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Complex-Conservative Treatment of Sars-Cov-2 Associated Early-Stage Avascular Necrosis of The Femoral Head

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Annotation. Avascular necrosis of bones (osteonecrosis) has developed as a bad consequence of the COVID-19 (SARS-CoV-2) pandemic that has swept the world. In 5-58% of patients with the type of covid-19 fertilizer, the bones were affected by avascular necrosis. In 39% of patients with SARS-CoV-2, avascular necrosis of the hip bone developed within a few months after atypical pneumonia. Avascular necrosis is a disease that often develops in people of working age (average age is 33-45 years) and leads to severe disability associated with the death of bone tissue in a particular area. Discussions about the pathogenesis of postcovid avascular necrosis, the possibility of its diagnosis and treatment in the early stages are subject to active discussion. Given that COVID-19 infection is common among young people and working-age people, early diagnosis and treatment of this form of osteonecrosis is of great social and economic importance.

Keywords: avascular necrosis of the femoral head with the etiology of COVID-19, glucocorticoids, diagnosis, conservative and surgical treatment.

Introduction

The new coronavirus was dubbed COVID-19 by SARS-CoV-2 and the infection that caused it (World Health Organization), causing the pandemic. The coronavirus has already claimed the lives of more than 7.2 million people [1]. Long-term COVID-19 complications in many patients were not only fatigue, shortness of breath, anxiety and depression, thoughtfulness or inability to concentrate, tachycardia, chest pain, very rare Hyena-Barre syndrome, pulmonary fibrosis, pulmonary thromboembolism, cardiomyopathy, emotional dysfunction, and Stroke [2], but also caused muscle and joint pain that was hos to avascular necrosis [3, 4].

According to various sources, avascular necrosis is observed in 5-58% of patients with severe type COVID-19 [5, 6]. de Vlas S.J. according to SARS-CoV-2, avascular necrosis of the thigh bone head developed within a few months after atypical pneumonia in 39% of patients [7]. Avascular necrosis most often developed in people of working age (the average age was 33-45). This manifested itself as a severe disability-causing disease associated with the loss of bone tissue in a particular area [8]. Osteonecrosis foci have also been identified in thigh and large calf bone vertebrae, shoulder bone head, hip and heel bone, as well as other areas of the skeleton [5].

In literature data, two possible mechanisms in the pathogenesis of the development of avascular necrosis after COVID-19 infection are discussed: the damage of the virus's bone tissue to blood vessels and the negative effects of glucocorticoids applied for the purpose of treating infection on bone tissue (Agarwala S.R., Hong N., Vlas S.J. etc).

After a new coronavirus infection, the search for methods for diagnosing avascular necrosis in the early stages and risk factors for its development continues. In a cited literature report, 3-4 stages of avascular necrosis (Ficat, 1964.) surgical treatment is indicated, while in the early stages (stages 1-2) conservative treatment technologies have not been sufficiently developed.

Materials And Methods

Articles were searched from PubMed, Scopus, and Google Scholar databases using the following keywords: COVID-19, avascular necrosis, diagnostics, surgery, and conservative treatment. The search term is the last 4 years. Of the 90 articles downloaded, 75 were selected. Publications related to the early diagnosis and treatment of avascular necrosis following COVID-19 infection have been selected.

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Main Part

Pathogenesis of avascular necrosis that occurs as a COVID-19 complication.

During COVID-19, SARS-CoV-2 virus penetrates directly into vascular endothelial cells via angiotensin-modifying enzyme-2 (AME2). These endothelial cells cause vascular damage not only in the lungs, but also in many other organs and tissues through the development of coagulopathy and diffuse inflammatory syndrome [9]. R. According to observations by Escher and other authors, patients with COVID-19 infection have a significant increase in the Villebrand factor, which confirms complete damage to the vascular endothelium [10]. In addition, in a patient infected with SARS-CoV, TRIM55 ubiquitin ligase in smooth muscle cells of the vessels induces the expression of the E3 gene, which in turn leads to inflammation of the vessel wall and accumulation of leukocytes [11]. In combination with hypercoagulation in the distal area from the site of Arterial obstruction, the likelihood of developing microthrombosis and bone osteonecrosis increases [12].

