический некроз костей (остеонекроз) как следствие перенесенного COVID-19 в условиях продолжающейся пандемии все чаще становится причиной выраженного болевого синдрома в области крупных суставов с нарушением их функции. Продолжается обсуждение патогенеза постковидного остеонекроза, возможности его выявления и лечения на ранних стадиях. Учитывая масштаб распространенности инфекции COVID-19 среди лиц молодого и трудоспособного возраста, выявление и лечение этой формы асептического некроза на ранних стадиях имеет важное социальное и экономическое значение.

Материал и методы. Поиск литературы проведен в базах данных eLIBRARY, PubMed, Scopus. Глубина поиска — 10 лет. Отобраны публикации, касающиеся ранней диагностики и лечения асептического некроза после перенесенного COVID-19.

Результаты. Форму остеонекроза, развившегося после перенесенного COVID-19, в настоящее время следует классифицировать по МКБ-10 как M87.3 – другой вторичный остеонекроз. В обзоре приводятся данные о возможных механизмах развития остеонекроза у пациентов, перенесших COVID-19, обосновывается необходимость выполнения МРТ для раннего выявления патологии, приводятся результаты лечения, способного оказывать влияние на оба механизма патогенеза и привести к обратному развитию процесса при условии начала лечения на ранней стадии заболевания.

Заключение. Повышение осведомленности врачей о патогенезе, методах диагностики и лечения ранних стадий позволит снизить риск развития запущенной стадии асептического некроза после перенесенного COVID-19, замедлит прогрессирование патологического процесса, отсрочит или даже предотвратит необходимость эндопротезирования суставов. Наша озабоченность основывается на продолжении пандемии и резко возросшей частоте асептического некроза после COVID-19, с одной стороны, и операций эндопротезирования у лиц молодого и среднего возраста по поводу асептического некроза головки бедренной кости, с другой стороны.

Ключевые слова: асептический некроз суставов после COVID-19, остеонекроз, COVID-19, глюкокортикоиды.

Торгашин А.Н., Родионова С.С. Остеонекроз у пациентов, перенесших COVID-19: механизмы развития, диагностика, лечение на ранних стадиях (обзор литературы).*Травматология и ортопедия России*. 2022;28(1):128-137. https://doi.org/10.17816/2311-2905-1707.

Alexander N. Torgashin; e-mail: alexander.torgashin@gmail.com

Рукопись получена: 23.11.2021. Рукопись одобрена: 15.02.2022. Статья опубликована онлайн: 22.02.2022.

Background

The COVID-19 pandemic caused by the novel coronavirus SARS-CoV-2 has already claimed the lives of more than 5 million people [1]. Recent research has observed in some patients, particularly those with extensive lung lesions and respiratory failure, the development of the long COVID-19 syndrome [2], which persists for more than 12 weeks after treatment completion and patient transfer to the "recovered" status [3]. Symptoms of long COVID-19 include fatigue, shortness of breath, anxiety and depression, heart palpitations, chest pains, inability to think or concentrate (currently referred to as "brain fog"), the rarer Guillain–Barre syndrome, pulmonary fibrosis, pulmonary thromboembolism, cardiomyopathy, sensory dysfunction, stroke [2], and muscle and joint pain, which may be a manifestation of aseptic bone necrosis [3, 4].

Previous studies have found that 5%–58% of patients with severe COVID-19 have presented with osteonecrosis [5, 6], with the femoral head being affected in most cases. Hui et al. reported that 39% of SARS-CoV-2 patients developed femoral head osteonecrosis within several months after atypical pneumonia [7]. Other foci of osteonecrosis have also been detected in the condyles of the femoral and tibial bones, the head of the humerus, the talus and calcaneus, and other areas of the skeleton [5].

At present, two possible mechanisms are currently being discussed regarding the pathogenesis of aseptic necrosis after a COVID-19 infection: the virus damage to bone tissue vessels and a negative effect of glucocorticoids (GCs) used in the treatment of infection on the bone tissue.

Scientists continue to search for ways to diagnose aseptic necrosis in its early stages after a new coronavirus infection and to determine the risk factors for its development. The presented literature discussed the possibility of conservative therapy in preventing disease progression, provided that aseptic necrosis is treated in its early stages. The ongoing pandemic emphasizes the relevance of these data for doctors from various specialties who monitor patients who recovered from COVID-19.

This review aimed to summarize the data on the pathogenesis of aseptic necrosis after COVID-19 infection and the diagnostic methods and treatment in the early stages of the disease.

Methods

We searched PubMed, Scopus, and eLIBRARY databases for articles using the keywords *COVID-19, osteonecrosis,* and *aseptic bone necrosis*, with a search depth of 10 years. We then selected articles concerning the early diagnostics and treatment of aseptic necrosis after COVID-19.

Results and discussion

Pathogenesis of aseptic necrosis caused by COVID-19 infection

Researchers have been discussing the role of the virus and glucocorticoid therapy in the pathogenesis of aseptic necrosis caused by COVID-19. For example, it has now been revealed that the SARS-CoV-2 virus directly penetrates vascular endothelial cells via angiotensin-converting enzyme-2 (ACE2), which is expressed by endothelial cells in the lungs and in many other organs and tissues, leading to vascular damage through coagulopathy and extensive inflammatory syndrome [8]. Escher et al.'s study on a patient with COVID-19 infection who had a significant increase in von Willebrand factor confirmed the destruction of the vascular endothelium [9]. In addition, after entering the body, SARS-CoV induces the expression of the TRIM55 ubiquitin ligase E3 gene in the vascular smooth muscle cells, consequently resulting in the inflammation of the vascular wall and aggregation of leukocytes [10]. Combined with hypercoagulation, these abnormalities cause microthrombosis and bone osteonecrosis distal to the site of arterial obstruction [11].

