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The possibility of osteoporosis and avascular necrosis caused by the COVID-19 pandemic. Analysis of literature

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The SARS-CoV-2 (COVID-19) coronavirus pandemic has prompted scientific research. Hypotheses regarding its pathogenetic mechanisms and treatment are formulated, unwanted consequences of the infection are determined. Objective. To provide useful information for clinicians about possible complications from the musculoskeletal system after COVID-19 for the timely application of effective methods of their prevention. Materials: Electronic databases PMC, PubMed and Scopus were used to search for the sources of information published from December 2019 to December 2021. The full text of the articles was reviewed to confirm their relevance to the stated purpose of the review. Results. Patients after a severe course of SARS-CoV-2 have a high risk of complications such as osteoporosis and avascular osteonecrosis due to a number of reasons. It is noted that hypocalcemia is considered as an indicator of the severity and progression of the course of COVID-19. Vitamin D deficiency increases the risk of contracting COVID-19 and is associated with increased severity and mortality from the infection. Decreased proliferation and differentiation of osteoblasts can provoke elevated levels of cytokines under cytokine storm conditions. Hypoxia caused by SARS-CoV-2 is an important factor in increasing the differentiation and activity of osteoclasts and, accordingly, increasing osteoresorption. The relationship between the development of avascular osteonecrosis and long-term use of high doses of corticosteroids in patients with severe acute respiratory syndrome has been established. Conclusions. Research of musculoskeletal complications after COVID-19 is ongoing for correct forecasting and effective prevention. The use of corticosteroids in the treatment of patients with COVID-19 should be considered. It is necessary to pay attention to the diagnosis of osteoporosis, since there are many risk factors for increased bone fragility in hospitalized patients. Patients suffering from the effects of COVID-19 will need a comprehensive recovery and rehabilitation treatment plan.

Пандемія коронавірусу SARS-CoV-2 (COVID-19) спонукала до проведення наукових досліджень. Сформульовано гіпотези щодо його патогенетичних механізмів і лікування, визначено небажані наслідки інфекції. Мета. Надати корисну для клініцистів інформацію про можливі ускладнення з боку опорно-рухової системи після перенесеного COVID-19 для вчасного застосовування ефективних методів їхньої профілактики. Методи. Електронні бази даних PMC, PubMed і Scopus використано для пошуку джерел інформації, опублікованих із грудня 2019 до грудня 2021 року. Переглянуто повний текст статей, щоб підтвердити їхню відповідність зазначеній меті огляду. Результати. Пацієнти після важкого перебігу SARS-CoV-2 мають високий ризик виникнення таких ускладнень, як остеопороз і аваскулярний остеонекроз, що обумовлено низкою причин. Відмічено, що гіпокальціємію розглядають як показник тяжкості й прогресування перебігу COVID-19. Дефіцит вітаміну D збільшує ризик зараження на COVID-19 і пов'язаний із тяжкістю та зростанням смертності від інфекції. Зменшення проліферації та диференціації остеобластів може спровокувати підвищений рівень цитокінів за умов цитокінового шторму. Гіпоксія, спричинена SARS-CoV-2, є важливим чинником підвищення диференціації й активності остеокластів і, відповідно, посилення остеорезорбції. Установлено взаємозв'язок між розвитком аваскулярного остеонекрозу та тривалим застосовуванням високих доз кортикостероїдів у пацієнтів із тяжким гострим респіраторним синдромом. Висновки. Тривають дослідження щодо ускладнень із боку опорно-рухової системи після COVID-19 для коректного прогнозування й ефективної профілактики. Використовувати кортикостероїди в лікуванні пацієнтів із COVID-19 слід зважено. Необхідно приділяти увагу діагностиці остеопорозу, оскільки в госпіталізованих пацієнтів є багато чинників ризику підвищеної крихкості кісток. Хворим із наслідками інфекції COVID-19 знадобиться комплексний план відновлення та реабілітаційного лікування.

Ключові слова. COVID-19, остеопороз, аваскулярний остеонекроз, кортикостероїди, довгострокові ускладнення.

Key words. COVID-19, osteoporosis, avascular osteonecrosis, corticosteroids, long-term consequences

Introduction

The coronavirus (SARS-CoV-2) (COVID-19) pandemic has caused an unprecedented response from the global scientific community. Various hypotheses were formulated regarding its pathogenic mechanisms and treatment. The pandemic of COVID-19 has caused great problems for the medical care of patients with diseases of the musculoskeletal system, such as pre-hospital care, emergency diagnosis and treatment, surgical interventions, anesthesia, as well as peri- and postoperative management [1]. Today, more and more attention is paid to complications after COVID-19, which can affect the life and health of patients. Many reports have been published about the long-term consequences of the infection, which also affect the musculoskeletal system [2, 3]. The presented article provides a review of the literature regarding the possibility of developing osteoporosis and avascular necrosis of bones after suffering from COVID-19.

