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## NEW VIEWS ON ETIOLOGY AND PATOGENESIS OF AVASCULAR NECROSIS OF FEMORAL HEAD IN PATIENTS WITH COVID 19

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### **Introduction**

Avascular necrosis of the femoral head (ANFH) is the necrosis of areas of the bone marrow of the femoral head with the development of local osteoporosis and osteonecrosis due to blood supply disorders. It is manifested by increasing pain, limited movement, and impaired hip joint function. It can cause disability of the patient.

### **Materials and methods**

scientific articles and Internet resources were used for this study, in particular, such databases as CyberLeninka and PubMed were used.

### **Discussion**

The causes and pathogenesis of osteonecrosis in nontraumatic cases are not fully understood. The most likely causes of the development of this disease were a combination of several causes: a previous coronavirus infection; treatment with (dexamethasone); previously existing and undiagnosed osteopenia; vitamin D deficiency. The relationship of ANFH development with a previous coronavirus infection is beyond doubt, since complaints of pain in the right TBS have a chronological connection with COVID-19, before which, the patient led an active lifestyle and did not experience any pain.

### **Key words**

Avascular necrosis of femoral head, alcoxol, dexametason,

**Introduction** The consequences of infection caused by the new coronavirus (SARS-CoV-2, severe acute respiratory syndrome-related coronavirus 2), COVID-19 (coronavirus disease 2019), is highly imaginative and is being actively studied all over the world.

In addition to respiratory symptoms, some patients have musculoskeletal manifestations, in particular arthralgia, myalgia, pain in the lower back, which can persist for a long time after infection, being one of the manifestations of the so-called postcovid syndrome. In the long term after COVID-19 a number of patients develop reactive arthritis, various autoimmune

disorders, including the onset of autoimmune diseases, as well as osteonecrosis (ON) [1]. Often, the extent of its development after COVID-19 is not



yet known. In the literature, there are descriptions of cases of OH after coronavirus infection, most often associated with the severe course of COVID-19 and the use of glucocorticoids [2,3].

**Etiology And Pathogenesis** There is no exact explanation of the mechanism of development, however, it is believed that this pathology may occur due to microvascular thrombosis, which is the result of damage to the endothelium[4]. The action of cytokines is another mechanism contributing to the damage of endothelial cells and subsequent thrombosis, as well as bone resorption. Interleukin (IL) 1 $\beta$ , tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) and IL-6, released during combustion, increase bone tissue resorption, which leads to early osteoporosis and micro-destruction of bone. Nuclear Factor Ligand receptor activator-kB (RANKL, receptor activator of nuclear factor kappa-B ligand), vascular endothelial growth factor and macrophage the colony-stimulating factor released during hypoxia can activate osteoclasts, block the synthesis and differentiation of osteoblasts, which is also associated with increased resorption and impaired bone formation [5,6]. In addition to indirectly enhancing bone resorption by increasing TNF- $\alpha$  synthesis, SARS CoV-2 protein 3a/X1 is able to increase osteoclastogenesis by influencing osteoclast progenitor cells.

Alcohol withdrawal is the most common etiological factor in adults with a dose-dependent effect: with an increase in the amount of alcohol consumed (ml per week), the risk of disease increases proportionally. Obviously, alcohol disrupts phospholipid metabolism and

distorts cytokine reactions, however, at this moment the mechanism of impaired bone metabolism and the development of ANGB due to consumption is not completely clear [18]. At the same time, it has been proven that patients with antiphospholipid syndrome have a risk of

ANGB is three times higher than in healthy people [19].

Another factor that may be the reason for the development of IT is the use of GC. Unfortunately, in the severe course of COVID-19, HA are necessary to suppress cytokine overexpression, however, it is necessary to remember their adverse effect on bone tissue due to activation of osteoclasts, an increase in their life span, as well as increased apoptosis of osteoblasts and osteocytes [7-9]. As a result, bone remodeling and repair are collapsing, suffering adaptation to loads [10]. It is also known that the use of HA leads to hyperplasia of adipose tissue of the bone marrow, fatty embolism and hypercoagulation, as a result of which intraosseous pressure increases and bone perfusion decreases

The pathophysiology of aseptic necrosis in children and adults is similar. A distinctive feature in children is the ability of epiphyseal cartilage tissue to grow and restore the height of the femoral head, unlike adults, in whom relatively thin



epiphyseal cartilage does not have the ability to regenerate, therefore progressive pathological changes are, as a rule, irreversible. [11].

