Review Article

Knee osteonecrosis after SARS-CoV-2 infection: a systematic case-based review

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Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus responsible for coronavirus disease 2019 (COVID-19). Patients with COVID-19 manifested symptoms mainly related to the respiratory system, but also the musculoskeletal system can be involved. COVID-19 has been described as a possible cause of knee osteonecrosis (ON). A systematic review was performed to investigate the hypothetical correlation between COVID-19 and knee ON.

Methods: Inclusion criteria were all articles reporting cases of knee ON after a diagnosis of SARS-CoV-2 infection. Considering that COVID-19 is an emerging disease, all levels of evidence studies were included.

Results: Finally, two case series and three case reports were included. We extracted data regarding demographic and clinical characteristics, details of magnetic resonance imaging (MRI), use of corticosteroids (CCS), temporal correlation between ON and COVID-19, treatment of the lesion and its outcomes. A total of seven cases of post-COVID knee ON have been described. Knee pain arose on average 11 weeks after the diagnosis of COVID-19. All patients had knee MRI showing ON. CCS were used to treat COVID-19-related symptoms in four cases. Conservative treatment was successful in five patients.

Conclusions: The correlation between COVID-19 and ON remains unclear. Probably post-COVID-19 ON has a multifactorial origin in which factors related to the patient, consequences of COVID-19 and CCS therapy add up to cause a reduction of blood supply and bone vitality until ON is triggered. A greater number of patients is needed to clarify the role of COVID-19 in the etiopathogenesis of knee ON.

Keywords: Knee; osteonecrosis (ON); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); coronavirus disease 2019 (COVID-19); systematic review

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Introduction

Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an RNA virus belonging to the Coronavirus family, which became pandemic in March 2020, causing coronavirus disease 2019 (COVID-19). Patients with COVID-19 can be asymptomatic or have flu-like symptoms, such as fever and cough which can progress to pneumonia and to severe acute respiratory syndrome (SARS). COVID-19 disease causes a systemic inflammatory response associated with possible impairment of other organs and multi-organ failure. The musculoskeletal system may also be involved (1-3). In the acute phase of the disease, fatigue, myalgia and arthralgia are common. Different musculoskeletal manifestations occur several weeks or months after SARS-CoV-2 infection (4,5), among which osteonecrosis (ON) of the knee has been described (5). ON is characterized by necrosis of the bone tissue and bone marrow of any bone segment, frequently involving the knee.

Highlight box

Key findings

- To our knowledge, this is the first review that analyzes cases of post-coronavirus disease 2019 (COVID-19) knee osteonecrosis (ON), analyzing the main characteristics of the individual case. Our main finding is that ON arose at an average of 11 weeks after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and with an average dose of 471 mg of prednisolone, thus prematurely and at lower doses compared to what is usually documented in the literature. These factors fuel the hypothesis of a potential trigger effect of the virus in the development of knee ON.

What is known and what is new?

- COVID-19 infection has a prothrombotic effect on the vessels. In this setting, COVID-19 could cause or favor the onset of ON.
- In this manuscript, we analyzed the main characteristics of patients who developed knee ON after COVID-19 to understand whether there was a correlation between COVID-19 infection and the onset of ON and whether COVID-related ON had its own characteristics or those which overlapped with other causes of ON.

What is the implication, and what should change now?

- In patients with a history of previous SARS-CoV-2 infection who develop arthralgia, especially knee pain, an early magnetic resonance imaging should be done to exclude the presence of ON. Furthermore, the use of corticosteroids in these patients is not recommended, as they could represent an important second-hit factor for ON.

ON was first described by Ahlbäck *et al.* in 1968 (6) without however recognizing a certain aetiology. Subsequently, several risk factors were identified, especially corticosteroids (CCS) (7). However, nowadays many cases of knee ON remain of uncertain cause. Some authors called the set of post-COVID manifestations as "long-COVID" (8). Other authors discussed whether long-COVID or "post-COVID syndrome" was the appropriate term (9).