Purpose: to provide useful information for clinicians about possible complications in the musculoskeletal system after suffering from COVID-19 for the timely application of effective methods of their prevention.

Material and methods

Three electronic databases (PMC, PubMed and Scopus) were used to search for relevant sources of information published between December 2019 and December 2021. Additional studies were identified by analyzing the relevant literature in the selected articles. The full text of the articles was reviewed to confirm their relevance to the stated purpose of the review.

Results and their discussion

Osteoporosis

Due to the prioritization of emergency services and the postponement of planned care, the treatment of many chronic diseases, including osteoporosis, is complicated, as resources are redistributed to fight the pandemic. An osteoporotic fracture significantly affects the physical, financial, and psychosocial status of a person, as well as their caregivers [4]. Although due to quarantine restrictions hospitalization due to fractures has significantly decreased [5, 6], it is necessary to take into account the possibility of developing osteoporosis and increasing the incidence of fractures in the future.

Patients hospitalized with COVID-19 have multiple factors that provoke bone fragility with a high risk of fractures. Available information indicates that most patients over 60 years of age are diagnosed with at least one concomitant disorder (ischemic heart disease, diabetes, etc.) [7], an increase in the level of proinflammatory cytokines (CXCL10, IFN-γ, IL-1β, IL-6, IL-8, IL-17, and TNF-α) [8]. Authors suggest a possible role for calcium levels as a useful laboratory marker of disease aggressiveness that can be easily assessed in emergency situations, helping clinicians predict disease severity in patients with COVID-19 [9, 10]. Currently, hypocalcemia is considered as an indicator of the severity and progression of the course of COVID-19 [9, 11, 12].

Regarding the impact of vitamin D deficiency or insufficiency on the course of the disease, conflicting information has been found. A serum total 25-hydroxyvitamin D (25(OH)D) level of less than 12 ng/ml (< 30 nM) has been found to be associated with a higher risk of mechanical ventilation (VLC) use and death [11]. Systematic review of the literature (28 studies) showed that vitamin D deficiency increased the risk of infection with COVID-19, being also associated with the severity and increased mortality rate of the infection [13]. The authors confirm that vitamin D (1,000 to 2,000 IU per day) should be administered to at-risk adolescents and adults to maintain normal 25(OH)D levels. The action of vitamin D is based on the impact on the development of cytokine storm in patients with COVID-19, which is considered as the main risk factor for fatal outcome. In addition, vitamin D deficiency is one of the main risk factors affecting the development of osteoporosis. An insufficient blood level of this vitamin triggers a decrease in calcium absorption, an increase in the level of parathyroid hormone with secondary activation of bone remodeling, mobilization of calcium from bones, which acts as a mechanism of bone tissue loss.

The interaction of SARS-CoV-2 glycoprotein with the human dipeptidyl peptidase-4 receptor (DPP-4/CD26) may be an important factor in virulence. Expression of DPP-4/CD26 receptors can be reduced *in vivo* by correcting hypovitaminosis D, further suggesting that optimizing vitamin D status may improve treatment outcomes in patients with COVID-19 [14].

However, there was a study (involving 445 patients hospitalized with COVID-19), in which no relationship between vitamin D levels and the severity of the disease was found. Instead, the authors noted that hypocalcemia is a reliable marker of severe progression of the COVID-19 infection [12].

It is necessary to take into account the impact of a decrease in other indicators on the state of bone tissue. Additional factors, namely: prolonged immobilization, loss of muscle mass, and treatment with high doses of glucocorticoids, can increase resorption

and, accordingly, lead to bone loss and increase the probability of falls provoking fractures in the elderly [15].

Considering the data obtained during the period of the COVID-19 pandemic, close attention should be paid to the diagnosis of osteoporosis. In particular, it is necessary to assess the risks of fracture, measure bone mineral density and use biochemical markers of bone metabolism (serum calcium, 25(OH)D, serum N-terminal propeptide of procollagen type 1 (PINP) [16].

Avascular osteonecrosis

Avascular osteonecrosis can be idiopathic or associated with a number of diseases, such as trauma, sickle cell anemia, vasculitis, etc. Early diagnosis is important because timely therapy can stop the progression of the condition and prevent the further development of avascular osteonecrosis [17]. A decrease in the proliferation and differentiation of osteoblasts is caused by an increase in the level of cytokines [18]. The development of avascular necrosis can probably be caused by excessive use of corticosteroids, hypercoagulation and increased bone resorption. There are several mechanisms of SARS-CoV-2 effect on bone resorption. One of them is angiotensin-converting enzyme-2 (ACE-2), a membrane protein located on the plasma membrane that is the entry point into cells. It is expressed in most tissues, in particular in compact and spongy bones.

