Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Advances in Oral and Maxillofacial Surgery 4 (2021) 100169

Contents lists available at ScienceDirect

Advances in Oral and Maxillofacial Surgery

journal homepage: www.sciencedirect.com/journal/advances-in-oral-and-maxillofacial-surgery

Impact of COVID-19 disease and its treatment on the development of maxillofacial complications

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ARTICLE INFO

Keywords:
Coronavirus
Covid-19
Maxillofacial
Complications
Osteomyelitis of the jaws
Osteonecrosis
Mucormycosis
Oral cavity lesions

ABSTRACT

The novel coronavirus spread worldwide in 2020, causing millions of deaths and disabilities. Even though the virus was considered a respiratory virus, its adverse effects can be detected in several body systems. The article describes COVID-19 disease and its complications in the maxillofacial area. Several complications develop either in response to therapeutic modalities used to treat the underlying disease, or due to overuse of particular medications namely glucocorticoids, antirheumatic agents, interleukin 6-inhibitors, and antibiotics. This article will describe a number of complications ranging from mild complications to severe ones such as osteonecrosis of the upper jaw and facial bones, ophthalmologic and neurological complications. It will also summarize recommendations that will help prevent or minimize these complications.

1. Introduction

Since SARS-CoV-2 virus (severe acute respiratory syndrome virus-2) was first reported in Wuhan, China in late 2019, it has been causing successive waves of infections in different countries worldwide. Death and other serious complications were often attributed to the associated pathologies of coagulopathy, a cytokine storm, and multiorgan failure. Several co-morbidities, obesity, and old age are considered the main factors contributing to the severity of the disease [1–3].

Even though the virus belongs to the category of respiratory viruses, it can adversely affect multiple tissues and organs. Shortness of breath and respiratory complications lead to a severe acute respiratory syndrome, followed by pneumonia, and other complications including heart damage, renal failure, and gastrointestinal tract disorders [4–7]. The disease also causes severe complications in the facial area, osteomyelitis or osteonecrosis of the jaw, thrombosis of the cavernous sinuses, vision loss, neurological complications, disability, and death [8–10].

This article aims to highlight various complications caused by COVID-19 or its therapeutic modalities in the maxillofacial region.

2. Materials

In this analysis, articles describing the changes and complications observed in the oral cavity and facial area in the early and late stages of COVID-19 disease were searched on the Internet. We used the following data sources: PubMed, Elsevier, Google Scholar, Google search, ResearchGate, Embase, Springer, Wiley, Lancet and grey literature. The following combinations of key words were searched: COVID-19; SARS-CoV-2; new coronavirus and oral changes, jaw osteomyelitis, jaw osteonecrosis, mucormycosis. The articles found were read and analyzed according to their importance. In addition, attention was paid to the effects of drugs used in the treatment of COVID-19 as a cause of complications or a factor increasing the susceptibility to complications. Bibliography of the selected articles were also screened for the same keywords.

3. Results

Articles included consisted of 25 letter-to-the editor, 80 case reports, 35 clinical trials, and 39 meta-analyses published during the pandemic period.

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https://doi.org/10.1016/j.adoms.2021.100169
Received 31 August 2021; Accepted 9 September 2021
Available online 11 September 2021