Rationale and knowledge gap

Is not clear whether SARS-CoV-2 infection could play a pathogenic role in causing knee ON. The study of demographic, clinical and imaging characteristics could give rise to the hypothesis of a further form of ON, i.e., post-COVID ON, in addition to primary and secondary ON. Identifying possible complications from COVID-19 is important for prevention and treatment, in order to reduce morbidity and improve the quality of life.

Objective

The primary aim of this systematic review was to analyze cases of knee ON after SARS-CoV-2 infection and their main demographic, clinical and imaging findings. Moreover, we evaluate the clinical and scientific evidence of COVID-19, to recognize it as a potential cause of knee ON. Our hypothesis was that knee ON could potentially be attributed to COVID-19 infection. To our knowledge, this is the first systematic review of knee ON after COVID-19 infection. We present this article in accordance with the PRISMA reporting checklist (available at https://aoj.amegroups.com/article/view/10.21037/aoj-23-67/rc).

Methods

An electronic search of PubMed, Scopus and Cochrane databases was carried out by two reviewers (P.Z. and G.F.P.) in order to identify eligible studies. The search was executed on 31 December 2023. The string research for the database was COVID-19 AND osteonecrosis. Inclusion criteria were all scientific articles reporting cases of ON of the knee after a diagnosis of SARS-CoV-2 infection. Considering that COVID-19 is an emerging and recently described disease, all levels of evidence studies were included. Two reviewers (P.Z. and G.F.P.) extracted authors, data regarding demographic and clinical characteristics, details of the magnetic resonance imaging (MRI), use of CCS, the

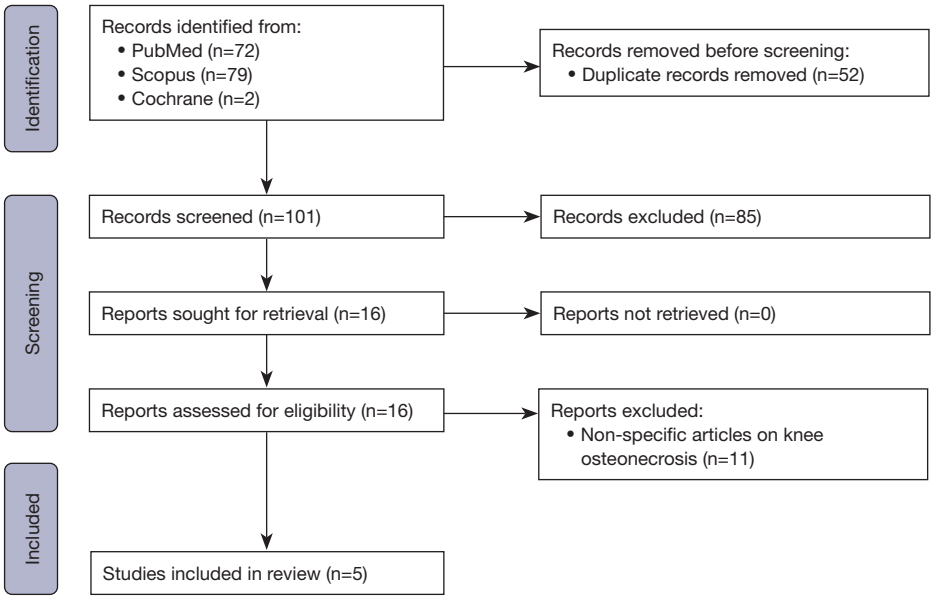

Figure 1 PRISMA 2020 flow diagram.

temporal correlation between ON and COVID-19, the treatment strategy of the lesion and its outcomes.

Results

The search identified 153 potentially eligible studies, as shown in the PRISMA 2020 diagram (*Figure 1*). After duplicate records were removed and records were screened for title and abstract, 16 studies were read in full text. Then, 11 articles were excluded because they were not specific for knee ON. Finally, three case reports and two case series were included, reporting cases of knee ON after SARS-CoV-2 infection for a total of seven cases (*Table 1*).