The development of aseptic necrosis can be divided into two successive phases: ischemia and regeneration [12].

The phase of ischemia begins long before the first clinical manifestations. The primary source of ischemic changes has not yet been determined. As such, the following are considered: pathology of blood vessels supplying the proximal epimetaphysis of the femur, changes in the blood transported by them or in the subchondral layer affecting the regeneration of the cartilage matrix [29]. According to Wingstrand et al. [28], ischemia of the femoral head with impaired blood flow does not always lead to the development of pain syndrome, which it is more often manifested only in the regeneration phase. There are no X-ray signs of the ischemic phase: the first

changes appear only in the initial stages of the regeneration phase, when revascularization and migration of osteoblastic precursor cells begin, which leads to a visible change in the structure of bone tissue.

The regeneration phase. As with any damage to bone tissue, after the occurrence of ischemia and necrosis, inflammatory mediators stimulate the appearance of stem cells in this area. This process is provided by the growth of blood vessels in the direction of epiphyseal cartilage. Since the beginning of the regeneration phase, two different processes have been taking place in the femoral head. On the one hand, compact subchondral bone and induced osteoclasts will maintain a negative appositional-resorption balance, on the other - spongy bone located in the center of the femoral head, it will have a positive appositional balance due to osteoblast activation. Radiologically, this pattern manifests itself in the form of a subchondral X-ray translucent line. The weakened subchondral bone will no longer be able to hold the overlying cartilage, and, consequently, the articular surface of the femoral head begins to collapse. In adults, such

changes lead to the rapid development of coxarthrosis, while in children it is possible to restore

the configuration of the head [29].

**Discussion.** The most likely causes of the development of this disease were a combination of several causes: a previous coronavirus infection; treatment with (dexamethasone); previously existing and undiagnosed osteopenia; vitamin D deficiency. The relationship of ANFH development with a previous coronavirus infection is beyond doubt, since complaints

of pain in the right TBS have a chronological connection with COVID-19, before which, the patient led an active lifestyle and did not experience any pain. With ANFH associated with taking GC, the interval between the appearance of

symptoms associated with ANFH and taking GC is usually 6-12 months, but with SARS-CoV-2003 this interval turns out to be shorter

(about 2-6 months) [20, 21]. Therefore, in the first year after a coronavirus infection

, special attention should be paid to the complaints of patients from the musculoskeletal system.

The most common cases of ANFH in the literature are after a severe course of a new coronavirus infection complicated by acute respiratory distress syndrome (ARDS). The development of ANFH in connection with ARDS was described back in 2003 after an outbreak of SARS. Among 539 patients with severe ARDS, the frequency of ANFH was 39.5% for men and 19.3% for women; and it developed more often in younger patients (in the group from 20 to 49 years old) [22]. In most of the described cases, the development of ANFH in ARDS patients was associated

using GC. B. Zhang and S. Zhang [23], a system for stratifying the risk of developing OH in patients with COVID-19 was proposed, according to which patients who did not receive HC have a low risk; the average risk is noted when receiving a cumulative dose of <2000 mg of GC during <1 week; high risk - when receiving a cumulative dose of  $\geq 2000$  mg in terms of prednisone during  $\geq 1$  week or during intravenous pulse therapy at a dose  $\geq 80$  mg/day for at least 3 days. M.D. McKee et al. [25] in 2001, it was shown that the total dose of HA that caused IT varied from 290 to 3300 mg in terms of on prednisone. In the work of G.M. Shetty [24], it was significantly higher and amounted to more than 5,000 mg in terms of prednisone, however

, due to persistent pain syndrome in the lumbar spine at the onset of the disease, patients received a total of 40 mg of dexamethasone, which is equivalent to 266 mg of prednisone. Perhaps this treatment also played an adverse role in the development of ANFH. COVID-19

appears to be able to increase the risk of ANFH even in the absence of HA therapy. In several studies, the average duration of the interval after COVID-19 was 58 days before the appearance of ANFH (GC was used in all cases). The development of ANFH has also been described with the appointment of low doses of HA in the presence of other risk factors for this pathology