Besides directly penetrating the vascular endothelium, the virus also exacerbates damage in bone tissue and intensifies general inflammation and cytokine storm, similar to SARS-CoV-1 [12], because of excessive activation of proinflammatory cytokines interferon-gamma (IFN-γ), tumor necrosis factor (TNF), interleukin-1 (IL-1), interleukin-6 (IL-6) [13], and chemotaxis of T-lymphocytes to the inflammation site [14], caused by the immune response. The resulting microthrombosis and direct damage to blood vessels by the virus lead to the development of aseptic necrosis [15].

However, this is not the only mechanism for the development of osteonecrosis due to COVID-19. The use of GCs has a greater impact on the risk

of aseptic necrosis in COVID-19 [16]. These drugs are used in COVID-19 because of their potential advantage over other drugs in reducing immunopathological tissue damage and early proinflammatory response by suppressing the expression of proinflammatory cytokines such as IL-1, IL-2, IL-6, TNF-α, and IFN-γ and the migration of leukocytes to inflammation sites, preventing the development of a cytokine storm [17]. In addition, previous studies also note the potential harm of GCs, including a delay in the elimination of the virus and the presence of adverse effects such as the development of diabetes, psychosis, systemic osteoporosis, and avascular bone necrosis [18, 19, 20].

The body then negatively reacted to the intake of GCs soon after recovery from COVID-19. Moreover, the follow-up of patients with atypical pneumonia suggested a decrease in bone mineral density (BMD) after recovery [21].

The degree of bone loss was largely influenced by the dose and duration of corticosteroids, which were the main therapy used to reduce inflammation during the initial infection and the subsequent early period of rehabilitation and recovery [5].

Depending on the medical institution, the frequency of use of GCs in severe COVID-19 patients varies from 28% to 70% [22]. Glucocorticoids are widely used in COVID-19 because of the positive experience with their use in patients with atypical pneumonia during the SARS-Co-V epidemic. Multicenter studies showed that early administration of dexamethasone reduced the duration of artificial lung ventilation use and overall mortality in patients with acute respiratory distress syndrome [23]. The RECOVERY clinical trial, one of the largest trials related to the treatment of COVID-19, demonstrated that this drug reduced the risk of death by 20% in severe COVID-19 patients who received artificial lung ventilation or those receiving oxygen [24]. Moreover, because corticosteroids have both direct and indirect negative effects on the bone, they are considered a predisposing factor in the development of avascular necrosis [25]. First, they affect the proliferation of mesenchymal stem cells by blocking RUNX2, preventing the formation of preosteoblasts and the transition of preosteoblasts to osteoblasts, consequently reducing the mature osteoblast count and shifting metabolism toward the formation of adipocytes from the mesenchymal cells [26, 27]. Under the influence of GCs, apoptosis of osteoblasts and osteocytes increases, and osteoclasts are activated because of their influence on the system of RANKL and DKK-1 signaling proteins [28].

The adverse effect of GCs on bone tissue is also demonstrated in their participation in lipid metabolism. The accumulation of low-density lipoproteins and the formation of fatty emboli blocks peripheral blood vessels leading to ischemic necrosis of the bone tissue. Free fatty acids formed during the hydrolysis of fat emboli damage the endothelial cells of capillaries and cause diffuse vasculitis and intravascular coagulation, exacerbating ischemic bone tissue necrosis [29].

Another negative effect of GC on bone tissue is when GCs act as a regulator of local blood flow and change the sensitivity of vessels to vasoactive substances such as endothelin-1, norepinephrine, and bradykinin, leading to vasoconstriction in the femoral head and increased bone ischemia. High doses of GCs decrease tissue plasminogen activator (t-PA) activity while increasing plasminogen activator inhibitor-1 (PAI-1) antigen levels in plasma, resulting to an increased plasma procoagulant potential and hypercoagulation state [30].

Fu et al. revealed that the expression of microRNA 596 (miR-596) in the bones of patients with steroid-induced avascular necrosis of the femoral head (SANFH) inhibits the proliferation and osteogenic differentiation of bone marrow stromal cells (BMSC), preventing the restoration of damaged bone [31].

Previous studies demonstrated the association of microRNA-17-5p (miR-17-5p) and miR-210 with the pathogenesis of steroid-induced osteonecrosis of the femoral head (SANFH) [32, 33]. Moreover, GCs' direct apoptosis of endothelial cells and suppression of vascular collagen synthesis prevent revascularization and restoration of bone tissue in the area of osteonecrosis [34].

As previously mentioned, the dose of GCs and the duration of therapy influence the development of osteonecrosis. For example, the dose of less than 1 to 2 mg/kg methylprednisolone in a short course of 3 to 5 days used during the atypical pneumonia epidemic in China in 2003 was recommended as an adjuvant treatment for COVID-19 [35]. This mode of administration pro-

vided a good therapeutic effect in patients with a strong inflammatory response and acute progression (according to lung CT) of the disease and did not lead to the development of osteonecrosis [36]. In addition, a previous study suggested that higher cumulative doses and longer treatment with steroids could lead to the development of osteonecrosis [37]. Other studies demonstrated a correlation between the maximum daily dose of GCs and femoral head osteonecrosis, which requires adequate control [38]. In an experiment on rabbits, Motomura et al., doses of 1 mg/kg, 5 mg/kg, 20 mg/kg, and 40 mg/kg of methylprednisolone resulted in incidence rates of osteonecrosis of 0%, 42%, 70%, and 96%, respectively [39].

