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COVID-19 and bone health

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Abstract. – A few patients who have recovered from COVID-19 develop persistent or new symptoms that last for weeks or months; this is called "long COVID" or "post-COVID-19 syndrome." Over time, awareness of the short- and long-term consequences of COVID-19 has increased. The pulmonary consequences are now fairly well established, but little is known about the extrapulmonary system of COVID-19, particularly its effects on bones. Current evidence and reports indicate a direct relationship between SARS-CoV-2 infection and bone health, with SARS-CoV-2 having a significant negative effect on bone health. In this review, we analyzed the impact of SARS-CoV-2 infection on bone health and assessed the impact of COVID-19 on the diagnosis and treatment of osteoporosis.

Key Words:
COVID-19, Bone health, Osteopenia, SARS-CoV-2, Cytokine storm, Long COVID.

Introduction

In December 2019, an outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) led to coronavirus disease 2019 (COVID-19). The World Health Organization (WHO) announced the outbreak as a global health emergency on 30 January 2020, and by 11 March 2020, it had been declared a pandemic. The spread and severity of the outbreak took a heavy toll on, as well as overburdening, the global health system, particularly because there were unavailable drugs against SARS-CoV-2[1]. SARS-CoV-2 is an RNA virus, and the first step in the pathogenesis of COVID-19 is that the SARS-CoV-2 virus invades target host cells. The spike protein (S) of SARS-CoV-2 helps the virus enter host cells by interacting with ACE2 receptors expressed on cell targets (such as alveolar cells, myocardial cells, testes, and bone cells)[2,3]. While 80% of infections lead to an asymptomatic or mild disease with common cold symptoms, including dry cough, headache, loss of taste, dyspnea, fatigue, and fever, COVID-19 can have multiple acute extrapulmonary clinical effects that are likely related to vascular pathology as well as long-lasting complications referred to as post-COVID-19 syndrome or long COVID, including fatigue or neurological sequelae[4-6]. Post-COVID-19 syndrome is a group of signs and symptoms present for 12 weeks. The associated musculoskeletal manifestations include fatigue, arthralgia, myalgia, new-onset back pain, muscle weakness, and poor physical performance[7,8]. Most adult patients who recover from COVID-19 after discharge have at least one symptom after six months, especially fatigue or muscle weakness, sleep difficulties, and anxiety or depression. More severe patients have an increased risk of abnormal lung diffusion, fatigue, muscle weakness, and anxiety or depression. The positive rate and titer of the neutralizing antibody in the serum were significantly lower than those in the acute stage, and there was an overall reduction in the quality of life[9]. The long course of rehabilitation for patients with long COVID challenges the economics of our healthcare systems, which are already overburdened by thousands of people worldwide who continue to be infected by COVID-19[10]. During the previous epidemic of severe acute respiratory syndrome (SARS), it was reported that bone necrosis and bone abnormalities with decreased bone density occurred during rehabilitation[11], partly because of the scope and duration of corticosteroid treatment, which are the main treatment[12,13]. A clinical study[14] found that the severe clinical incidence rate in patients with lower BMD was significantly higher than in patients with higher BMD. Therefore, vertebral BMD is a powerful independent predictor of mortality in COVID-19 patients. Another study[15] illustrated that COVID-19 and its treatment had

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adverse effects on the bone health of COVID-19 survivors. These effects are more prominent in elderly and frail patients; therefore, the risk of bone loss and falls in these patients should be closely monitored. In fact, it has been revealed that the degree of local or systemic bone loss is related to the degree of inflammatory reaction, and inflammation-induced bone loss can continue after effective treatment and intervention for inflammatory diseases[16]. Therefore, a better understanding of the pathogenesis of SARS-CoV-2 in inducing bone loss will help improve treatment and preventative measures during the current pandemic. In this review, we summarize the impact of SARS-CoV-2 infection on bone mass and assess the impact of COVID-19 on the diagnosis and treatment of osteoporosis.

Methods

This review summarizes and analyzes a series of scientific studies on the possible effects of SARS-CoV-2 infection on bone health. An electronic literature search was performed using Medline/PubMed, Web of Science, and Google Scholar. The keywords used were as follows: COVID-19 and bone health; factors influencing bone health and COVID-19; COVID-19 and cytokine storm; and COVID-19 and osteopenia. Relevant articles retrieved were reviewed and critically analyzed.