**Conclusion.** After a coronavirus infection, it is possible to develop avascular necrosis of the femoral head, including multifocal, even in the absence of severe COVID-19. Caution is required regarding the development of avascular necrosis in patients who have undergone COVID-19 and have complaints of abdominal pain, including of a permanent nature, in the first 3 months after the disease, when the risk is maximum, especially in the presence of appropriate risk factors



(osteoporosis, osteomalacia, systemic connective tissue diseases, diseases blood, the use of GC and others)

## REFERENCES

1. Cipollaro L, Giordano L, Padulo J, Oliva F, Maffulli N. Musculoskeletal symptoms in SARS-CoV-2 (COVID-19) patients. *J Orthop Surg.* 2020;15(1):178. doi: 10.1186/s13018-020-01702-w
2. 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
3. Bagaria V. Usual and unusual musculoskeletal sequelae of COVID 19! *Indian J Orthop.* 2021;55(S2):518-519. doi: 10.1007/ s43465-021-00412-7
4. Sardu C, Gambardella J, Morelli MB, 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
5. Takayanagi H, Kim S, Koga T, Nishina H, Isshiki M, Yoshida H, et al. Induction and activation of the transcription factor NFATc1 (NFAT2) integrate RANKL signaling in terminal differentiation of osteoclasts. *Dev Cell.* 2002;3(6):889-901. doi: 10.1016/s1534- 5807(02)00369-6
6. Hasan LK, Deadwiler B, Haratian A, Bolia IK, Weber AE, Petrigliano FA. Effects of COVID-19 on the musculoskeletal system: Clinician's guide. *Orthop Res Rev.* 2021;13:141-50. doi: 10.2147/ORR.S321884
7. Weinstein RS, Jilka RL, Parfitt AM, Manolagas SC. Inhibition of osteoblastogenesis and promotion of apoptosis of osteoblasts and osteocytes by glucocorticoids. Potential mechanisms of their deleterious effects on bone. *J Clin Invest.* 1998;102(2):274-282. doi: 10.1172/JCI2799
8. O'Brien CA, Jia D, Plotkin LI, Bellido T, Powers CC, Stewart SA, 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
9. Weinstein RS, Chen J-R, Powers CC, Stewart SA, Landes RD, Bellido T, et al. Promotion of osteoclast survival and antagonism of bisphosphonate-induced osteoclast apoptosis by glucocorticoids. *J Clin Invest.* 2002;109(8):1041-1048. doi: 10.1172/JCI14538
10. Weinstein RS, Wan C, Liu Q, Wang Y, Almeida M, O'Brien CA, 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