Another study on the clinical use of methylprednisolone demonstrated that a dose of 5 mg/kg per day resulted in the development of osteonecrosis in every fifth patient, compared with the control group of patients receiving 1 mg/kg per day, who did not develop the disease [40]. Moreover, increasing the dose of prednisolone for every 10 mg also increased the incidence rate of osteonecrosis by 3.6% [41].

The increasing cumulative dose of glucocorticosteroids used in a retrospective study of 539 patients with acute respiratory syndrome also increased the incidence rate of osteonecrosis [42].

Zhao et al. noted a nonlinear relationship between the cumulative dose and osteonecrosis. They found that when the total dose of methylprednisolone was below 5 g, the risk of osteonecrosis remained relatively low. However, increasing the total dose from 5 to 10 g dramatically increased the risk, with highest risk in patients at a cumulative dose of 10 to 15 g. Because a low cumulative dose of corticosteroids (methylprednisolone less than 5 g) is believed to be relatively safe in patients with acute respiratory syndrome, clinicians are advised to avoid using high doses of corticosteroids, especially a cumulative dose of more than 10 g [37]. Rademaker et al. demonstrated that a dose of 700 mg prednisolone is the threshold for the onset of the femoral head necrosis [43]. In addition, Chan et al. suggested that cumulative doses of methylprednisolone greater than 2000 mg or hydrocortisone greater than 1900 mg are predictors of osteonecrosis [44].

In addition to dosage, the duration of therapy also affects the development of osteonecrosis. In a study of 1137 patients with atypical pneumonia, an incidence rate of osteonecrosis of 1.29 (95% CI, 1.09–1.53; p = 0.003) for every 10 days of treatment was shown to indicate the importance of reducing the duration of administration of steroids to reduce the risk of osteonecrosis [37]. Studies suggested that even a weekly intake of GCs could induce a high risk of osteonecrosis if the dose of oral methylprednisolone exceeded 300 mg, (i.e., approximately 1 mg/kg per day in a patient weighing 60 kg for 5 days). On the basis of these data, the authors drew attention to the importance of examining patients in the presence of the previously mentioned risks for the early detection of aseptic necrosis due to COVID-19 [45].

Diagnostics of aseptic necrosis in COVID-19 survivors

Zhao et al. demonstrated that MRI is recommended at months 3, 6, and 12 after the end of glucocorticoid intake [46]. Others also pointed out this time interval between the intake of corticosteroids and the development of aseptic necrosis of the femoral head [47]. A retrospective study of patients who recovered from COVID-19 detected osteonecrosis (21 of 23 patients) using MRI 3 months after completion of treatment, although the examination was also performed at an earlier time [48].

Besides MRI diagnostics, scientists have been searching for new predictors of the disease. For example, PAI-1 decrease is a sensitive method for screening patients at high risk of osteonecrosis [49]. In addition, B. Wei and W. Wei suggested the use of microRNA 423-5p as a biomarker in which the blood level is significantly increased in patients with steroid-induced osteonecrosis. Moreover, laboratory parameters of the coagulogram in most cases have been noted to remain within normal values [50].

Treatment of aseptic necrosis associated with previous COVID-19 infection

Timely detection of aseptic necrosis due to COVID-19 and its treatment with GCs reduces the risk of progressing to its advanced stage, which will inevitably lead to joint arthroplasty. In addition, if osteonecrosis is diagnosed at an early stage (I or II), then 92%–97% of patients will not need surgical intervention [51], and conservative treatment may result in recovery [52].

As in the case of idiopathic osteonecrosis or secondary osteonecrosis not associated with COVID-19, treating the disease in its early stage is mainly aimed at reducing pain, slowing down the disease progression, preventing subchondral bone collapse, and restoring the joint function.

Conservative treatment of early stages of aseptic necrosis after COVID-19 enables to avoid endoprosthetics which is fraught with a high risk of aseptic instability in young and middle-aged patients.

At present, no protocol for the treatment of early-stage osteonecrosis following COVID-19 has been standardized. In clinical practice, pharmacotherapy is usually combined with joint unloading, which has proven its efficiency particularly in steroid-induced osteonecrosis [53]. The joint is unloaded with the help of crutches for a period of at least 3 months in case of localization of the femoral head osteonecrosis, and in case of localization in other bones, a cane and an orthosis are used instead of crutches [54].

Agarwala et al.'s study on the successful use of antiresorptive drugs, including glucocorticoid-induced osteonecrosis, to treat secondary osteonecrosis in its early stages in adults [55] reported the drugs' ability to slow down the disease progression and reduce the need for surgical intervention. In the United States, the American Association of Hip and Knee Surgeons reported that the proportion of bisphosphonates in the treatment of femoral head osteonecrosis is 10% [56]. Their aim was to reduce the intensity of resorption both in the zone of osteonecrosis, reducing the risk of subchondral bone collapse [57], and in the surrounding bone tissue [58], given the possibility of a generalized BMD deficiency in COVID-19 patients [21]. However, from a legal point of view, prescribing this group of drugs for osteonecrosis can only be off-label because their annotations do not indicate the possibility of their use in this pathology.

