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Dysimmunity and inflammatory storm: Watch out for bone lesions in COVID-19 infection

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ABSTRACT

At the end of 2019, a new kind of pneumonia which was proven to be supported by novel coronaviruses named SARS-CoV-2 emerges and it seems to be more complicate in its clinical course and management. Related researches have demonstrated that SARS-CoV-2 serves roles in respiratory, intestinal and neuronal diseases. Given the growing cases of COVID-19, analyzing the relevance between COVID-19 and fragile patients who suffer from bone destruction is entirely indispensable. Accordingly, the recapitulatory commentary is necessary to advance our knowledge on COVID-19 and orthopedics. In this article, we particularly clarify the possible relationship between the newly COVID-19 infection and bone lesions from the standpoints of dysimmunity and inflammatory storm.

Introduction

It has been approved that inflammation-induced pathogenesis in COVID-19 infection has a strong correlation with incidence of cardiovascular metabolic diseases and gastrointestinal injury [1]. Simultaneously, oxidative stress and inflammation responses as interdependent and interconnected processes that co-exist in the inflame milieu [2].

The pneumonia patients constantly suffer from hypoxaemia. Senile patients with SARS-CoV-2 infection always stand perennial disability, such as pulmonary fibrosis and respiratory insufficiency [3]. Bone owns a quite hypoxic microenvironment, the hypoxia of organism will affect heterogeneous pO_2 in bone marrow in a degree.

Not only those inflammatory responses, but also the innate immune system is biologically intertwined with the processes of bone homeostasis. When subjected to SARS-CoV-2, host cell-mediated and humoral immune responses are rapidly activated and take defensive measures [4]. Massive immune cells were recruited in alveolar cells as the disease progresses. To initiate an antiviral response, Pattern recognition receptors (PRRs) were involved in innate immune responses to identify the invasion of the virus. This recognition event results in the activation of downstream signaling cascade, including NF-κB, activator protein1 (AP-1) and interferon regulatory factor-3 (IRF3). Concomitantly, these transcription proteins translocate into nuclear and prompt expression of type 1 IFNs and other pro-inflammatory cytokines to defend against viral infection and dissemination at the entry site [5].

Hypotheses

As for severe COVID-19 infection, Huang et al. found that patients who need ICU monitoring had much higher concentrations of cytokines and chemokines than other ones, such as IL-1β, IFN-α, IL-1RA and IL-8, suggesting that the inflammatory storm was involved in infection severity [6]. Significantly high release of blood pro-inflammatory mediators also responds to lung injury and viral replication, including TNF-α, IL-2, IL-10 and IP-10. However, studies on the correlation between pro-inflammatory cytokine responses and bone metabolism in COVID-19 patients are still lacking. In this special background, will inflammatory disorder and immune imbalance affect bone metabolism after COVID-19 infection?

Justification of proposed hypotheses

The role of inflammatory factors has been closely associated with bone loss and early osteoclastogenesis [7]. It has been reported that the deficiency of ACE2 in mesenchymal stem cells (MSCs) increases the expression of TNF-α, which may be responsible for skeleton dysfunction and adverse structure outcomes [8]. As is accepted, inflammatory cytokines promote osteoclastogenesis by regulating RANK/RANKL/OPG

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axis in direct [9]. Concretely, they drive up bone resorption by promoting RANK expression on monocytes. At the same time, they downregulate osteoblastic production by restraining OPG. It's conjecturable that, if RANKL is not resolved by normal homeostatic system, the inflammation stimuli initiated by SARS-CoV-2 can become chronic in nature and lead to the secretion of a plenty of pro-inflammatory cytokines. In these signaling cascades of osteoclastogenesis, it is quite evident that TNF-α regulate the activation of calcium signaling and the auto-amplification of NFATc1, which has an active acceleration in osteoclast expression [10]. Some other pro-inflammatory cytokines, such as IL-1β and IL-2, have also been studied in the context of bone loss or arthritis [11,12]. In parallel, inflammation storm seems to share the commonness in the progress of bone healing. Dysregulated inflammation responses lead to increased bone resorption, thereby leading to subsequent bone destruction and arthritis.

Hypoxia signaling is an intervention factor for osteoclast differentiation and osteoblast formation. Literature indicates that hypoxia boosts the overproduction of pro-osteoclastogenic cytokines, including receptor activator of nuclear factor-B ligand (RANKL), vascular endothelial growth factor (VEGF), macrophage colony-stimulating-factor (M-CSF), leading to osteoclasts activation [13]. Simultaneously, hypoxia inducible factor (HIF-1) was proven to facilitate osteoclast differentiation by overexpressing RANKL and nuclear factor of activated T cells cytoplasmic 1 (NFATc1) [14]. As for osteoblasts, hypoxia signaling seems to exhibit inactive effects on osteogenesis capacity, which was linked to angiogenesis-induced bone-forming and the intervention of canonical osteoblastic Wnt signaling [15,16]. Therefore, SARS-CoV-2 induced hypoxaemia is most likely to mediate bone destruction and disturb bone matrix.