The patients were four males and three females, with a mean age of 60.4 years (although two cases were under 30 years old but their age was not better specified). The onset of knee symptoms was on average 11 weeks after the diagnosis of COVID-19 disease. Patients reported persistent knee pain. Both gradual and progressive onset of pain were described. A previous knee trauma was reported in one case. CCS were used to treat COVID-19-related symptoms in four out of seven cases, with an average dosage of 471 mg of prednisolone. In all cases MRI of the knee was performed. The medial femoral condyle of the knee was the most commonly affected by ON. In four out of seven cases, the radiographic presentation was represented by the typical pattern of avascular necrosis (AVN). In one case the MRI also reported a rupture of the medial meniscus. In five out of seven cases, a conservative treatment—mainly based on bisphosphonates—was applied with excellent results. In one case a unicompartmental knee replacement was performed as surgical procedure. Moreover, one patient is waiting for undergoing total knee replacement. For conservatively treated cases, patients presented a good remission of symptoms at a mean of 11.8 weeks of follow-up (*Table 2*).

Discussion

Key findings

We performed a systematic review of knee ON cases after COVID-19 by collecting the main demographic, clinical and imaging findings. Our main finding was that the onset of knee ON can occur after COVID-19 disease. ON is more commonly associated with the use of CCS (10,15,16). However, in the current review, ON also occurs in the absence of corticosteroid use. Furthermore, even when CCS were used, ON occurred earlier and with lower doses of CCS than commonly reported in the literature. This could be due to the COVID-effect on bone and vessels. However, the onset of ON at early times and at lower doses of CCS could also be associated with patient comorbidities and not only to COVID disease (17,18). SARS-CoV-1 and SARS-CoV-2 presented similarities regarding ON presentation.

Table 1 Characteristics of included studies

Study	Cases	Age	Sex	COVID-19 symptoms	COVID-19 treatment	Use of CCS
Angulo-Ardoy 2021 (10)	1 of 1	78 y	F	Mild fever, dyspnea, cough. Hospitalized	Hidrocloroquine, lopinavir, ritonavir, CCS and oxygen supply	A total dose of 165 mg of prednisone over 9 days to treat her bonchospasm
Agarwala 2022 (11)	1 of 2	20s	F	NR	CCS	Oral MPS 16 mg three times a day for 15 days (cumulative steroid dose equivalent to 900 mg of prednisolone)
	2 of 2	Late teens	M	NR	CCS	MPS and dexamethasone tablet over 19 days with a dose equivalent to 1,413 mg of prednisolone
Malinowski 2022 (12)	1 of 2	45 y	M	Severe flu-like symptoms with dyspnea. Not hospitalized	No CCS were administered	No
	2 of 2	47 y	M	Severe flu-like symptoms, fever, pneumonia. Not hospitalized	No CCS were administered	No
Muñoz García 2023 (13)	1 of 1	60 y	F	Pneumonia	Oxygen supply, asunercept, oral and IV CCS	Oral and IV CCS during hospitalization. Upon discharge MPS 16 mg per day for 1 month, gradually tapered off
Thannheimer 2022 (14)	1 of 1	72 y	M	NR	No CCS were used, aspirin 100 mg	No

y, years; M, male; F, female; COVID-19, coronavirus disease 2019; CCS, corticosteroids; NR, not reported; MPS, methylprednisolone; IV, intravenous.