In addition to the direct entry of the virus into the vascular endothelium, SARS-CoV-2 also enhances the lesion process, which includes SARS-CoV-1 [13] bone tissue, general inflammation, and a cytokine storm. Anti-inflammatory cytokines: interferon gamma (IFN-γ), tumor necrosis factor (TFN), interleukin-1 (IL-1), interleukin-6 (IL-6) [14] and chemotaxis of T-lymphocytes to the site of inflammation caused by the immune response are observed [15]. In this case, microthrombosis and direct damage of blood vessels by the virus can lead to the development of avascular necrosis [16].

However, this is not the only mechanism for the development of osteonecrosis after COVID-19. The use of glucocorticoids is more at risk of developing avascular necrosis in COVID-19 [17]. Their use in COVID-19 reduces the expression of anti-inflammatory cytokines such as IL-1, IL-2, IL-6, TNF. It is based on its potential advantage over other drugs to reduce immunopathological tissue damage and anti-inflammatory early response reaction through [18]. At the same time, a number of authors note the potential damage to glucocorticoids, including the presence of side effects such as delayed viral excretion, diabetes, psychosis, systemic osteoporosis in bones, and avascular necrosis [19, 20, 21].

The body's negative reaction when taking glucocorticosteroids (GCS)appears soon after the patient recovers from COVID-19. Thus, when patients with atypical pneumonia were examined after recovery, it was found that there was a possibility of a decrease in the mineral density (MD) of bone tissue.

The degree of loss of mineral density of bone tissue largely depends on the dosage and duration of corticosteroids. Glucocorticosteroids have been a key component of therapy aimed at reducing inflammation during initial infictation, subsequent rehabilitation as well as, initial recovery [22].

The likelihood of glucocorticoid use in patients with COVID-19 ranges from 28% to 70% gacha in various medical institutions [23]. The widespread use of glucocorticoids in COVID-19 infection is based on positive experience in their use in patients with atypical pneumonia during the SARS-Co-V epidemic. Studies have shown that early use of dexamethasone may reduce the duration of mechanical ventilation and overall mortality in patients with acute respiratory distress syndrome (ARDS) [24]. According to the results of the RECOVERY clinical trial in the treatment of COVID-19, this drug reduces the risk of death by 20% in patients who are on artificial lung ventilation or who are taking oxygen with a severe type of COVID-19 [25]. However, corticosteroids are a factor that has a direct and indirect negative effect on the bone, predisposing to the development of avascular necrosis [26]. First of all, they affect the proliferation of mesenchymal cells: block RUNX2, prevent the formation of preosteoblasts, their transformation into osteoblasts. This reduces the number of mature osteoblasts and leads the metabolism to the formation of adipocytes from mesenchymal cells [27,28]. The action of glucocorticoids increases the apoptosis of osteoblasts and Osteocytes, while osteoclasts are activated due to their effects on the RANKL and DKK-1 signaling protein system [29].

The negative effects of glucocorticoids on bone tissue are also manifested through their effect on lipid metabolism. The accumulation of low-density lipoproteins, the appearance of fatty emboli, in turn, leads to thrombosis of peripheral blood vessels and, consequently, ischemic necrosis of bone tissue. Free fatty acids formed during the hydrolysis of fat emboli damage the endothelial cells of capillaries, causing diffuse vasculitis and intravascular coagulation, which increases ischemic necrosis of bone tissue [30].

Another manifestation of the negative effect of glucocorticoids on bone tissue is that glucocorticoids, which act as a regulator of local blood flow, alter the sensitivity of the vessels to vasoactive substances such

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as endothelin-1, norepinephrine and bradykinin. This leads to vasoconstriction in the thigh bone head, which in turn increases bone ischemia. High doses of glucocorticoids decrease tissue plasminogen activator (t-PA) activity and increase plasma plasminogen activator inhibitor-1 (PAI-1) antigen levels, which increases plasma procoagulant potential and hypercoagulation status [31].