Impact of SARS-Cov-2 Infection on Bone Mass

Conventional laboratory strains of mice cannot be infected efficiently with SARS-CoV-2, and SARS-CoV-2 lung infection in K18-hACE2 mice provides a model for studying severe infections that recapitulate the features of COVID-19 in humans[17,18]. In 2021, Awosanya et al[19] first used this mouse model to find that compared with uninfected mice, mice infected with SARS-CoV-2 will depict a sharp increase in osteoclastic development, as well as a large amount of bone loss within two weeks after infection. Importantly, even asymptomatic mice demonstrated significant bone loss independent of reduced activity after infection. In 2022, Qiao et al[20] infected hamsters with COVID-19 using intranasal infection, established a golden Syrian hamster model and continuously collected bone tissue after infection. Micro-computed tomography analysis demonstrated that COVID-19 infection led to severe bone loss in hamsters, and bone loss extended from infection to recovery, especially in the long and trabecular bones of the lumbar vertebrae. Such bone loss is associated with cytokine dysregulation induced by SARS-CoV-2, as circulating pro-inflammatory cytokines not only upregulate osteoclastic differentiation in bone tissues but also trigger an amplified pro-inflammatory cascade in skeletal tissues to augment their pro-osteoclastogenesis effect[20]. The two aforementioned studies[19,20] demonstrated that in a mouse model of COVID-19, infection with SARS-CoV-2 significantly increased osteoclastic production and led to a large amount of bone loss after infection. One of the most common conditions associated with COVID-19 is the so-called "cytokine storm[21-23]." The cytokine storm caused by COVID-19 is considered to be related to the severity of COVID-19[24]. Cytokine storms have recently become a key aspect of COVID-19 because affected patients depict high levels of several key pro-inflammatory cytokines such as IL-1, IL-2, IL-6, IL-10, IL-17, and TNF-α, as well as IFN-γ, IP-10, VEGF-A, GM-CSF, and MCP-1[21,25]. Among them, IL-1 is a representative inflammatory cytokine that can stimulate osteoclastogenesis, inhibit bone formation by directly activating a RANK-mediated signaling pathway, and strongly promote bone and cartilage destruction[26,27]. TNF-α and IL-6 are positive regulators of osteoclastogenesis and negative regulators of osteoblastogenesis. TNF-α, in some stages of differentiation, inhibits osteoblastic activity and stimulates osteoclastic proliferation and differentiation. IL-6 has been proven to trigger direct osteoclastic formation and induce bone resorption[28,29]. IL-8 is a well-known inflammatory cytokine associated with a neutrophil response that can stimulate osteoclastic production and promote osteolysis. In addition, TNF-α promotes the production of IL-8 and amplifies the promotional effect of IL-8 on osteoclastic formation[30]. IL-17A plays a major role in bone loss and cartilage damage and inhibits chondrogenesis derived from human MSCs by suppressing protein kinase A (PKA) activity and SOX9 phosphorylation[31]. The aforementioned studies depict that SARS-CoV-2 can directly act on osteoclasts and osteoblasts and affect bone metabolism (Figure 1). Further research is required to explore the long-term effects of SARS-CoV-2 infection on bone health.