Although alendronic acid 70 mg once a week is considered a possible bisphosphonate for the entire period of treatment of patients with aseptic necrosis [59], a disadvantage of oral bisphosphonates is their low compliance. Hence, using intravenous forms, primarily of zoledronic acid at a dose of 5 mg, given the frequency of administration (once a year), is considered promising [60]. In addition to a direct antiresorptive effect, which results in a decrease in bone tissue edema [61], intravenous bisphosphonates have a significant analgesic effect, improving the quality of life of patients [60].

Because bisphosphonates are contraindicated in patients with impaired nitrogen excretion by the kidneys [62], denosumab is used at a dose of 60 mg twice a year as an antiresorptive drug for aseptic necrosis [62].

However, a previous study noted that antiresorptive drugs should be simultaneously administered with calcium preparations at a dose of 500 to 1000 mg/day and cholecalciferol at a dose of at least 1000 IU/day or alfacalcidol at a dose of at least 0.5 to 0.75 μg/day [63].

Prescribing cholecalciferol during a pandemic is recommended to influence the course of COVID-19. This decreases the severity of the infection course and increases the survival rate [64, 65], as shown by a slowdown in the rate of viral replication, a decrease in proinflammatory cytokine concentration, and an increase in antiinflammatory cytokine concentration [64]. However, this mechanism of action of cholecalciferol has a low evidence base. Observational and clinical studies conducted on the effect of vitamin D and the associated risk of respiratory tract infections are contradictory, with some reporting a reduction in risk, whereas others do not [64, 66]. These conflicting results are probably due to the heterogeneity of the patient population and vitamin D dose. Therefore, conclusions on their possible impact on the course of COVID-19 should only be drawn after the results of well-designed vitamin D trials have been established.

In addition, the use of cholecalciferol and especially of alfacalcidol is important in the complex therapy of osteonecrosis. A previous study established that the serum concentration of 1.25 (OH) 2D3 (16.7 ± 7.9 mg/ml) is significantly lower in patients with idiopathic femoral head osteonecrosis than in the control group (26.9 mg/ml) ± 13.7 mg/ml) ($p < 0.01$) [64]. The authors considered this decrease as an adverse condition for the development and progression of osteonecrosis.

Another reason for prescribing cholecalciferol was the relationship between the osteonecrosis development and low BMD [67], as cholecalciferol is currently used in combination with calcium preparations as the basic therapy for maintaining bone metabolism at low BMD values with primary and secondary osteoporosis [68].

Considering the relationship between osteonecrosis and microcirculation disorders, dipyridamole is used orally at a dose of 25 mg 3 times a day for 3 weeks (as an inhibitor of platelet aggregation and angioprotective agent) at day 1 of osteonecrosis diagnosis [69]. Iloprost can also be prescribed to reduce intraosseous pressure and improve the microvasculature condition as its efficiency in the treatment of osteonecrosis has been previously noted [70]. However, because of the high risk of a decrease in blood pressure, iloprost infusion should be performed exclusively in a hospital or outpatient setting in the presence of a resuscitation team [71].

Anticoagulants, particularly sodium enoxaparin, can be administered subcutaneously at a dose of 4000 IU (0.4 ml) to 6000 IU (0.6 ml) per day for 2 to 12 weeks if patients with osteonecrosis present with hypercoagulation or hypofibrinolysis. This is recommended in complex therapy to prevent the disease progression at stages 1 to 2 of ARCO [72]. Because anticoagulants in tablets showed a similar effect to subcutaneous drugs in the treatment of COVID-19, their use (e.g., apixaban at a dose of 2.5 mg 2 times a day for 12 weeks) is considered no less effective [73].

Since physiotherapy can reduce the symptoms of the disease in some cases [74], pulsed electromagnetic therapy, hyperbaric oxygen therapy, ozone therapy, and extracorporeal shock wave therapy can also be used in the complex treatment of osteonecrosis. However, their efficacy in the treatment of osteonecrosis due to COVID-19 requires further evaluation.

In a previously described conservative therapy, the focus of the affected area of the femoral head can be tunneled (decompressed) in the initial stages to reduce pain and improve blood supply [75].

Conclusions

Recent studies have discussed two mechanisms for the development of osteonecrosis after COVID-19: the influence of GCs used to treat the infection and the ability of SARS-CoV-2 to impair bone metabolism. In the latter case, osteonecrosis develops either because of microthrombosis and bone tissue malnutrition associated with the virus's direct damage on blood vessels or because of the vascular wall inflammation in combination with an increase in blood coagulability caused by an increase of proinflammatory cytokines as an immune response to the infection. According to general opinion, performing dynamic MRI three to six months after COVID-19 infection, in addition to searching for new predictors of the disease, can help decrease the incidence rate of osteonecrosis and prevent the consequences due to late diagnosis (arthroplasty).

Disclaimers

Author contribution

Torgashin A.N. — literature review, writing the draft, editing.

Rodionova S.S. — writing the draft, editing.

All authors have read and approved the final version of the manuscript of the article. All authors agree to bear responsibility for all aspects of the study to ensure proper consideration and resolution of all possible issues related to the correctness and reliability of any part of the work.

