The Risk of Osseointegration in the Coronavirus Disease 19 Pandemic

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Abstract: Coronavirus disease 19 (COVID-19) is associated with respiratory complications but also with alterations on bone metabolism. Coronavirus disease 19, therefore, might be a risk factor for osseointegration. Recent studies suggest that severe acute respiratory syndrome coronavirus 2 is related with bone abnormalities mainly for act via renin-angiotensin system. This report aims to list the bone alterations caused by coronavirus disease 19 and the possible consequences on the peri-implant bone healing. The current data add to the accumulating knowledge that coronavirus disease 19 may negatively impact the osseointegration and it requires further research.

Key Words: Bone, COVID-19, osseointegration, renin–angiotensin system

BRIEF REPORT

Coronavirus disease 2019 (COVID-19) is a major risk factor for respiratory death worldwide, mainly for causing pulmonary complications such as pneumonia and acute respiratory failure. In addition, patients with COVID-19 are already associated with low serum calcium level,1 decreased bone mineral density2 and osteonecrosis.3 Given the search of a favorable bone for implant placement, it is crucial to understand the consequences of COVID-19 on bone metabolism. Even though there is a lack of studies identifying COVID-19 as a risk factor in implantology.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus strain affect enzyme angiotensin-converting enzyme 2 (ACE2) expressed in epithelial cells of the respiratory tissues.1 Besides the lungs, osteoblasts and osteoclasts express ACE2 on bone tissue.4 Severe acute respiratory syndrome coronavirus 2 infection causes deficiency of ACE2 and low production of Ang-(1–7).3 Angiotensin-converting enzyme 2 downregulates angiotensin II (Ang II) and synthetizes Ang-(1–7).3 Angiotensin II is responsible for bone reabsorption5 and Ang-(1–7) has essential function to maintaining bone structure.4 Consequently, ACE2 targeted by severe acute respiratory syndrome coronavirus 2 may decrease bone mass. Thus, the depletion of ACE2 on bone tissue could impair osseointegration.

Another point, severe hypocalcaemia was highly prevalent in severe acute respiratory syndrome patients.1 Thus, it could imply a down regulation of calcium delivered during the osseointegration. Furthermore, COVID-19 promotes an excessive inflammation by proinflammation cytokines as interleukin-1, interleukin-6, and tumor necrosis factor α.6 In attempt to stop this extreme inflammation, one of most proposed treatment to COVID-19 is the corticotherapy.6 Prolonged corticotherapy can suppress bone mineral mass and bone formation.6 Additionally, diabetes, smoking, vitamin D deficiency are conditions associated with severe COVID-19 patients and risk factors for osseointegration.

Our present report may encourage studies to analyze peri-implant bone healing in patients who have had COVID-19. Although the infected patient could be asymptomatic, diagnostic tests can be necessary to avoid metabolic effects of COVID-19 on bone tissue. This information reinforces the concerns about bio-safety. In conclusion, the current article adds to the accumulating knowledge that COVID-19 is possible risk factor in implantology.

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Acute Invasive Fungal Rhinosinusitis and Coronavirus Disease 2019

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Abstract: Acute invasive fungal rhinosinusitis (mucormycosis) is a rare, highly fatal disease. This opportunistic fungal infection causes

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COVID-19, fungal infection, mucormycosis, steroid and CD8

The aim of this study was to explore the potential underlying factors that may increase the incidence of mucormycosis among COVID-19 patients.

DIAGNOSIS

Rhino-orbital-cerebral mucormycosis is the most common type of Mucorales infection. The infection is transmitted by inhalation into the nose and sinuses. This severe form of fungal infection usually causes tissue necrosis via angioinvasion and thrombosis. Patients typically present with offensive black necrotic crusty nasal discharge, facial pain, blurring of vision, numbness, headache, and/or proptosis. Without early treatment, visual loss, brain infarction with paralysis of the cranial nerves, and even death could be the ultimate result of the disease. The examination of the nose shows black necrotic tissue with possible orbital (Fig. 1A-B) and brain involvement, and similar black eschars are often seen over the hard palate.

Computed tomography (CT) imaging is crucial for the diagnosis as it shows bone destruction (Fig. 1C). Magnetic resonance imaging is more sensitive than CT in the detection of orbital and brain involvement (Fig. 1D). Sometimes, cerebro-vascular fungal invasion may cause fungal aneurysms, which can lead to hematogenous dissemination of the disease. The ethmoid sinus is usually the most commonly involved area; however, fungal invasion may occur through the lamina papyracea to reach the orbit, extraocular muscles, and optic nerve. It may also extend through the cribiform plate to the brain.