Cases of ON had been reported during SARS-CoV-1 infection too (19,20). The aetiology of ON is not yet clear, but alterations of the microcirculation may be a trigger (21). Both SARS-CoV-1 and SARS-CoV-2 enter cells via the angiotensin-converting enzyme 2 (ACE2) receptor which triggers the inflammatory response. ACE2 receptor is present in several tissues, including the musculoskeletal system for example smooth muscle, synovial tissue, cartilage and blood vessels (22). The virus damages the endothelial pathway particularly represented at the vascular level and triggers an important inflammatory response, with leucocytic activation and aggregation (23,24). This strong inflammation of the vessels could predispose to thrombosis and both macro and micro infarctions. A recent study reported significant vascular alteration in lower limbs after COVID-19 (25). The hypoxia and inflammatory response triggered by the virus activates several cytokines including CXCL10, IL-17, and TNF-α, which cause inhibition of osteoblasts and activation of osteoclasts initiating processes similar to those of osteoporosis (26-31). CCS are often used to treat the most severe forms of COVID-19 to reduce the systemic inflammatory response. Patients who had higher or longer doses of CCS had an elevated risk of developing ON (32,33).

Strengths and limitations

As limitation of the study, only case reports and case series with a low level of evidence have been analyzed. Secondly, the total number of cases of ON in the literature is too few to define the "post-COVID ON" as new form of ON, although a correlation between COVID-19 and ON is likely. The small sample size led to heterogeneous and incomplete data, inevitably influencing the results. Another limitation is the presence of some risk factors such as the use of CCS, previous trauma and meniscal tears, which can

Table 2 Knee ON characteristics

Study	Knee trauma	Knee signs and symptoms	Knee MRI features	Time between diagnosis of COVID-19 and onset of knee symptoms	Time between onset of knee symptoms and knee MRI	Knee treatment	Resolution
Agarwala 2022 (11)	NR	Pain in both knees	Bilateral ON of femoral condyles and patella	25 days	NR	Oral alendronate 70 mg/ week in two divided doses along with a single dose of intravenous zoledronic acid 5 mg + calcium, vitamin D and anti-inflammatory medications	No progression of ON at 3-month but still symptomatic. The patient was able to resume her routine activities comfortably
	NR	Complaints of pain in the right knee and both hips	ON of the right knee involving the distal femur and proximal tibia	4 months	NR	Oral alendronate 70 mg/ week in two divided doses along with a single dose of intravenous zoledronic acid 5 mg	Clinically better at 3 months of follow-up
Angulo-Ardoy 2021 (10)	NR	Increased pain and swelling in her right knee	Broken internal meniscus, dislodged to femorotibial recess; chronic sprain in collateral internal ligament and oedema due to osteochondral damage in medial condyle surface measuring 20 mm × 28 mm with collapse	1 month	2 weeks	Waiting for total knee replacement	–
Malinowski 2022 (12)	No	Sudden onset knee pain, persisted during rest and night, pain during extension and varus stress. Pain on palpation of the MFC	Diffuse increase in signal in the MFC and the medial aspect of the intercondylar region in STIR, FSE and PD sequences. The signal intensity in the subchondral bone is only slightly affected	3 months	7 weeks	Crutches, no weight bearing, ossein-hydroxyapatite complex, calcium, vitamin D_3, vitamin K_2, pentoxifylline, vitamin C, and acetylsalicylic acid	Remissions at 10 weeks. Complete resolution at 5 months
	No		Diffuse increase in signal in the MFC	10 weeks	4 weeks		Full remission of symptoms at 3 weeks follow-up MRI
Muñoz García 2023 (13)	Yes	Progressive pain in the internal interline and suprapatellar area	Massive bone infarcts in the metaphysis of the femur, external femoral condyle and proximal metaphysis of the tibia	7 months	3 months	Magnetotherapy, quadriceps electrostimulation, and kinesiotherapy	Clinical improvement at 3 months of follow-up
Thannheimer 2022 (14)	No	Antero medial knee pain	Diffuse edema and ON of the MFC and MTP + MFC osteochondral defect	1 month	1 month	UKA	–

ON, osteonecrosis; MRI, magnetic resonance imaging; COVID-19, coronavirus disease 2019; NR, not reported; MFC, medial femoral condyle; STIR, short tau inversion recovery; FSE, fast spin echo; PD, proton density; MTP, medial tibial plateau; UKA, unicompartmental knee arthroplasty.

cause ON too. However, to our knowledge, our review is the first that summarizes the main characteristics of ON after COVID-19 infection.