SARS-CoV-2-induced hypoxia is an important factor in increasing the differentiation and activity of osteoclasts and, accordingly, enhancing osteoresorption: it increases the expression of pro-osteoclastic cytokines, such as receptor activator of nuclear factor-B ligand (RANKL), vascular endothelium growth factor (VEGF), macrophage colony-stimulating factor (M-CSF), hypoxia-inducible factor (HIF- 1) [19]. At the same time, the differentiation of osteoblasts is disturbed.

These factors are associated with COVID-19 and may lead to the development of avascular osteonecrosis.

During the SARS-CoV-1 pandemic in 2003, patients received very high doses of corticosteroids. The results of the study suggest that while long-term use of steroids can cause bone damage, short-term use has limited effect. A large number of patients with SARS-CoV-1 experienced arthralgia of large joints without any abnormalities, for the most part, on magnetic resonance imaging. The main musculoskeletal complications of SARS-CoV-1 were osteonecrosis and bone loss, which did not occur due to the disease itself, but due to long-term treatment with high doses of steroids [20]. In 2009, a three-year study was completed in which the relationship between the development of avascular osteonecrosis and treatment with corticosteroids, which was prescribed to patients with severe acute respiratory syndrome (SARS) [21]. In 39 % of patients, avascular osteonecrosis of the femur developed within 3–4 months after starting treatment. Two more cases of avascular osteonecrosis of the hip joint were observed in a year, and 11 cases of this disease were diagnosed in 3 years, namely: 1 in hip joint, 10 in other areas. In total, 58 % of the cohort was diagnosed with avascular osteonecrosis in 3 years of observation. The only factor associated with avascular osteonecrosis of the hip was the total dose of corticosteroids received. These data suggest that these drugs for the treatment of COVID-19 may result in avascular osteonecrosis in patients [22].

A. Sulewski et al. [23] included a group of 10 individuals with COVID-19 who developed symptoms of joint dysfunction classified as avascular bone necrosis confirmed by magnetic resonance imaging. At the same time, the exclusion criteria were previous injury of the affected joint, steroid treatment and severe chronic diseases (diabetes and hypertension were not exclusion criteria). The authors concluded that SARS-CoV-2 can infect bone with symptoms of avascular osteonecrosis 1–3 weeks after infection. It is necessary to manage the disorder with medication or, in the diagnosed final stage of avascular necrosis, to carry out endoprosthetic repair.

Other experts reported 3 patients in whom the mean dose of steroid equivalent to prednisone was 758 mg (400–1250 mg). One of them developed avascular osteonecrosis of the femur after COVID-19 and a total corticosteroid dose of 1250 mg (intravenous methylprednisolone 80 mg daily for 9 days, followed by 350 mg oral prednisone for 28 days) in 45 days; in the second patient, after oral administration of dexamethasone for 10 days (60 mg, which is equivalent to 400 mg of prednisolone) — in 57 days, in the third — after intravenous administration of methylprednisolone (500 mg, which is equivalent to 625 mg of prednisolone) — in 45 days. Medication with bisphosphonates made it possible to avoid surgical intervention [24].

To prevent steroid-induced avascular osteonecrosis, these drugs should be considered only in patients with septic shock or in critical cases [25]. Individuals at an early stage of avascular osteonecrosis are recommended physiotherapy and combined pharmacotherapy with bisphosphonates [26].

Conclusions

Information presented in the literature review suggests that patients with severe SARS-CoV-2 are

at high risk for complications such as osteoporosis and avascular osteonecrosis. Despite the debate about the pros and cons of using corticosteroids for the treatment of coronavirus disease, it is an indisputable fact that their long-term use in high doses leads to the development of avascular osteonecrosis [27]. Therefore, we urge judicious use of corticosteroids in the treatment of patients with COVID-19 and do not recommend them as routine therapy. It is also necessary to pay close attention to the diagnosis of osteoporosis, since in hospitalized patients there are many factors that can provoke increased bone fragility. Patients suffering from the mid- and long-term effects of the COVID-19 infection will need a comprehensive recovery and rehabilitation treatment plan to overcome them. Research on complications in the locomotor system continues today for more accurate prognosis and effective prevention.

Conflict of interest. The authors declare no conflict of interest.

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THE POSSIBILITY OF OSTEOPOROSIS AND AVASCULAR NECROSIS CAUSED BY THE COVID-19 PANDEMIC. ANALYSIS OF LITERATURE

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