Funding source. This study was not supported by any external sources of funding.

Competing interests. The authors declare that they have no competing interests.

Ethics approval. Not applicable.

Consent for publication. Not required.

References

1. WHO coronavirus disease (COVID-19) Dashboard. Available from: https://covid19.who.int/table.
2. Leung T.Y.M., Chan A.Y.L., Chan E.W., Chan V.K.Y., Chui C.S.L., Cowling B.J. et al. Short- and potential long-term adverse health outcomes of COVID-19: a rapid review. *Emerg Microbes Infect.* 2020;9(1):2190-2199. doi: 10.1080/22221751.2020.1825914.
3. Mahase E. Covid-19: What do we know about «long covid»? *BMJ*. 2020;370:m2815. doi: 10.1136/bmj.m2815.
4. Agarwala S.R., 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.
5. Griffith J.F. Musculoskeletal complications of severe acute respiratory syndrome. *Semin Musculoskelet Radiol.* 2011;15(5):554-560. doi: 10.1055/s-0031-1293500.
6. Hong N., Du X.K. Avascular necrosis of bone in severe acute respiratory syndrome. *Clin Radiol.* 2004;59(7):602-608. doi: 10.1016/j.crad.2003.12.008.

7. Lv H., de Vlas S.J., Liu W., Wang T.B., Cao Z.Y., Li C.P. et al. Avascular osteonecrosis after treatment of SARS: a 3-year longitudinal study. *Trop Med Int Health*. 2009;14 Suppl 1(Suppl 1):79-84. doi: 10.1111/j.1365-3156.2008.02187.x.
8. Sardu C., Gambardella J., Morelli M.B., Wang X., Marfella R., Santulli G. Hypertension, Thrombosis, Kidney Failure, and Diabetes: Is COVID-19 an Endothelial Disease? A Comprehensive Evaluation of Clinical and Basic Evidence. *J Clin Med*. 2020;9(5):1417. doi: 10.3390/jcm9051417.
9. Escher R., Breakey N., Lämmle B. Severe COVID-19 infection associated with endothelial activation. *Thromb Res*. 2020;190:62. doi: 10.1016/j.thromres.2020.04.014.
10. Gralinski L.E., Ferris M.T., Aylor D.L., Whitmore A.C., Green R., Frieman M.B. et al. Genome Wide Identification of SARS-CoV Susceptibility Loci Using the Collaborative Cross. *PLoS Genet*. 2015;11(10): e1005504. doi: 10.1371/journal.pgen.1005504.
11. Oxley T.J., Mocco J., Majidi S., Kellner C.P., Shoirah H., Singh I.P. et al. Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. *N Engl J Med*. 2020;382(20):e60. doi: 10.1056/NEJMc2009787.
12. Channappanavar R., Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. *Semin Immunopathol*. 2017;39(5):529-539. doi: 10.1007/s00281-017-0629-x.
13. Van Reeth K., Van Gucht S., Pensaert M. Correlations between lung proinflammatory cytokine levels, virus replication, and disease after swine influenza virus challenge of vaccination-immune pigs. *Viral Immunol*. 2002;15(4):583-594. doi: 10.1089/088282402320914520.
14. Nie S., Han S., Ouyang H., Zhang Z. Coronavirus Disease 2019-related dyspnea cases difficult to interpret using chest computed tomography. *Respir Med*. 2020;167:105951. doi: 10.1016/j.rmed.2020.105951.
15. Polyakova Yu.V., Papichev E.V., Akhverdyan Y.R., Sivordova L.E., Zavodovskiy B.V. [New coronavirus infection - direct and indirect impact on patients with diseases of the musculoskeletal system and connective tissue]. *Sovremennye problemy nauki i obrazovaniya* [Modern problems of science and education]. 2021;(6). (In Russian). Available from: https://science-education.ru/ru/article/view?id=31342.
16. Mushtin N.E., Tsed A.N., Dulaev A.K., Ilyushchenko K.G., Shmelev A.V. [A variant of the new coronovirus infection Covid-19 for the development of osteonecrosis]. In: *Meditsinskaya pomoshch' pri travmakh, novoe v organizatsii i tekhnologiyakh, rol' natsional'noi obshchestvennoi professional'noi organizatsii travmatologov v sisteme zdravookhraneniya RF: sbornik tezisov* [Medical care for injuries, new organization and technology, the role of the national professional organization of traumatologists in the healthcare system of the Russian Federation]. St. Petersburg: 2021. p. 98-99. (In Russian).
17. 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.
18. Russell B., Moss C., Rigg A., Van Hemelrijck M. COVID-19 and treatment with NSAIDs and corticosteroids: should we be limiting their use in the clinical setting? *Ecancermedicalscience*. 2020;14:1023. doi: 10.3332/ecancer.2020.1023.
19. Russell B., Moss C., George G., Santaolalla A., Cope A., Papa S. et al. Associations between immune-suppressive and stimulating drugs and novel COVID-19-a systematic review of current evidence. *Ecancermedicalscience*. 2020;14:1022. doi: 10.3332/ecancer.2020.1022.
20. Arabi Y.M., Fowler R., Hayden F.G. Critical care management of adults with community-acquired severe respiratory viral infection. *Intensive Care Med*. 2020;46(2):315-328. doi: 10.1007/s00134-020-05943-5.
21. Lau E.M., Chan F.W., Hui D.S., Wu A.K., Leung P.C. Reduced bone mineral density in male Severe Acute Respiratory Syndrome (SARS) patients in Hong Kong. *Bone*. 2005;37(3):420-424. doi: 10.1016/j.bone.2005.04.018.
22. Yang X., Yu Y., Xu J., Shu H., Xia J. Liu H. et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020;8(5):475-481. doi: 10.1016/S2213-2600(20)30079-5.
23. Villar J., Ferrando C., Martínez D., Ambrós A., Muñoz T., Soler J.A. et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. *Lancet Respir Med*. 2020;8(3):267-276. doi: 10.1016/S2213-2600(19)30417-5.
24. RECOVERY Collaborative Group, Horby P., Lim W.Sh., Emberson J.R., Mafham M., Bell J.L. et al. Dexamethasone in Hospitalized Patients with COVID-19 — Preliminary Report. *N Engl J Med*. 2021; 384(8):693-704. doi: 10.1056/NEJMoa2021436.
25. Powell C., Chang C., Naguwa S.M., Cheema G., Gershwin M.E. Steroid induced osteonecrosis: An analysis of steroid dosing risk. *Autoimmun Rev*. 2010;9(11):721-743. doi: 10.1016/j.autrev.2010.06.007.
26. Koromila T., Baniwal S.K., Song Y.S., Martin A., Xiong J., Frenkel B. Glucocorticoids antagonize RUNX2 during osteoblast differentiation in cultures of ST2 pluripotent mesenchymal cells. *J Cell Biochem*. 2014;115(1):27-33. doi: 10.1002/jcb.24646.
27. Matthews B. Involvement of the osteoblast in Paget's disease of bone. *Medicine*. 2009. Available from: https://www.semanticscholar.org/paper/Involvement-of-the-osteoblast-in-Paget%27s-disease-of-Matthews/c20b73cf3d1e1d6ed15801a3ac5e230459fcf1b7.
28. O'Brien C.A., Jia D., Plotkin L.I., Bellido T., Powers C.C., Stewart S.A. et al. Glucocorticoids act directly on osteoblasts and osteocytes to induce their apoptosis and reduce bone formation and strength. *Endocrinology*. 2004;145(4):1835-1841. doi: 10.1210/en.2003-0990.
29. Koo K.H., Kim R., Kim Y.S., Ahn I.O., Cho S.H., Song H.R. 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.