In the early stages of the disease, neither a CT scan nor magnetic resonance imaging can detect the lesions. Therefore, once a diagnosis is suspected, a biopsy should be performed using nasal endoscopy for direct microscopic examination and culture. Histologic examination and detection of mucorales fungi is very difficult. These organisms are not easily recognized on

Key Words: COVID-19, fungal infection, mucormycosis, steroid therapy, tissue necrosis
hematoxylin-eosin staining. Periodic Schiff acid and methanamine silver stains are the best methods for fungal detection, even they can highlight fungal fragments. Mucorales hyphae are characteristic. They are wide (5–15 microns), irregularly branched, with rare septations. This is in contrast to Aspergillus, which is narrow (2–5 microns) with regular branches and many septations. Real-time polymerase chain reaction is sometimes needed to accurately detect fungi.9,10

TREATMENT

Patients with mucormycosis usually require combined medical and surgical therapies. Control of diabetes is very important for treatment, with starting systemic antifungal medications, such as amphotericin-B (the liposomal type is preferred) as early as possible to avoid nephrotoxicity. However, antifungal drugs cannot penetrate the devascularized tissue; therefore, they should be used in line with surgical debridement of this necrotic tissue, with restoration of aeration and drainage of involved sinuses using nasal endoscopy.4,12 During debridement, it is essential to clean the margins to stop the spread of fungal infection. Also, local irrigation of the nasal cavity with a mixture of normal saline and amphotericin B (1000 mL/50 mg) may be used.3 As there is a high risk of infection transmission of the coronavirus, a surgeon who is dealing with debridement should take all necessary precautions during the procedure.

IMPACT OF CORONAVIRUS DISEASE 2019

Little is known about the impact of COVID-19 on invasive fungal infections. Several reports have suggested a potential increased risk of developing mucormycosis in COVID-19 patients. John et al13 found that 94% of COVID-19 patients who developed mucormycosis were diabetic, with 67% having poorly controlled diabetes. In addition, COVID-19 infection was severe in 95% of patients. It has further been suggested that patients with diabetic ketoacidosis are susceptible to fungal infections. Diabetic ketoacidosis is a serious, acute complication of diabetes. It may develop under stressful conditions, such as severe infection, surgery, noncompliance to insulin therapy, pancreatitis, vasculitis, and treatment with drugs that may aggravate hyperglycemia in diabetes patients.2 Coronavirus disease 2019 (the causative virus of COVID-19), were found in the pancreatic islets.13 The virus may, however, directly induce beta cell injury and impede insulin secretion.13 This observation could explain the diabetogenic state and diabetic ketoacidosis in some COVID-19 patients.

The severe acute respiratory syndrome coronavirus (SARS-COV) causes damage to the pancreatic islets, leading to acute diabetes and ketoacidosis. High levels of angiotensin-converting enzyme 2 receptors, which are the sites of entry of SARS-COV (the causative virus of COVID-19), were found in the pancreatic islets.13 The virus may, however, directly induce beta cell injury and impede insulin secretion.13 This observation could explain the diabetogenic state and diabetic ketoacidosis in some COVID-19 patients.

Dexamethasone and methylprednisolone have been incorporated into most protocols for the treatment of COVID-19, especially in moderate and severe cases. Steroids may reduce hospital stay and the mortality rates in COVID-19 patients, especially those with dyspnea. As glucocorticoids have an immunosuppressive effect, they could increase the susceptibility to fungal infections.6,16 Al-Tawfiq et al.17 stated that systemic steroids could exaggerate the underlying glycemic control and impede the body’s immune system. It has also been suggested that steroids could impair migration, ingestion, and phagolysosome fusion in macrophages, which may explain their suppressive effects on the patients’ immunity.18 Garg et al,14 advised avoidance of using steroids in mild COVID-19 cases (without hypoxemia) and Szarpak19 reported that the use of corticosteroids should be carefully monitored to achieve a therapeutic effect with the lowest possible dose in the shortest possible time, in order to minimize the reduction of the patient’s immunity.