Comparison with similar researches

Post-COVID-19 ON has already been reported. Bagaria *et al*. (34) reported several sequelae after COVID-19 including two cases of spontaneous ON. Shetty (18) reported cases of femoral head necrosis with and without the use of CCS. When CCS were used, ON had an early onset as usually reported (35). Thankappan *et al.* (36) described an unusual case of atraumatic ON of the proximal humerus metaphysis. The metaphyseal area is richly vascularized and necrosis in this area is quite rare. Similarly, Ghosh *et al.* (37) reported one rare case of vertebral bone marrow necrosis 1-month after COVID-19. The authors associated the complication primarily with the inflammatory and prothrombotic response associated with COVID-19. The post-mortem analysis did not isolate the virus in the knee joint environment in positive patients (38). We described seven cases of knee ON after COVID-19. Thannheimer *et al.* (14) presented a case of knee ON that occurred about one month after the diagnosis of COVID-19. The patient was seen for the first time in September 2020 with a clinical and radiographic picture of a medial meniscus posterior horn tear in the absence of bone edema, subchondral insufficiency fracture of the knee (SIFK), or ON. However, the chronological relationship between the onset of symptoms and the execution of the MRI is not documented. Therefore, we cannot exclude that the MRI was performed in the "window period", as described by Nakamura (39), and that the ON process had already begun, although not visible on the first MRI. In October 2020, the arthroscopy confirmed the meniscus tear, so a medial meniscectomy was performed. Sixteen days after the procedure the patient was positive for SARS-CoV-2. Subsequent MRI shows typical images of spontaneous ON of the knee (SONK). Several authors have previously hypothesized that the arthroscopic procedure could cause ON, and called it post-operative or post arthroscopy ON (40,41). In the author's case report, the two possible causes of ON were meniscal tear and arthroscopy. Malinowski *et al.* (12) found some distinctive features on the MRI of two patients with knee ON after COVID-19. On the MRI, the bone edema was diffuse in the whole femoral condyle [mostly in short tau inversion recovery (STIR)], soft tissue edema and there was no subchondral bone thickening, in contrast to classic SONK. Nonoperative treatment was successful in a few weeks. The authors referred to this form of ON as transient post-COVID-19 spontaneous ON of the knee (PCT-SONK). Angulo-Ardoy *et al.* (10) described a case of post-COVID-19 ON. However, the patient was affected by knee osteoarthritis and meniscal injury (severity not specified) and performed knee surgery the previous year (not better specified). He also took CCS, lopinavir and ritonavir. He also performed three negative polymerase chain reaction (PCR) on the nasopharyngeal tract. The diagnosis of COVID-19 was made only on the basis of the chest X-Ray. In this case, there are several risk factors for ON, in particular drug therapy. The patients described by Agarwala *et al.* (11) presented a typical picture of AVN, probably associated with the use of CCS. The authors argued that COVID-19 makes one susceptible to necrosis, given that in their case AVN occurred with a low dose of CCS and with an early onset. Muñoz García *et al.* (13) described one case of ON occurring 7 months after COVID disease. However, prolonged use of both intravenous and oral CCS was employed. Additionally, the authors mentioned an unspecified intra-articular injection, so we cannot exclude the possibility of intra-articular corticosteroid use. The MRI they conducted showed typical images of AVN. In their case report, CCS likely played a primary role in the onset of the necrotic lesions visible on the MRI.