30. Kerachian M.A., Séguin C., Harvey E.J. 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.
31. Fu L., Liu H., Lei W. MiR-596 inhibits osteoblastic differentiation and cell proliferation by targeting Smad3 in steroid-induced osteonecrosis of femoral head. *J Orthop Surg Res.* 2020;15(1):173. doi: 10.1186/s13018-020-01688-5.
32. Yamasaki K., Nakasa T., Miyaki S., Yamasaki T., Yasunaga Y., Ochi M. Angiogenic microRNA-210 is present in cells surrounding osteonecrosis. *J Orthop Res.* 2012;30(8):1263-1270. doi: 10.1002/jor.22079.
33. Jia J., Feng X., Xu W., Yang S., Zhang Q., Liu X. et al. MiR-17-5p modulates osteoblastic differentiation and cell proliferation by targeting SMAD7 in non-traumatic osteonecrosis. *Exp Mol Med.* 2014;46(7):e107. doi: 10.1038/emm.2014.43.
34. Weinstein R.S., Wan C., Liu Q., Wang Y., Almeida M., O'Brien C.A. et al. Endogenous glucocorticoids decrease skeletal angiogenesis, vascularity, hydration, and strength in aged mice. *Aging Cell.* 2010;9(2):147-161. doi: 10.1111/j.1474-9726.2009.00545.x.
35. Xu Y., Chen Y., Tang X. Guidelines for the diagnosis and treatment of coronavirus disease 2019 (COVID-19) in China. *Glob Health Med.* 2020;2(2):66-72. doi: 10.35772/ghm.2020.01015.
36. Zheng Y., Xiong C., Liu Y., Qian X., Tang Y., Liu L. et al. Epidemiological and clinical characteristics analysis of COVID-19 in the surrounding areas of Wuhan, Hubei Province in 2020. *Pharmacol Res.* 2020;157:104821. doi: 10.1016/j.phrs.2020.104821.
37. Zhao R., Wang H., Wang X., Feng F. Steroid therapy and the risk of osteonecrosis in SARS patients: a dose-response meta-analysis. *Osteoporos Int.* 2017;28(3):1027-1034. doi: 10.1007/s00198-016-3824-z.
38. Shen J., Liang B.L., Zeng Q.S., Chen J.Y., Liu Q.Y., Chen R.C. et al. [Report on the investigation of lower extremity osteonecrosis with magnetic resonance imaging in recovered severe acute respiratory syndrome in Guangzhou]. *Zhonghua Yi Xue Za Zhi.* 2004;84(21):1814-1817. (In Chinese).
39. Motomura G., Yamamoto T., Irisa T., Miyanishi K., Nishida K., Iwamoto Y. Dose effects of corticosteroids on the development of osteonecrosis in rabbits. *J Rheumatol.* 2008;35(12):2395-2399. doi: 10.3899/jrheum.080324.
40. Marsh J.C., Zomas A., Hows J.M., Chapple M., Gordon-Smith E.C. Avascular necrosis after treatment of aplastic anaemia with antilymphocyte globulin and high-dose methylprednisolone. *Br J Haematol.* 1993;84(4):731-735. doi: 10.1111/j.1365-2141.1993.tb03153.x.
41. Mont M.A., Pivec R., Banerjee S., Issa K., Elmallah R.K., Jones L.C. High-Dose Corticosteroid Use and Risk of Hip Osteonecrosis: Meta-Analysis and Systematic Literature Review. *J Arthroplasty.* 2015;30(9):1506-1512.e5. doi: 10.1016/j.arth.2015.03.036.
42. Guo K.J., Zhao F.C., Guo Y., Li F.L., Zhu L., Zheng W. The influence of age, gender and treatment with steroids on the incidence of osteonecrosis of the femoral head during the management of severe acute respiratory syndrome: a retrospective study. *Bone Joint J.* 2014;96-B(2):259-262. doi: 10.1302/0301-620X.96B2.31935.