The lack of oxygen reduces the energy supply of cell membrane. At the same time, the metabolic disorder of oxygen evokes intracellular free radicals to damage membrane transport proteins [17]. The deleterious effects of oxidative stress in bone metabolism have elicited much attention in recent years. Oxygen free radicals, especially reactive oxygen species, maintain homergy in bone biology. An extensive variety of intracellular signaling events are involved in osteoclast activation, including the regulation of mitogen-activated protein kinases (MAPKs) and intracellular Ca^{2+} levels [18]. In addition, excessive free radicals hamper osteoblast adhesion to worsen bone homeostasis in further. Especially, hypoxaemia can also give rise to Ca^{2+} metabolism disorder, which may injury osteocyte. With the imbalance between oxygen delivery and consumption in COVID-19 patients, not only do we need to search novel treatment for minimizing lung damage, but also attract attention on succeeding hypoxia-induced cascade reactions in the whole biological system.

As osteoblasts and osteoclasts exist in approach with immune cells in medullary cavity, it's no wonder that immune system shares massive regulatory cytokines, signaling molecules and transcription factors with bone biology. Osteoclasts take responsibility for bone resorption, which share a collaborative precursor with macrophages and dendritic cells [19]. In the antiviral innate immune, IRF3 emerges as a key molecule in regulating immune responses. On the other hand, it has been found to be associated with the expression of c-Jun and MARK, leading to NFATc1 activation and bone loss [20]. The activation of NF-κB signaling is directly associated with osteoclast differentiation and function. At the same time, it impairs both the differentiation of MSCs towards the osteogenesis and osteoblast-mediated bone-forming capacity [21]. Apart from that, NF-κB and AP-1 stimulate the expression of many elements which required for inflammatory cytokines, driving up osteoclast activity and usually implicated inhibition on proliferation and differentiation of osteoblasts [22].

In patients who suffered from SARS-CoV-2, lymphopenia is the most common property, along with that is the drastically reduced numbers in CD4+ T cells, CD8+ T cells and B cells [23]. Such patients exhibit a proinflammatory state with functional defects in innate and adaptive immune cell populations. In view of multiple cytokines of the adaptive immune response serve dual roles in the regulation of skeleton, there is a deeply rooted nexus between the immune system and skeletal homeostasis. Various studies demonstrated that immune cells (B and T cells), which secrete RANKL and TNF-α under a complicated internal environment, facilitate osteoclast formation and bone resorption [24]. Moreover, especially T cells, can affect the differentiation and activity of bone cells by a paracrine and juxtacrine pathway. Unlike T cells, under physiological conditions, B cells are a significant source of osteoprotegerin (OPG) which is an important osteoclastogenesis inhibitory factor [25]. Analyzing the inner link, we can infer that immune imbalance could disturb bone metabolism in a large extent, which exhibit a tendency to bone destruction in immunization, although the truth remains to be verified.

The management of COVID-19 in orthopedics

Patients with bone destructive diseases or fractures may confront a greater risk of infection of COVID-19. Simultaneously, this virus can affect the development of bone metabolism to a certain degree. We should attach attention to SARS-CoV-2 infection-related bone destruction in the setting of this pandemic and beware of the clinical management of COVID-19 patients in orthopedics.

For patients who previously need orthopedic surgeries, we usually firstly focus on the solution of virus infection. Considering that SARS-CoV-2 may aggravate existing underlying disease and worsen bone metabolism, if the cardiopulmonary function is acceptable the surgery, the surgery should be operated on the basis of strict protection and relevant surgical strategies should be formulated. The operation can be performed using a minimally invasive approach and shorten the operation time to reduce the amount of intraoperative bleeding and reduce operating room infection. At the same time, medical staff should also pay attention to self-precautionary consciousness. Those entering the operating room should be uniformly trained, including how to properly donning and doffing protective clothing, hats, medicals masks, latex gloves, etc. Finally, medical waste needs to be trained in a unified manner. The rooms of pneumonia caused by the novel coronavirus should be single. We should remain vigilant and monitor the development of fever and respiratory symptoms as well.

For infected patients who are free from bone lesions, health education is a major method of controlling risk factors. We need to inform the patients about the possible bone destruction and joint inflammation through the health education. Similarly, the mental health of the patient cannot be ignored. Meanwhile, regular exercise or physical activity practice should be carried on, not only can it strengthen the immune system to defend infection, but also have a positive effect on bone quality and strength. For the infected elderly who have taken a turn for the better, it's important to routinely supplement calcium and vitamin D3 to prevent decreased bone matrix. Apart from that, combining to the therapeutic experiences from SARS-CoV, we especially need to pay attention to the prescription and avoide the occurrence of femoral head necrosis steroids [26].

Conclusions

It's conjecturable that cytokine storm-induced systemic inflammation and immunologic dissonance ultimately increase bone resorption and restrain bone formation in bone marrow microenvironment. Various kinds of pathological factors seem to share undesirable commonness in the process of bone healing. In clinic, it's essential to take precautions against the incidence of bone destruction and arthritis associated with COVID-19. Standard interventions to manage is the foundation of nursing and we need a team-based care model to resolve orthopedic problem in this special background.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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