As mentioned above, the development of osteonecrosis is influenced by both the dosage of glucocorticoids and the duration of treatment. Lessons learned from the 2003 Chinese SARS outbreak showed that methylprednisolone with a dose of less than 1-2 mg/kg is recommended as an adjuvant treatment for COVID-19 in a short course of 3-5 days [32].

This method of application, coupled with a strong inflammatory reaction and positive treatment effects in patients with acute progression of the disease (according to pulmonary computed tomography), does not lead to the development of osteonecrosis in the bones [33]. However, longer treatment with steroids in high cumulative doses leads to the development of osteonecrosis [34]. According to some researchers, there is a relationship between the maximum daily dose of glucocorticoids and osteonecrosis of the thigh bone head, which requires adequate control [35].

G. Motomura and others ' experiments on rabbits concluded that when using 1 mg/kg, 5 mg/kg, 20 mg/kg, and 40 mg/kg methylprednisolone in groups, the likelihood of developing osteonecrosis is 0%, 42%, 70%, and 96%, respectively [36].

The experience of clinical use of methylprednisolone at a dose of 5 mg/kg per day showed that this leads to the development of osteonecrosis in every fifth patient, with patients taken at a dose of 1 mg/kg per day not developing the disease unlike the control group [37]. Increasing the dose of prednisolone every 10 mg increases the risk of developing osteonecrosis by 3.6% [38].

Particular importance is attached to the cumulative dose of GKS. In a retrospective study involving 539 patients with Acute Respiratory Syndrome (ARS), the rate of development of osteonecrosis was associated with an increase in the total dose of the drug [39].

With a total dose of methylprednisolone less than 5 g, the risk of developing osteonecrosis was relatively lower. However, as the total dose increased from 5 g to 10 g, the risk increased dramatically (R. Zhao and other Autors).

J. Rademaker et al showed that prednisolone at a dose of 700 mg was the limit for the onset of hip skull necrosis [40]. M.H.M. Chan et al pointed out that cumulative doses of more than 2,000 mg of methylprednisolone or more than 1,900 mg of hydrocortisone are predictors of osteonecrosis [41].

The duration of treatment also affects the development of osteonecrosis. A study of 1,137 patients with atypical pneumonia found that every 10th day of treatment, the probability of osteonecrosis was 1.29 (95% CI 1.09-1.53; p = 0.003), which, according to the authors, indicates the importance of reducing the duration of steroid use to reduce the risk of osteonecrosis [38]. Weekly intake of glucocorticoids: there is an opinion that if the dose of methylprednisolone taken per oral exceeds 300 mg, that is, if a patient with a weight of 60 kg for 5 days exceeds about 1 mg/kg per day, the risk of developing osteonecrosis may be higher. Based on these data, the authors focused attention on examining patients with the above risk for early detection of avascular necrosis after contracting COVID-19 [42].

Diagnosis of avascular necrosis of femoral head in patients who have undergone COVID-19

The standard method in the diagnosis of aseptic necrosis of the head of the thigh is the xisoblang X-ray examination method, which has not lost its relevance even in the diagnosis of postcovid avascular necrosis.

F.S. According to Zhao and others, MRI is recommended in 3, 6 and 12 months after the end of glucocorticoid intake [43].

A retrospective study of patients after COVID-19 found osteonecrosis after treatment was completed in 21 of 23 patients using MRI after 3 months [44].

The use of magnetic resonance spectroscopy (MRS) examination method in hip skull avascular necrosis makes it possible to fully study the changes in the ratio of chemicals in the damaged area caused by ischemia.

In addition to the diagnosis of MRI, new forecasts of the disease are also constantly being sought with the help of laboratory methods. A reduction in plasminogen activator inhibitor-1 (PAI-1) in blood plasma has been shown to be a highly sensitive method for examining patients at high risk of osteonecrosis

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[45]. B. Wei and W. Wei proposed the use of microRNA 423-5p as a biomarker, with levels significantly increased in the blood in patients with glucocorticosteroid-induced osteonecrosis. At the same time, it has been noted that in most cases the coagulogram indicators remain in the form of normal values [46].