43. Rademaker J., Dobro J.S., Solomon G. Osteonecrosis and human immunodeficiency virus infection. *J Rheumatol.* 1997;24(3):601-604.
44. Chan M.H., Chan P.K., Griffith J.F., Chan I.H., Lit L.C., Wong C.K. et al. Steroid-induced osteonecrosis in severe acute respiratory syndrome: a retrospective analysis of biochemical markers of bone metabolism and corticosteroid therapy. *Pathology.* 2006;38(3):229-235. doi: 10.1080/00313020600696231.
45. Richards R.N. Short-term Corticosteroids and Avascular Necrosis: Medical and Legal Realities. *Cutis.* 2007;80(4):343-348.
46. Zhao F.C., Li Z.R., Guo K.J. Clinical analysis of osteonecrosis of the femoral head induced by steroids. *Orthop Surg.* 2012;4(1):28-34. doi: 10.1111/j.1757-7861.2011.00163.x.
47. Mirzai R., Chang C., Greenspan A., Gershwin M.E. The pathogenesis of osteonecrosis and the relationships to corticosteroids. *J Asthma.* 1999;36(1):77-95. doi: 10.3109/02770909909065152.
48. Zhao F.C., Hu H.X., Zheng X., Cang D.W., Liu X., Zhang J.Z. et al. Clinical analysis of 23 cases of steroid-associated osteonecrosis of the femoral head with normal initial magnetic resonance imaging presentation. *Medicine (Baltimore).* 2017;96(49):e8834. doi: 10.1097/MD.0000000000008834.
49. Sun W., Li Z., Shi Z., Wang B., Gao F., Yang Y. et al. Relationship between post-SARS osteonecrosis and PAI-1 4G/5G gene polymorphisms. *Eur J Orthop Surg Traumatol.* 2014;24(4):525-529. doi: 10.1007/s00590-013-1223-0.
50. Wei B., Wei W. Identification of aberrantly expressed of serum microRNAs in patients with hormone-induced non-traumatic osteonecrosis of the femoral head. *Biomed Pharmacother.* 2015;75:191-195. doi: 10.1016/j.biopha.2015.07.016.
51. Hsu S.L., Wang C.J., Lee M.S., Chan Y.S., Huang C.C., Yang K.D. Cocktail therapy for femoral head necrosis of the hip. *Arch Orthop Trauma Surg.* 2010;130(1):23-29. doi: 10.1007/s00402-009-0918-5.
52. Wong T., Wang C.J., Hsu S.L., Chou W.Y., Lin P.C., Huang C.C. Cocktail therapy for hip necrosis in SARS patients. *Chang Gung Med J.* 2008;31(6):546-553.
53. Wang W., Zhang N., Guo W., Gao F. Combined pharmacotherapy for osteonecrosis of the femoral head after severe acute respiratory syndrome and interstitial pneumonia: two and a half to fourteen year follow-up. *Int Orthop.* 2018;42(7):1551-1556. doi: 10.1007/s00264-018-3907-x.
54. Klumpp R., Trevisan C. Aseptic osteonecrosis of the hip in the adult: current evidence on conservative treatment. *Clin Cases Miner Bone Metab.* 2015;12(Suppl 1):39-42. doi: 10.11138/ccmbm/2015.12.3s.039.
55. Agarwala S., Banavali S.D., Vijayvargiya M. Bisphosphonate Combination Therapy in the Management of Postchemotherapy Avascular Necrosis of the Femoral Head in Adolescents and Young Adults: A Retrospective Study From India. *J Glob Oncol.* 2018;4:1-11. doi: 10.1200/JGO.17.00083.
56. Ramachandran M., Ward K., Brown R.R., Munns C.F., Cowell C.T., Little D.G. Intravenous bisphosphonate therapy for traumatic osteonecrosis of the femoral head in adolescents. *J Bone Joint Surg Am.* 2007;89(8):1727-1734. doi: 10.2106/JBJS.F.00964.