Interaction Between COVID-19 and Osteoporosis

Osteoporosis is a multifactorial metabolic bone disease characterized by low bone mass, normal mineralization, and abnormal bone microarchitecture[32]. Studies[33] have found that patients with osteoporosis are more likely to be infected with SARS-CoV-2 and have more severe osteoporosis after COVID-19, and some COVID-19 patients have osteoporosis as a complication. Mi et al[34] found that microRNA-4485 (miR-4485) is upregulated in COVID-19 patients and negatively regulates osteogenic differentiation. MiR-4485-5p has been demonstrated to negatively regulate bone remodeling *in vitro* and *in vivo*. TLR-4 may be a target of miR-4485. Overexpression of miR-4485 induced by SARS-CoV-2 inhibits osteogenic differentiation, thereby providing a promising target for anti-osteoporosis therapy in COVID-19 patients. A recent study[35] also found that miR-4485 was significantly upregulated in the bronchoalveolar fluid and blood samples of infected COVID-19 ARDS patients, suggesting that miRNAs may play a role in COVID-19-related bone changes. Oxidative stress plays an important role in the pathogenesis of COVID-19. Oxidative stress from both endogenous and exogenous sources has deleterious effects on aging and SARS-CoV-2 infection[36,37]. Morbidity and mortality related to COVID-19 are closely associated with age. Like other viruses, they can induce senescence and exacerbate the senescence-associated secretory phenotype (SASP), which is composed largely of pro-inflammatory, extracellular matrix-degrading, complement-activating, and procoagulatory factors secreted by senescent cells. SASP factors can contribute to a "cytokine storm," tissue-destructive immune cell infiltration, endothelialitis, fibrosis, and microthrombosis[38,39]. Oxidative stress affects bone remodeling, is considered one of the initiating factors for impaired osteoblastic bone, and accelerates the progression of osteoporosis[40]. There are various causes of male osteoporosis, one of which is low testosterone level[41]. Salonia et al[42] analyzed data from a cohort of 286 symptomatic SARS-CoV-2-infected men who had not taken any steroids or antivirals and had suggestive chest radiographs or computed tomography scans. Men with COVID-19 had significantly lower total testosterone levels than healthy controls. A cohort study[43] displayed that more than 50% of men who had recovered from COVID-19 still had circulating testosterone levels suggestive of hypogonadism at the 7-month follow-up.

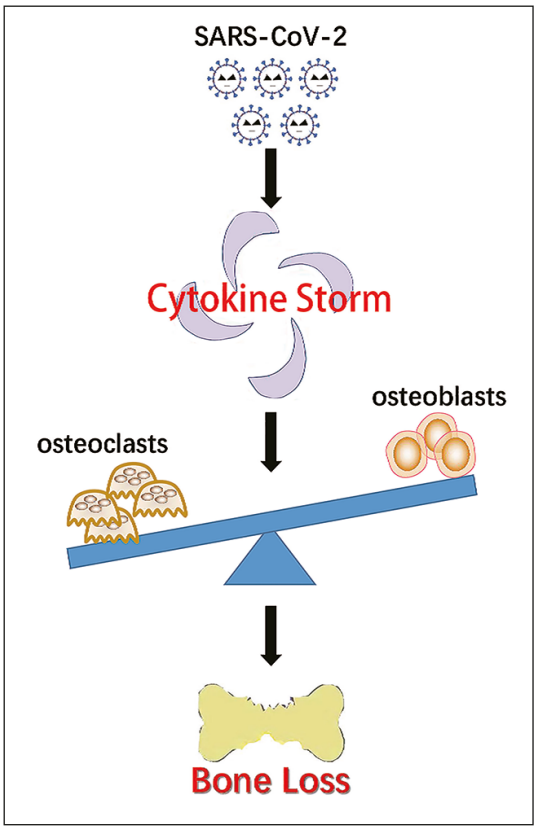

Figure 1. SARS-CoV-2 infection induces bone loss: the balance between osteoblasts and osteoclasts is destroyed, resulting in bone loss.

Grandys et al[44] have demonstrated that a lower serum testosterone concentration is associated with enhanced inflammation and a worse lipid profile in men. The higher severity and mortality observed in male COVID-19 patients could be linked to lower testosterone protective effects. Illness severity has been associated with testosterone deficiency, particularly in elderly patients[45]. Sex steroid deficiency is associated with bone loss and increased fracture risk while circulating sex steroid levels are associated with bone mineral density and fracture risk in elderly men[46,47]. Therefore, we recommend that elderly men who have recovered from COVID-19 have their bone mineral density tested regularly and take medication to prevent osteoporosis under the guidance of a physician, if necessary.