Treatment of avascular necrosis of femoral head associated with COVID-19 infection performed

Timely detection of avascular necrosis as a COVID-19 complication and its treatment with glucocorticoids can reduce the risk of developing an active stage of the disease, but this will inevitably lead to arthroplasty of the joints in the future. However, if the diagnosis of osteonecrosis is made at an early stage (I or II), 92-97% of patients will not need surgical intervention [47] and can lead to recovery using conservative treatment treatments [48].

In the early stages of treatment such as idiopathic osteonecrosis or secondary osteonecrosis unrelated to COVID-19, the primary goal of treatment is to reduce pain, slow disease progression, prevent subchondral bone compression, and restore joint function. Conservative treatment in the early stages of post-COVID-19 avascular necrosis distances the joints from the practice of total endoprotezing due to the high risk of developing aseptic instability in young and middle-aged patients.

Currently, there is no standardized protocol for treating the early stage of osteonecrosis after COVID-19. Clinical practice uses a combination of pharmacotherapy and joint decompression, and has shown its effectiveness, including in steroid-induced osteonecrosis [49]. Decompression into the joints is carried out for at least 3 months. Osteonecrosis in the skull of the thigh bone can be used by tentacles, and when necrosis is detected in other skeletal localizations, rods and orthoses can be used in addition to the elbow [50].

Successful use of antiresorbtive drugs for the treatment of secondary osteonecrosis associated with glucocorticoids in adults in the early stages S. It was highlighted by Agarwala et al [51]. The ability of antiresorbtive drugs to slow disease progression and reduce the need for surgical intervention has been proven. According to reports from the American Academy of Orthopedic Surgeons (AAOS), the proportion of bisphosphonates in the treatment of osteonecrosis of the thigh bone is 10% [52]. Their use is aimed at reducing the intensity of resorption in the area of osteonecrosis, which reduces the risk of impression of the subchondral bone [53] and the surrounding bone tissue [54]. Alendronic acid is considered as a possible bisphosphonate for the entire period of treatment for patients with aseptic necrosis - 70 mg once a week [55]. However, the disadvantages of peroral applied bisphosphonates are their low compatibility. In this regard, the use of intravenous forms, primarily zoledronic acid at a dose of 5 mg, is considered promising (once a year), taking into account the frequency of intake [56].

In addition to its direct antirezorbtive effect, it reduces bone tissue swelling [57], as well as intravenous bisphosphonates have a significant analgesic effect, which improves the quality of life of patients [58].

Bisphosphonates cannot be used in patients with impaired excretion of nitrogen residues through the kidneys [59]. In these cases, there is experience in using denosumab at a dose of 60 mg twice a year as an antirezorbtive drug for avascular necrosis [60].

The use of antiresorbtive drugs requires the simultaneous use of calcium preparations at a dose of 500-1000 mg per day and the use of cholecalcidol at a dose of at least 1000 IU/day or at a dose of at least 0.5-0.75 MCG per day [61].

Prescribing cholecalciferol during a pandemic is recommended, first of all, to affect the course of COVID-19. In this case, the severity of the course of infection decreases, and the survival rate increases [62, 63]. These effects are explained by a slowdown in viral replication rates and an increase in the concentration of anti-inflammatory cytokines [64]. However, this mechanism of action of cholecalciferol has a weak base of evidence, as follow-up and clinical studies on the effects of Vitamin D and The associated risk of respiratory infections are the opposite: some report a decrease in risk, while others do not [65, 66]. These conflicting results are thought to be related to the heterogeneity of the patient population and the dose of vitamin D. Therefore, the results of well-developed tests of Vitamin D should be expected before drawing conclusions about their possible effect on the body.

Another argument for prescribing cholecalciferol is the relationship between the development of osteonecrosis and a decrease in the mineral density of the bones is hypothesized [67]. The use of cholecalciferol in combination with calcium preparations is currently the main treatment method for slowing

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bone metabolism against the background of primary and secondary osteoporosis as well as maintaining bone mineral density [68].