11. Clinical and radiographic outcomes after femoral varus derotation osteotomy for Legg-Calvé-Perthes disease at 25 years follow-up: what are the determinants of outcome in the long term? / B.K. Aydin, H. Sofu, M.N. Konya, T. Er, V. Sahin // *Hip Int.* 2016. Vol. 26, No 3. P. 301-306. DOI: 10.5301/HIPINT.5000329
12. Catto M. Pathology of aseptic bone necrosis. In: *Aseptic Necrosis of Bone* / Ed. by Davidson J.K. Amsterdam: Excerpta Medica. 1976. P. 3-100.
13. Jo'raboyeva Gulhayyo Baxtiyor Ранняя диагностика патологии при ревматоидном артрите. *The American Journal of Medical Sciences and Pharmaceutical.* 2021. Issue: 08 Pages: 21-25.
14. Davlatov Sh.Q., Saydaxmedov Z.I., Mahmudov U.I. CLINICAL AND FUNCTIONAL STATUS OF THE CARDIOVASCULAR SYSTEM IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE WITH COVID-19. SCIENTIFIC ASPECTS AND TRENDS IN THE FIELD OF SCIENTIFIC RESEARCH: a collection scientific works of the International scientific online conference (30th December, 2023) - Poland, Warsaw : "CESS", 2023. 16 (151), 50-53
15. Saydaxmedov, Z. I., & Mahmudov, U. I. (2023). Dynamics Of Glycemic Variability In Patients With Type 2 Diabetes Mellitus During Deprescribing Therapy Depending On The Presence Of Severe Comorbid Pathology. *Innovative Developments And Research In Education*, 2(24), 243-249.
16. Mamlakat, Y., & Kamola, N. (2022). Postcovid syndrome: arterial hypertension. *European journal of modern medicine and practice*, 2(3), 135-138.
17. Shermatov, R. M. ., Nishanova, Z. X. ., Nasirdinov, M. Z., Ogli Xabibullayev, S. R. ., & Bobojonov, S. S. U. . (2021). The Content Of Vitamin D Metabolites In Rachit In Children Of Early Age Who Received Specific Prevention. *The American Journal of Medical Sciences and Pharmaceutical Research*, 3(06), 131-138. <https://doi.org/10.37547/TAJMSPR/Volume03Issue06-21>
18. Lucey M.R., Mathurin P., Morgan T.R. Alcoholic hepatitis // *N. Engl. J. Med.* 2009. Vol. 360, No 26. P. 2758-2769. DOI: 10.1056/NEJMra0805786
19. Goldblatt J., Sacks S., Beighton P. The orthopedic aspects of Gaucher disease // *Clin. Orthop. Relat. Res.* 1978. No 137. P. 208-214.
20. Zhang N-F, Li ZR, Wei H-Y, Liu Z-H, Hernigou P. Steroidinduced osteonecrosis: The number of lesions is related to the dosage. *J Bone Joint Surg Br.* 2008;90-B(9):1239-1243. doi: 10.1302/0301-620X.90B9.20056
21. Aaron RK, Voisinet A, Racine J, Ali Y, Feller ER. Corticosteroidassociated avascular necrosis: dose relationships and early diagnosis: *Ann N Y Acad Sci.* 2011;1240(1):38-46.



22. Guo KJ, Zhao FC, Guo Y, Li FL, 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 Jt J.* 2014;96-B(2):259-262. doi: 10.1302/0301-620X.96B2.31935

23. Zhang B, Zhang S. Corticosteroid-induced osteonecrosis in COVID-19: A call for caution. *J Bone Miner Res.* 2020;35(9): 1828-1829. doi: 10.1002/jbmr.4136

24. Shetty GM. Double trouble - COVID-19 and the widespread use of corticosteroids: Are we staring at an osteonecrosis epidemic? *Indian J Orthop.* 2022;56(2):226-236. doi: 10.1007/s43465-021-00546-8

25. Mahmudov, U. I. (2023). COMPARATIVE CHARACTERISTICS OF CLINICAL AND LABORATORY PARAMETERS OF PATIENTS OF THE DIABETIC FOOT DEPARTMENT, DEPENDING ON THE PRESENCE OR ABSENCE OF DIABETES MELLITUS. *SO 'NGI ILMY TADQIQOTLAR NAZARIYASI*, 6(12), 355-360.

26. Khodjayeva Gulnora Abdubannonovna NOVATEUR PUBLICATIONS JournalNX- A Multidisciplinary Peer Reviewed Journal ISSN No: 2581 - 4230 VOLUME 9, ISSUE 10, October -2023 CLASSIFICATION OF ABDOMINAL TUBERCULOSIS

27. THE RELATIONSHIP BETWEEN CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) AND CARDIOVASCULAR DISEASE (CVD) Davlatov Shohjaxonbek Qurbonbek o'g'li Fergana Public Health Medical Institute 6-TOM / 12-SON / 2023-YIL / 15-DEKABR (93-104)

28. Intracapsular pressure in transient synovitis of the hip / H. Wingstrand, N. Egund, N.O. Carlin, L. Forsberg, T. Gustafson, G. Sundén // *Acta Orthop. Scand.* 1985. Vol. 56, No 3. P. 204-210. DOI: 10.3109/17453678508992995

29. Guerado E., Caso E. The physiopathology of avascular necrosis of the femoral head: an update // *Injury.* 2016. Vol. 47, No Suppl. 6. P. S16-S26. DOI: 10.1016/S0020-1383(16)30835-X