Explanations of findings

Our review showed that ON arose at an average of 11 weeks after SARS-CoV-2 infection and with an average dose of 471 mg of prednisolone, thus prematurely and at lower doses compared to what is usually documented in the literature (16,42-44). A cumulative methylprednisolone (MPS)-equivalent dose of <5,000 mg for less than 10 days is reported as safe to prevent ON after COVID-19 but it may not be sufficient in the presence of other risk factors (45). Shetty (14) proposed a set of recommendations for prevention, early diagnosis and treatment of ON in COVID-19. In the authors' opinion, is not possible to determine if COVID-19 infection is the cause of a further form of knee ON with its own characteristics. Now we still recognize two main distinct conditions: SONK and secondary ON of the knee (41). These forms differ in risk factors, clinical picture and imaging. The main characteristics are summarized in *Table 3*. The cause of ON after SARS-CoV-2 infection is more likely to be multifactorial. Therefore, the SARS-CoV-2 infection

Table 3 Characteristics of ON after SARS-CoV-2 infection

Variables	ON after SARS-CoV-2 infection	Spontaneous ON	Secondary ON
Age	60.4 years	>55 years	<45 years
Gender	M:F = 4:3	M:F = 1:3	F > M with SLE
			M > F with alcohol as associated factor
Onset of pain	Mainly sudden, 11 weeks after COVID infection	Sudden	Gradual
Bilaterality	No	<5%	>80%
Location on bone	Epiphysis metaphysis	Epiphysis	Multiple
Condylar involvement	One or more, diffuse	One condyle	Epiphysis, metaphysis and diaphysis
Femur and tibia affected	2 of 7	No	20%
Other joint involvement	Not at the same time	No	>90% (hip, shoulder, ankle)
Associate factors	CCS in 4 out of 7 cases	None	CCS, alcohol, tobacco, other
Associated disease	COVID	None	SLE, Gaucher's disease, thrombophilia, sickle cell, Caisson disease
MRI features	Diffuse bone marrow edema (mostly in STIR)	Bone marrow edema (STIR, PD, T1)	Signs of AVN, hypointense serpentine line with a well-defined border and a rim or double halo sign, adjacent to the proximal border of the osteonecrotic bone
	Soft tissue edema	Semi-lunar shaped lesion	
	No subchondral bone thickening	Subchondral bone thickening	
	Signs of AVN	Peripheral sclerosis	

ON, osteonecrosis; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; F, female; M, male; SLE, systemic lupus erythematosus; COVID, coronavirus disease; CCS, corticosteroids; MRI, magnetic resonance imaging; STIR, short tau inversion recovery; PD, proton density; AVN, avascular necrosis.

may play a synergistic effect with other risk factors, such as the use of antiviral drugs and CCS, a predisposition of the patient, other risk factors such as previous traumas, previous surgery or coexisting intra-articular pathologies or comorbidities related to the patient.

Implications and actions needed

Higher numbers of cases are needed to confirm if the post-COVID-19 ON has specific symptoms or MRI features. This study lays the foundations for further analysis with higher numbers of patients and hypothesizes the presence of a further form of ON with peculiar characteristics.

Conclusions

The primary aim of this systematic review was to analyze cases of knee ON after SARS-CoV-2 infection and their main demographic, clinical and imaging findings. Infection with SARS-CoV-2 is associated with a wide spectrum of musculoskeletal manifestations including knee ON. Surgeons should pay attention to the onset of knee pain after a declared positivity to SARS-CoV-2. Prolonged follow-up is important since MRI evidence of ON can develop within 1 year after initiation of high-dose CCS therapy (45,46). Great care must be taken in the use of CCS in these patients. In the author's opinion, is not clear the correlation between COVID-19 and ON. As proposed by Shetty (18), post-COVID-19 ON probably has a multifactorial origin in which factors related to the patient, consequences of COVID-19 (inflammation, endotheliitis, hypercoagulability, heart failure) and CCS therapy (bone damage) add up to cause a reduction of blood supply and bone vitality until ON is triggered. Further studies with a higher level of evidence and a higher number of patients are needed to clarify the role of COVID-19 in ON onset.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://aoj.amegroups.com/article/view/10.21037/aoj-23-67/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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