Taking into account the recorded relationship between osteonecrosis and microcirculation disorders, from the first days after the diagnosis of osteonecrosis (as an inhibitor of platelet aggregation and an angioprotective agent), dipyridamol is administered 3 times per oral per day from a dose of 25 mg, for 3 weeks. [69]. Iloprost can be prescribed in order to reduce intra-bone pressure and improve the condition of microcirculation. The effectiveness of this drug in the treatment of osteonecrosis has been noted earlier [70]. It is desirable that Iloprost received it under the supervision of a doctor in intensive care units under inpatient conditions, due to the risk of drastically lowering blood pressure when infused [71].

Anticoagulants are recommended in patients with avascular necrosis of the hip head postcovid etiology as a complex therapy for hypercoagulation or hypofibrinolysis in the 1-2 stages of development of the disease (according to the classification of Ficat). In particular, Enoxyparin-sodium is prescribed subcutaneous injection from a dose of 4,000 IU (0.4 ml) to 6,000 IU (0.6 ml) per day at a duration of 2 to 12 weeks. [72]. It is clear that in the treatment of COVID-19, anticoagulants in the form of tablets also have no less effect than subcutaneous drugs, for example, the use of apixaban at a dose of 2.5 mg 2 times a day for 12 weeks [73].

In patients with avascular necrosis of the head of the thigh, a complex of treatment with topical application of anticoagulant therapy i.e. girudotherapy has not been developed. Much research and study is needed on the complex-conservative treatment of hip skull avascular necrosis caused by ischemia using girudotherapy in the early stages.

In some cases, the symptomatic physiotherapy method allows pain relief [74]. In this regard, impulse electromagnetic therapy, hyperbaric oxygenation, ozonotherapy, extracorporeal shock-wave therapy can be used in the complex treatment of avascular necrosis. However, further research is required to assess their effectiveness in treating osteonecrosis after COVID-19.

In order to reduce pain in the early stages and improve blood supply, it is possible to tunnel (decompression) the affected area of the head of the thigh bone after conservative therapy prescribed earlier [75].

Conclusion

At the end of our article, the method of magnetic resonance spectroscopy in the early diagnosis of avascular necrosis of the femoral head, which occurred after SARS-CoV-2, will have great advantages in the future. Through it, patients have the opportunity to clearly choose exactly what type of treatment (conservative/surgical) they will receive in the early stages of the disease. In addition to the diagnosis of the disease, the method of Ultra-sonic duplex scanning of the blood vessels of the legs is also important in predicting the prospect of the disease and choosing a treatment method. Currently, according to existing publications, two separate mechanisms for the development of avascular necrosis after COVID-19 are being discussed: the action of glucocorticoids used to treat infection and the contribution of the COVID-19 virus itself to impaired bone metabolism. In the latter case, the development of osteonecrosis is associated with increased blood clotting under the influence of antiinflammatory cytokines due to microtrombosis and impaired blood supply to bone tissue against the background of direct damage to blood vessels by the virus or the development of inflammation of the endothelial floor of the vascular wall, as well as increased immune response to infection. Also, the role of local girudotherapy in the complex-conservative treatment of the disease in the early stages i.e., in stages 1-2 is noted separately. Improving local microcirculation and Thrombolysis therapy the affected area is important in the elimination of venous stasis in the venous blood vessels. The complex conservative treatment that we propose is distinguished by its effectiveness, unlike the traditional conservative treatments that exist.

At the end of our conclusion, in a patient with avascular necrosis of the femoral head, which has developed under the influence of COVID-19, the consequences of the disease can be assessed by dynamic radiography, MRI, MCKT and UT-duplex examinations for periods of 6, 9, 12, 18 months. It is also advisable to make the coagulation content of blood taxable in dynamics. Through conservative treatment of the disease in the early stages (stage I-II, Ficat), it will be necessary to create treatment technologies aimed at improving local blood circulation.

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