3.1. Oral mucosa

Most case reports reported oral lesions that manifested in the early stages of the disease. In articles published in the early stages of the pandemic, potentially persistent conditions in the oral cavity, such as geographic tongue, and fissured tongue have been linked to Covid-19 disease. In addition, multifactorial clinical conditions in patients such as white spots on the tongue, palate, lips, numerous painful ulcers, non-specific nodules, small rashes, petechiae, geographical and cracked tongue, pustular enanthema, desquamative gingivitis, erythema were all attributed to Covid-19 without substantiation [11–18]. Scientists have analyzed the occurrence of such symptoms in the acute phase of the disease, ie in the early stages, as one of the first signs of Covid-19. This was explained by the fact that the virus enters the body through the angiotensin converting enzyme 2 (ACE 2) receptors and the abundance of these receptors in the mucous membranes of the mouth, tongue, salivary glands, as well as in the lungs, gastrointestinal tract [19–22]. Soares explained this hypothesis by an immunohistochemically method by detecting viral spike-protein in necrotic foci on the lip [23]. Some scientists have questioned this hypothesis, suggesting that changes in the oral cavity (candidiasis, ulcers) may be due to the simultaneous and continuous use of many drugs and due to their side effects. Compromised health, weakened immunity, and other systemic disorders caused by SARS-CoV-2 virus, existing saprophytes and conditionally pathogenic viruses, as well as bacteria all contribute to pathologic changes in the oral cavity during this period [24–27]. Most of these articles capture images showing changes in the oral cavity of patients, which is not enough to diagnose the condition, requiring a deeper approach to the issue.

Another notable feature was the histological and microscopic examination of a biopsy sample at the lesion site, in which inflammatory infiltrate, epithelial vacuolization, exocytosis, foci of necrosis in the intrinsic layer, and vascular thrombi were observed. It has been reported that thrombi are endothelial cells and are fibrin-based [22,28–31].

Finally, Favia et al. were able to classify oral cavity lesions based on the clinical conditions observed in 123 patients, whereby lesions of the oral mucosa are divided into 4 groups: [31].

1. Probable, pre-existing conditions, all para-physiological lesions prevalent in the general population (geographical tongue or tongue fissures).
2. SARS-CoV-2-related lesions. The author considered that the changes that occurred during the acute period of the disease, in conjunction with general symptoms, or within 1 week after the onset of general symptoms were virus-related. For example, early petechiae are a sign of vasculitis caused by SARS-CoV-2. Such changes were observed in 65% of patients.
3. Treatment-related changes. Injuries that occurred after the start of Covid-19 special therapy; For example, late petechiae or bullous angina are the results of angina-anticoagulant therapy, candidiasis-corticosteroid, and antibiotic treatment.
4. Conditions associated with poor oral hygiene. (plaque, wound-necrotic gingivitis) [31].

3.2. Salivary glands

There are sources in the literature that have observed acute or chronic sialoadenitis in the Covid-19 patients, and this was hypothesized to be one of the first signs of the disease. In the clinical cases reported in the articles, cases of acute parotitis/intraparotid lymphadenitis were confirmed by ultrasonography, MRI, and observed in the acute phase of coronavirus disease. This was attributed to the abundant ACE2 receptors in the salivary glands which constitute one of the organs where the virus enters. There are hypotheses that the virus, which enters the salivary gland epithelial cells through ACE2 receptors, replicates and causes lysis and inflammation [32–35]. It was noted that the presence of a certain concentration of SARS-CoV-2 virus in the saliva allows early and easy diagnosis of Covid-19 using saliva testing [36–38].

3.3. Osteonecrosis/osteomyelitis

In clinical practice, serious complications and osteonecrosis osteomyelitis of the maxillofacial bones, especially osteomyelitis of the upper jaw, have been observed after COVID-19. Coagulopathies and the development of microthrombi occurring in this disease also disrupt microcirculation and the occurrence of a local ischemic state, which is likely to be the cause of the osteonecrosis of the jaw. One of the theories related to the origin of osteonecrosis is the presence of viral particles in the blood vessels, the production of large amounts of cytokines, namely interleukin-1 (IL-1), gamma interferon (IFN-b), alpha tumor necrosis factor (TNF-α) which cause lymphocytic vasculitis, whereas T helpers, and T-killer cells induce B cell migration, resulting in increased degradation processes [39]. The development of osteonecrosis can be also induced by certain drugs. Few studies were in the form of clinical, cohort, randomized trials that described such a complication observed during a pandemic [40].

There are analytical articles and letters to the publisher that some drugs used in the treatment of COVID-19 may cause osteonecrosis of the bones. According to them, bisphosphonates, chemotherapeutic drugs, immune drugs, as well as long-term rheumatic drugs used in the treatment and rehabilitation of SARS-CoV-2, interleukin-6 inhibitors, corticosteroids also increase the risk of upper jaw osteomyelitis or osteonecrosis [65–67].