Interactions of SARS-CoV-2 with Calcium and Vitamin D Homeostasis

Vitamin D is important in maintaining bone mass, calcium homeostasis, and extraskeletal health, including the immune response to acute re-

spiratory illnesses, which is pertinent during the COVID-19 pandemic[48-51]. Based on our current knowledge, there is general agreement that serum 25(OH)D < 30 nmol/L in the older population should be avoided, as skeletal effects of vitamin D deficiency, such as a decrease in BMD, secondary hyperparathyroidism, and mineralization defects, appear to be most evident and are most likely to occur below this threshold[52]. Vitamin D is known not only for its importance in calcium and phosphate metabolism but also for its biological actions in immunomodulation. It has been depicted that vitamin D plays a central role in regulating innate and adaptive immune responses, promoting the antiviral effect mechanism, reducing the expression of pro-inflammatory cytokines, and inducing a tolerance response[53-56]. This is because of the presence of the vitamin D receptor in most cell types, especially immune cells, including activated T and B lymphocytes and macrophages[57]. Moreover, vitamin D suppresses the pro-inflammatory cytokines IL-17 and interferon-gamma and increases the production of the anti-inflammatory cytokine interleukin 10 by CD4+ T cells, which are much greater in T cells in women than in men. Similarly, anti-CD3- and anti-CD28-stimulated peripheral blood mononuclear cells from men generated substantially fewer regulatory CD4+CD25+FoxP3+ T lymphocytes in response to vitamin D in comparison with cells from women, but this sex difference disappeared when estradiol was added[58]. This may be one of the reasons why men report COVID-19 more seriously than women. Risk factors for vitamin D deficiency include race, high BMI, winter season, high geographical latitude, and inadequate dietary intake[59]. There has been increasing attention paid to the potential role of vitamin D deficiency in susceptibility to and severity of acute COVID-19[60]. Low vitamin D levels are associated with an increased risk of SARS-CoV-2 infection and a worse prognosis, including in-hospital mortality and the need for invasive mechanical ventilation[61,62]. In an observational study of 447 COVID-19 patients, Nielsen et al[63] observed that vitamin D deficiency was associated with an increased risk of progressing to a more severe COVID-19 outcome. Possible key factors in hypercoagulability in COVID-19 include direct virus-induced endothelial damage and resulting inflammation[64]. The feedback loop between COVID-19-associated coagulopathy and vitamin D also involves platelets since vitamin D deficiency stimulates PLT activation and aggregation and increases fibrinolysis and thrombosis[65]. Notably, a recent study[66] demonstrated that the clinical outcome of COVID-19 patients requiring hospitalization was improved by the administration of vitamin D, as well as significantly reducing the hospital length of stay, reducing the duration of supplemental oxygen, and improving the clinical status (as assessed by the WHO scale). In conclusion, there have been some large-scale clinical trials[66] on the benefits of vitamin D supplementation for the prevention and mitigation of COVID-19, covering various types of studies, such as cohort studies, case–control studies, and randomized controlled trials. We are confident that data from more rigorous and valid clinical studies will continue to confirm the exact effect of vitamin D supplementation on COVID-19.

Steroid Therapy and Bone Health

Glucocorticoids (GCs) have received particular attention for their anti-inflammatory and immunosuppressive properties. GCs are widely used in current clinical practice to treat inflammatory, allergic, and autoimmune diseases. The major mechanisms of GC actions include inhibiting innate and adaptive immune activity. In particular, an important role is played by inhibiting pro-inflammatory cytokines and chemokines and inducing proteins with anti-inflammatory activity[67-69]. GCs are recommended to treat COVID-19 in patients requiring oxygen therapy with or without mechanical ventilation. Many controversial studies[70] have reported the early use of GCs to treat COVID-19 in non-hospitalized patients, and their use is generally unrecommended. The decision to commence GC therapy should be based not only on the severity of COVID-19 but also on careful consideration of benefit-risk profile of the individual patient, including the monitoring of adverse events[71-73]. The severity and prognosis of COVID-19 are closely related to the degree of the inflammatory response[74]. Low-dose systemic steroids for selected COVID-19 patients who are critically ill or require supplemental oxygen can be considered[75]. However, routine corticosteroid use, especially in patients with mild symptoms or those who are in the early stages of the disease, may be avoided unless they are indicated for other reasons, such as the exacerbation of asthma or chronic obstructive pulmonary disease (COPD), septic shock, or ARDS, on an individual basis[76]. Long-term use of high-dose corticosteroids results in ste-