The tendency of COVID-19 infection to form thrombi may provide iron availability to fungi, which enhances the growth of the organism. Increased serum ferritin and decreased iron binding capacity of transferrin in COVID-19 infection may supply the fungi with the iron needed for their growth.20 Further, Jose et al,13 reported that an increase in circulating ketone bodies in ketoacidosis with its high pH may increase the availability of free iron, by inhibiting the sequestration of iron by transferrin and ferritin. This high pH and increased availability of free iron may promote fungal growth in susceptible patients.

In addition, widespread vascular endothelial injury has been noted in postmortem autopsy in COVID-19 patients.21 Indeed, endothelial damage is well known to be the first step in the pathogenesis of mucormycosis.13 Jung et al,12 reported that SARSCOV-2 enters endothelial cells by endocytosis via the binding of its spike glycoprotein to angiotensin-converting enzyme 2, which is abundantly expressed in the respiratory epithelium. This endothelial damage could lead to local ischemia and necrosis. Necrotic tissue may thus provide fertile media for fungal growth and also impair leukocytic function.12

The use of broad-spectrum antibiotics, which may cause fungal flare-ups, and hospitalization with possible nosocomial infection might contribute to the causation of mucormycosis among COVID-19 patients.1,4,13 Jose et al,18 stated that many COVID-19 patients may develop respiratory complications that could require hospitalization and long-term mechanical ventilation with strong antibiotics as a part of the treatment protocol. This may predispose the patients to various nosocomial infections and/or superinfections (bacterial or fungal), especially if the host is immunocompromised. Indeed, nosocomial mucormycosis of the thigh in a COVID-19 patient has been described by Boodman and Cheng,23 yet it has not been reported in rhino-orbital-cerebral mucormycosis.

All these factors alone or in combination could be included in increasing the prevalence of mucormycosis among COVID-19 patients.

CONCLUSIONS

Mucormycosis is an aggressive fungal infection with a high mortality rate. Early diagnosis and treatment are crucial for this life-threatening disease. Classically, it occurs in immunocompromised patients, and uncontrolled diabetes is the most common risk factor. Steroids for COVID-19 may increase infections and mortality rate. Steroids may reduce hospital stay and the mortality rates in COVID-19 patients, especially those with dyspnea. As glucocorticoids have an immunosuppressive effect, they could increase the susceptibility to fungal infections.6,16 Al-Tawfiq et al.17 stated that systemic steroids could exaggerate the underlying glycemic control and impede the body’s immune system. It has also been suggested that steroids could impair migration, ingestion, and phagolysosome fusion in macrophages, which may explain their suppressive effects on the patients’ immunity.18 Garg et al,14 advised avoidance of using steroids in mild COVID-19 cases (without hypoxemia) and Szarpak19 reported that the use of corticosteroids should be carefully monitored to achieve a therapeutic effect with the lowest possible dose in the shortest possible time, in order to minimize the reduction of the patient’s immunity.

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is an important diagnostic tool; however, it carries a risk of airborne transmission of SARS-CoV-2 during aerosol-generating endoscopic procedures. In addition, caution should be taken during surgical debridement of the lesions. Head and neck surgeons should be aware of the increasing prevalence of mucormycosis among COVID-19 patients, especially in high-risk individuals.

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Pregnancy Promotes the Recurrence of Cerebellar Hemangioblastoma?

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Abstract: Cerebellar hemangioblastomas with pregnancy is rare, but coexistence of pregnancy and recurrent cerebellar hemangioblastomas is rather rare. And coexistence of other diseases during pregnancy usually leads to misdiagnosis because of pregnancy reaction. A 29-year-old woman, at the 8th week of pregnancy, complained of nausea, vomiting, and episodic posterior occipital pain and was misdiagnosed pregnancy reaction without any special treatment during her several visits to local hospital. The patient was diagnosed cerebellar hemangioblastomas 14 years ago, after surgery, she received regular re-examination without recurrence. At the 15th week of pregnancy, the situation of the patient got worse, and she was admitted to our hospital. Brain magnetic resonance imaging showed a lesion in cerebellum. It was considered to be cerebellar hemangioblastomas and was confirmed finally by postoperative pathological examination. In clinical practice, differential diagnosis is of great importance during pregnancy because many other diseases can mimic pregnancy reaction. In this patient, the intracranial hypertension caused by recurrent cerebellar hemangioblastomas was misdiagnosed as pregnancy reaction and it was suggested that the change of hormones, neuroendocrine, and...