Medication-related osteonecrosis of the jaw (MRONJ) - the exact etiopathogenesis of which is unknown, is more common in Asian peoples than in the United States or Europe. Jawbones are more sensitive to drugs than other bones. This can be attributed to the high (adverse) effects of drugs due to the remodeling of the facial-jaw area (especially alveolar growth and periodontium) due to high vascularity, metabolic rate, and constant mechanical impact. The development of jaw osteomyelitis occurs due to inhibition of angiogenesis, reduction of innate or acquired immunity, persistent micro-trauma, inflammatory or existing effects of infectious processes [69].

Because osteonecrosis of the jaw is a very severe, untreatable process that lasts for years, special attention must be paid to the factors contributing to its etiology. Histologically, MRONJ appears similar to osteomyelitis, and it is not clear whether infection is the cause or consequence of bone exposure. Interleukin-6 mediates a wide spectrum of biological activities including activation of T cells, differentiation of B cells, induction of acute phase reactants, proliferation of fibroblasts, and damage to cartilage and joints [68]. The drugs tocilizumab and sarilumab recommended by WHO for the treatment of Covid-19 have been scientifically proven to reduce the risk of death. Tocilizumab is a widely used drug primarily in the treatment of rheumatoid arthritis and retains human monoclonal antibodies that inhibit interleukin-6 (IL-6R) receptor signal transmission. However, restoration of T-lymphocyte numbers due to the blockade by these drugs of IL-6 in COVID-19 and that they cause osteonecrosis, requires further investigation. It has been noted that denosumab of the same composition causes MRONJ, and the presence of pathogenic infection in the oral cavity (periodontitis, periodontal disease) in dental patients, even in minor operations (tooth extraction), increases the risk of complications by several times [70–73].

Leflunomide (Arava) -modified antirheumatic drug has been used for many years, often with bisphosphonates and methotrexate. Studies have shown that induced RANK-L blocks the differentiation of osteoclasts and inhibits tyrosine kinases. This drug, like the above mentioned immunosuppressants, increases the risk of MRONJ during bone modulation and antiangiogenic therapy. Specifically, as a result of taking alendronic acid for 2 years and leflunomide for 6 years, 102 patients examined in clinical practice were reported to have been diagnosed with bilateral osteonecrosis of the maxilla after tooth extraction. In two more case reports, spontaneous necrosis of alveolar processes was observed when

methotrexate was used. Lymphoproliferative disorders have been reported in osteonecrosis associated with methotrexate. In addition, there are some other anti-angiogenic drugs - bevacizumab, aflibercept, sunitinib, temsirolimus, and everolimus - that have been reported to cause osteonecrosis of the jaw [73–75]. There is also evidence in the literature that the bisphosphonate group and other drugs commonly used in the treatment of tumors and osteoporosis cause osteonecrosis [76–79]. It has been suggested that in such cases, adverse oral conditions, minor surgery, or trauma may contribute to the development of the disease on the background of bone changes caused by drugs [80–82].

Although treatment of rheumatic and autoimmune complications in patients who had Covid-19 is important for maintaining their health, the risk of osteonecrosis of the maxillofacial bone must be considered when choosing drugs. Elimination of autoimmune condition such as long-term elevation of C-reactive protein, interleukin-6, and rheumatoid factor in patients with Covid-19, normalization of blood values, and recovery of the patient's condition is certainly primary, but GPs and rheumatologists are advised to choose drugs that have fewer side-effects. MRONJ-is a very serious complication and difficult to treat. Given that the facial jaw area is close to the brain, the probability as a cause of death and disability in patients is very high [83–85].

Another group of drugs that are widely used in the treatment of Covid-19 is corticosteroids. Dexamethasone, and prednisolone are consistently recommended in countries around the world to stabilize the condition of patients not only in the acute phase of ARDS and pneumonia but also during the rehabilitation period. Sources report that glucocorticoids (GCS) reduce the negative effects of inflammatory mediators during cytokine storms, leading to improved pulmonary ventilation, reducing the risk of death [86,87].