roid-induced avascular necrosis of the femoral head (SANFH). Long GC therapy might also contribute to "long-COVID-19 syndrome," which manifests in fatigue and psychological symptoms, and some post-COVID-19 patients display such adverse reactions to GCs as neuromuscular weakness and neuropsychiatric disorders[74]. Moreover, corticosteroid use is considered one of the most common causes of avascular necrosis (AVN) development. The pathogenesis of steroid-induced AVN is not well established, but postulated mechanisms include fat emboli, fat hypertrophy, a hypercoagulable condition, vascular endothelial dysfunction, and bone marrow stem cell abnormality[77-79]. Early discovery of AVN may decrease a patient's morbidity using bisphosphonate combination therapy. The most sensitive and least invasive test for the early diagnosis of AVN is hip MRI. Hence, it is recommended that, upon early suspicion, an early MRI be advised[77]. The efficacy of corticosteroids has been confirmed in several clinical studies[80-83], and they are widely used in clinical practice to treat patients with COVID-19.

Impact of the COVID-19 Pandemic on Osteoporosis Diagnosis and Treatment

The COVID-19 pandemic has affected every aspect of medical care, including diagnosis and screening for acute and chronic disease management. In particular, the ramifications of the pandemic for osteoporosis care have been widespread[84-86]. The use of standard screening procedures to assess osteoporosis and fracture risk declined dramatically early in the pandemic, while the rates of fragility fractures remained largely unchanged[85]. Many primary care and specialist clinics temporarily closed, paused, or slowed their schedules for screening dual-energy X-ray absorptiometry (DXA) scans, or there were interruptions to the supply of medications and reductions in parenteral medication delivery[87,88]. Telemedicine, which has witnessed widespread uptake during the COVID-19 pandemic, is an alternative to in-person visits for patients with osteoporosis as well as those with other conditions[89]. In patients with newly diagnosed osteoporosis, treatment initiation should not be delayed because of the pandemic, especially in the case of a recent fracture. In most cases, starting oral bisphosphonate administration using telemedicine is relatively safe and effective[90]. If patients are already undergoing bisphosphonate therapy and cannot visit their doctor on time, they may be able to safely delay their treatment for several months. Bone turnover markers gradually return to baseline after bisphosphonate discontinuation, and bone mineral density (BMD) is maintained or slowly decreases over the years[91,92]. Patients undergoing denosumab treatment should continue with it on a biannual basis, and self-injections can be considered in unavoidable circumstances such as the pandemic[90]. In patients who cannot continue denosumab within seven months of the last injection, a temporary transition to oral bisphosphonates is strongly recommended[90,93]. For patients undergoing treatment with romosozumab, the treatment should not be delayed for more than 2-3 months as much as possible. Rapid bone loss was observed after romosozumab discontinuation[90]. Moreover, treatment for osteoporosis patients includes non-pharmacological treatments such as weight-bearing exercise, which is essential for improving strength and balance and may reduce the risk of falls and fractures[94]. One study[95] found that this group of osteoporosis patients who received telemedicine services demonstrated high compliance and lowered COVID-19 lethality than patients of the same age. For many, the option of receiving care remotely through telemedicine has been readily accepted, and satisfaction with telemedicine visits has been high overall[96].

Conclusions

The persistence of various symptoms in people who have recovered from COVID-19 (collectively referred to as "long COVID") is a major health issue worldwide. The present review summarizes the implications of COVID-19 on bone health as well as the correlation between the two. Numerous possibilities suggest that SARS-CoV-2 affects bone health, either directly or indirectly. SARS-CoV-2 causes a significant upregulation of osteoclastic production and substantial bone loss after infection in patients. In summary, robust studies are warranted along with long-term follow-up of recovered COVID-19-infected patients to fully understand the long-term effects of COVID-19 on bone health.

Conflict of Interest

The Authors declare no conflict of interests.

Informed Consent

Not applicable.

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Ethics Approval
This article does not involve human participants or animals performed by any authors.

Authors' Contribution
All authors contributed to study conception and design. Data collection and analysis were performed using Q.-G. Wei, J.-W. Cheng, and C.-L. Hu. The manuscript was prepared using Q.-G. Wei, J.-W. Cheng, C.-L. Hu, M.-J. zheng, and X.-X. He. All the authors have read and approved the final manuscript.

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