57. Karim A.R., Cherian J.J., Jauregui J.J., Pierce T., Mont M.A. Osteonecrosis of the knee: review. *Ann Transl Med.* 2015;3(1):6. doi: 10.3978/j.issn.2305-5839.2014.11.13.
58. Zywiel M.G., McGrath M.S., Seyler T.M., Marker D.R., Bonutti P.M., Mont M.A. Osteonecrosis of the knee: a review of three disorders. *Orthop Clin North Am.* 2009;40(2):193-211. doi: 10.1016/j.ocl.2008.10.010.
59. Hong Y.C., Luo R.B., Lin T., Zhong H.M., Shi J.B. Efficacy of alendronate for preventing collapse of femoral head in adult patients with nontraumatic osteonecrosis. *Biomed Res Int.* 2014;2014:716538. doi: 10.1155/2014/716538.
60. Cross M., Macara M., Little E., Chan M., Little D., Buchbinder R. et al. Efficacy of zoledronate in treating osteonecrosis of femoral head: a randomized controlled trial Abstracts. *Osteoarthritis and Cartilage.* 2018;26(Suppl 1):S309-S310. doi: 10.1016/j.joca.2018.02.622.
61. Agarwala S., Vijayvargiya M. Single Dose Therapy of Zoledronic Acid for the Treatment of Transient Osteoporosis of Hip. *Ann Rehabil Med.* 2019;43(3):314-320. doi: 10.5535/arm.2019.43.3.314.
62. Rolvien T., Schmidt T., Butscheidt S., Amling M., Barvencik F. Denosumab is effective in the treatment of bone marrow oedema syndrome. *Injury.* 2017;48(4):874-879. doi: 10.1016/j.injury.2017.02.020.
63. Rodionova S.S., Elovoy-Vronskiy A.A., Bernakevich A.I. [Alfacalcidol or cholecalciferol in combination with ibandronic acid in the treatment of postmenopausal systemic osteoporosis]. *Osteoporoz i osteopatii* [Osteoporosis and Bone Diseases]. 2014;17(1):21-24. (In Russian).
64. Grant W.B., Lahore H., McDonnell S.L., Baggerly C.A., French C.B., Aliano J.L. et al. Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. *Nutrients.* 2020;12(4):988. doi: 10.3390/nu12040988.
65. Annweiler C., Hanotte B., Grandin de l'Eprevier C., Sabatier J.M., Lafaie L., Célarier T. Vitamin D and survival in COVID-19 patients: A quasi-experimental study. *J Steroid Biochem Mol Biol.* 2020;204:105771. doi: 10.1016/j.jsbmb.2020.105771.
66. Kakodkar P., Kaka N., Baig M.N. A Comprehensive Literature Review on the Clinical Presentation, and Management of the Pandemic Coronavirus Disease 2019 (COVID-19). *Cureus.* 2020;12(4):e7560. doi: 10.7759/cureus.7560.
67. Gangji V., Soyfoo M.S., Heuschling A., Afzali V., Moreno-Reyes R., Rasschaert J. et al. Non traumatic osteonecrosis of the femoral head is associated with low bone mass. *Bone.* 2018;107:88-92. doi: 10.1016/j.bone.2017.11.005.
68. Belaya Z.E., Belova K.Yu., Biryukova E.V., Dedov I.I., Dzeranova L.K., Drapkina O.M. et al. [Federal clinical guidelines for diagnosis, treatment and prevention of osteoporosis]. *Osteoporoz i osteopatii* [Osteoporosis and Bone Diseases]. 2021;24(2):4-47. (In Russian). doi: 10.14341/osteo12930.
69. Torgashin A.N., Rodionova S.S., Shumsky A.A., Makarov M.A., Torgashina A.V., Akhtyamov I.F. et al. [Treatment of aseptic necrosis of the femoral head. Clinical guidelines]. *Nauchno-prakticheskaya revmatologiya* [Rheumatology Science and Practice]. 2020;58(6):637-645. (In Russian).
70. Jäger M., Zilkens C., Bittersohl B., Matheney T., Kozina G., Blondin D. et al. Efficiency of iloprost treatment for osseous malperfusion. *Int Orthop.* 2011;35(5):761-765. doi: 10.1007/s00264-010-0998-4.
71. Claßen T., Becker A., Landgraeber S., Haversath M., Li X., Zilkens C. et al. Long-term Clinical Results after Iloprost Treatment for Bone Marrow Edema and Avascular Necrosis. *Orthop Rev (Pavia).* 2016;8(1):6150. doi: 10.4081/or.2016.6150.
72. Glueck C.J., Freiberg R.A., Sieve L., Wang P. Enoxaparin prevents progression of stages I and II osteonecrosis of the hip. *Clin Orthop Relat Res.* 2005;(435):164-170. doi: 10.1097/01.blo.0000157539.67567.03.
73. Billett H.H., Reyes-Gil M., Szymanski J., Ikemura K., Stahl L.R., Lo Y. et al. Anticoagulation in COVID-19: Effect of Enoxaparin, Heparin, and Apixaban on Mortality. *Thromb Haemost.* 2020;120(12):1691-1699. doi: 10.1055/s-0040-1720978.
74. Trancik T., Lunceford E., Strum D. The effect of electrical stimulation on osteonecrosis of the femoral head. *Clin Orthop Relat Res.* 1990;(256):120-124.
75. Rajagopal M., Balch Samora J., Ellis T.J. Efficacy of core decompression as treatment for osteonecrosis of the hip: a systematic review. *Hip Int.* 2012;22(5):489-493. doi: 10.5301/HIP.2012.9748.

AUTHORS' INFORMATION

✉ *Alexander N. Torgashin* — Cand. Sci. (Med.)
Address: 10, Priorova str., Moscow, 127299, Russia
https://orcid.org/0000-0002-2789-6172
e-mail: dr.torgashin@gmail.com

Svetlana S. Rodionova — Dr. Sci. (Med.), Professor
https://orcid.org/0000-0002-2726-8758
e-mail: rod06@inbox.ru