GCS initially weaken the immune response and reduce capillary dilation and exudation, leukocyte infiltration, and phagocytosis. Also, they inhibit the proliferation of fibroblasts in the advanced stages. The nuclear transcription factor binds to kB (NF-kB) receptors and reduces the secretion of inflammatory mediators (cytokines, chemokines, cell adhesion molecules, inflammatory enzymes) and their receptor blockade. At the same time, it was suggested that, due to several side effects, such as hyperglycemia, hypokalemia, hypocalcemia, immunosuppression, there may be a risk of developing various infections and prolonging the treatment period [88].

In his analytical article, Dalto combined 13 articles on the development of osteonecrosis as a result of treatment of COVID-19 with glucocorticosteroids and noted and explained that glucocorticosteroids cause avascular necrosis, psychosis, and adrenal dysfunction. Studies in animals and humans have shown that GCS inhibits the maturation of osteoblasts and leads to apoptosis. Stimulation of macrophage colony-stimulating factor (M-CSF) binds to an activator of the nuclear factor-kappa B receptor (RANKL) in osteoblasts and stromal cells and decreases the production of osteoprotegerin, which in turn leads to a decrease in osteoblast function and the activation of osteoclastogenesis. Glucocorticosteroids inhibit hydroxysteroid dehydrogenase type 2 (HSD2, an enzyme that inactivates GCs) and affect osteoblast stagnation, number, and bone formation due to prednisolone. In addition to the production of sex hormones, bone morphogenetic protein, insulin growth factor, and osteocalcin secretion are also reduced, which also hurts intestinal absorption of calcium [89–91].

In addition, high doses of corticosteroids increase Willebrand factor levels in plasma. Willebrand factor (vWF) is produced and stored in endothelial cells, so an increase in its concentration means endothelial cell damage. Vascular glucocorticosteroid injuries induce platelet adhesion and aggregation, leading to thrombosis and avascular necrosis. Hormone treatment of Covid-19 has been shown to increase the risk of developing avascular necrosis as it exacerbates coagulopathy. Shetty noted that minor injuries in such patients, particularly tooth extraction, may contribute to the development of osteonecrosis [92–94]. Mehta noted that corticosteroids should be used only in refractory septic shock and acute respiratory distress syndrome due to decreased renal function and induction of avascular necrosis [95]. Yang, Tang, Zhang, and other Chinese scientists have repeatedly stated that this group of drugs causes osteonecrosis and have recommended that treatment should be monitored for calcium intake, vitamin D and MRI, MSCT if necessary [96–98]. In addition, Yong Xiong et al. stated that glucocorticoids reduce the response of antibodies to viral clearance, causing osteoporosis and avascular necrosis [99]. Law et al. explained that pelvic necrosis develops due to high doses of these drugs [100]. Literature sources have reported that patients treated for Covid-19 have developed osteomyelitis or osteonecrosis of other bones (foot, palm, umbilical cord) under the influence of steroids and other factors [100–107].

3.4. Vascular, thrombotic and neurological complications

Boymuradov et al. described the clinical course of coronavirus complications in 52 patients with osteomyelitis of the jaw, neurological symptoms (trigeminal nerve paresthesia, facial nerve paresis, headache), unilateral chronic hemisinusitis, and orbital fissure syndrome. The authors found that despite the complex treatment, the inflammatory process was very slow and progressive, the sequestration process was delayed for 1 year, and sequestration was observed in a small number of patients (28.9% of patients). Cavernous sinus thrombosis, facial vein thrombophlebitis, removal of facial and jawbones, loss of vision, and other serious injuries are complications that can lead to disability and death in patients, reducing the quality of life [41–43].

