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Letter to the Editor

COVID-19 and the bone: underestimated to consider

Dear Editor,

Since the initial outbreak of Novel Coronavirus disease 2019 (COVID-19), the epidemic has rapidly spread worldwide and turned into a pandemic. Updated data until 30th May 2020, there were 216 countries involved with more than 8,525,000 confirmed cases and 456,900 deaths[1]. Although the direct clinical effect of COVID-19 on bone was not quantified, linked to previous studies on the pathogenesis and molecular mechanism of SARS-CoV and MERS-CoV, we write to express our speculation and concerns with the effect of COVID-19 on the bone.

Our speculation of COVID-19 infection may affect the skeletal system through multiple mechanisms (Figure 1). First, Angiotensin-converting enzyme 2 (ACE2) may induce bone resorption. ACE2 is a receptor for the spike glycoprotein of the COVID-19 based on the high degree homology of the receptor-binding domain between the COVID-19 and SARS-CoV[2]. Also, ACE2 is a pivotal enzyme of renin angiotensin system (RAS) which catalyzes the cleavage of angiotensin (Ang) II into Ang-(1-7), then targets to MasR. Latest study revealed that ACE2 and MasR were also expressed by osteoblasts and osteoclasts, meanwhile, the activation of ACE2/Ang-(1-7)/MasR axis could reduce the bone resorptive milieu by inhibited the expression of receptor activator of nuclear factor-kappaB ligand (RANKL)[3]. Therefore, when COVID-19 targets to ACE2, the ACE2 expression was downregulated, thus the ACE2/Ang-(1-7)/MasR cascade was attenuated and the bone homeostasis turned to unbalanced, resulting in accelerating both osteoclastogenesis and osteoblastogenesis process. Second, inflammatory factors and cytokines storm may be a vital reason for bone loss. High amount of inflammatory cytokines, such as IL-1β, IL-6, TNF-α, G-CSF, IP-10, MCP-1, MIP-1α were detected in patients infected with COVID-19, especially those who required ICU admission[4]. These factors may play a role in different aspects of the osteoclastogenic pathway from osteoclast formation to enhance bone resorptive capacity via RANK/RANKL/OPG signaling. Hence, if the acute high concentration of cytokines induced by COVID-19 was not controlled completely and turned into chronic status, these inflammatory cytokines may recruit osteoclasts, trigger bone loss and resist bone formation. Third, immunosuppression also contributes to bone destruction. Under the infection of COVID-19, the immune system was attacked followed with reduction of lymphocytes in peripheral blood, mainly T cells and B cells. In such a situation, T cells were activated and differentiated into Th17 cells, which produced IL-17 and upregulated RANKL to facilitate osteoclast differentiation that degraded the bone matrix, leading to bone destruction[5]. In addition, hypoxaemia was common to see in COVID-19 infected patients who demanded for high-level oxygen support with ICU care4. The production of pro-osteoclastogenic cytokine was stimulated and osteoprotegerin (OPG) was inhibited mediated by hypoxia inducible factor (HIF-1α) under the circumstance of hypoxia. Moreover, the acidosis followed hypoxia upregulated RANKL and nuclear factor of activated T cells cytoplasmic 1 (NFATc1), acting to facilitate osteoclast formation and bone destruction[6].

In terms of COVID-19 infected patients with severe illness, corticosteroids were frequently used to treat for hyperinflammation and immunosuppression as previous pandemics (2002 SARS-CoV and 2012 MERS-CoV), although the corticosteroids might delay viral clearance and deteriorate lung injury[7]. In addition, it's well known that utilization of corticosteroids may show negative effect on bone mass which tend to elevate levels of RANKL and M-CSF while reducing OPG levels, leading to promote osteoclastic activity and bone resorption.

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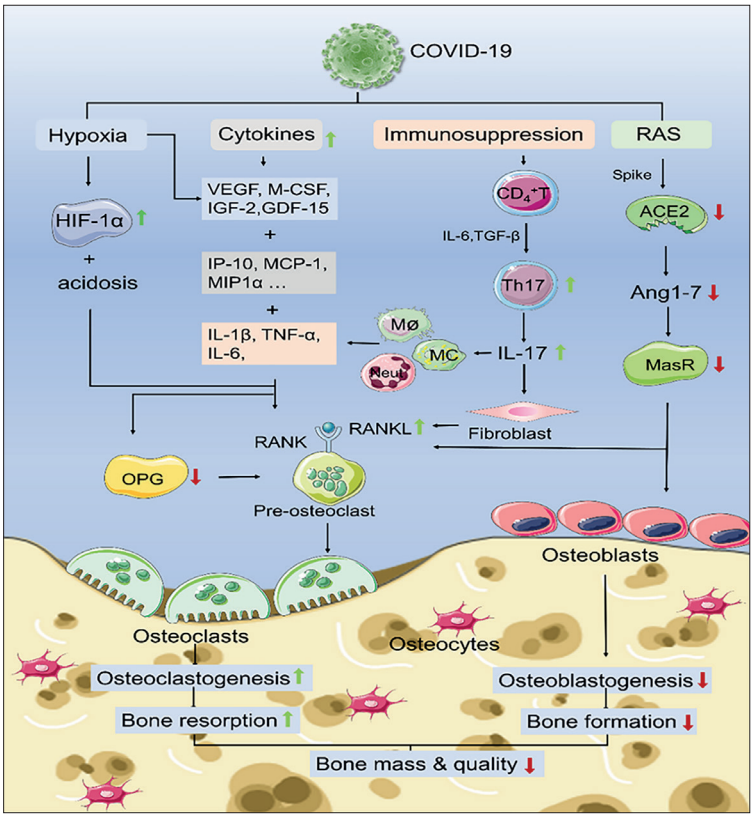

Figure 1. Speculation of COVID-19 induced bone loss. COVID-19 infection may affect skeletal system through several mechanisms, including Angiotensin-converting enzyme 2 (ACE2)-dependent bone resorption, inflammatory cytokines storm, immunosuppression and hypoxaemia. All these factors may act on one or more aspects of the process from osteoclasts/osteoblasts generation to activation *via* multiple pathways like HIF-1α, RANK/RANKL/OPG, ACE2/Ang1-7/MasR pathways, leading to increased bone resorption and bone loss. Mø: Macrophage, MC: Mast cell, Neut.: Neutrophils, RAS: Renin-Angiotensin System.

In conclusion, patients infected with COVID-19 may face a risk of disruption of bone homeostasis balance. Meanwhile, most patients are elderly with unsatisfactory bone mass. Thus, we urge clinicians to pay attention towards COVID-19 infection-related bone health, also supplementation of calcium and vitamin D are routinely recommended to raise 25(OH)D concentrations to protect bone health from COVID-19 interference.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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