Turbin described the clinical condition of 2 adolescents with polysinusitis, orbital cellulitis, periorbital edema, local hemorrhage, superior ophthalmic venous thrombophlebitis, cavernous and dural venous sinus, facial venous thrombosis, retromaxillary, and intracerebral radiological changes due to COVID-19. Patients underwent endoscopic frontal sinusotomy, total ethmoidectomy, upper jaw antrostomy, and removal of thickened, purulent, polypous mucosa. No fungi were observed in the cultures, gram-positive cocci, mainly C beta-hemolytic streptococci were grown [44]. Hypercoagulability in COVID-19 has been shown to lead to ocular vascular thrombosis, leading to blindness, as well as observed other ophthalmic complications (symptoms of dryness, foreign body sensation, pain, conjunctivitis, decreased visual acuity) [45–47].

3.5. Opportunistic deep infections

Abuse and overuse of drugs in the treatment of coronavirus disease can lead to the pathogenicity of saprophytic bacteria and fungi in the body. Invasive fungi have also been reported in the literature as a cause of osteonecrosis. Naturally, the constant and consistent use of antibiotics promotes the development of fungi. Fungi belonging to the family Mucorales are highly adhesive and cause mucormycosis. Phygomycetes and Zygomycetes, which belong to this family, have a high degree of adhesion-lethality. Although these fungi are found in the nasal mucosa in the form of saprophytes, they become aggressive and cause disease in uncontrolled diabetic patients, in cases of hemodialysis, immunodeficiency, when taking high doses of glucocorticosteroids, in presence of burns and injuries, and other concomitant diseases [48–52].

Moorthy et al. observed facial and jaw bone necrosis, inflammation, vision loss, ptosis, sinusitis, palatal and alveolar necrosis in 18 patients with COVID-19 in India. In this case, the long-term treatment of patients with glucocorticoids and the proliferation of uncontrolled diabetes fungi are the main cause of the development of mucormycosis. Mucorales and in 2 cases Aspergillosis fungi have been reported to be the cause of unpleasant profound changes. 14 patients underwent necrotic upper jaw removal surgery, all patients underwent endoscopic sinus surgery, and 9 patients underwent intracranial extension. Occlusion of the central ciliary artery and retinal artery due to this disease was the main cause of blindness in 12 patients, and 7 patients had to have their eyes removed to prevent the spread of the fungus to the base of the brain [53].

Waizel-Haiat observed thickening of the mucous membrane in the maxillary, ethmoidal, sphenoidal, and lateral sinuses in MSCT, and

subsequent necrotic changes in a 24-year-old woman who underwent Covid-19 on the background of symptoms such as the left eyelid, periorbital edema, ptosis, and decreased sensation on this side. Rhino-orbital-cerebral mucormycosis and other complications of Covid-19 resulted in the death of the patient. Rhizopus fungus has been reported to be the cause of the disease [54]. Amanda Werthman: in a Somali woman, the clinical course of Covid-19 was characterized by psychological disorders such as ptosis, ophthalmoplegia, a dry black film on the palate, which the doctor described as rhino-orbital-cerebral mucormycosis, staphylococci were found along with fungi in the cultured bioptate [55].

Alekseyev et al. observed the brain abscess, changes in the area of the temporal lobe, cavernous sinus due to mucormycosis in a 41-year-old man. Due to rhinocerebral mucormycosis, the patient had partial removal of the nasal septum, complete sinus cavity, sphenoidal and ethmoidal bones, palatal bone, and other necrotic tissue [56].

Similar conditions lead to deep and irreversible changes that damage the brain and nerves through the nasal and nasal adjacent cavities. In addition to the rhinocerebral form, it can cause disease in the lung, gastrointestinal, skin, and disseminated cases [57–59]. Increased blood glucose in patients, ketoacidosis, acidic shift of pH reduce the resistance of neutrophils to normal activity, ie against fungi and bacteria. The change in pH releases iron-protein complexes, which causes fungi to take advantage of free iron and become more active. In this disease, along with osteonecrosis of the maxillofacial bones, severe ophthalmological (loss of vision, ptosis, diplopia, periorbital edema, apex orbital syndrome) and neurological (cranial nerve palsy) and psychological changes are noted. In all cases, surgical intervention combined with medication is required [60–64].

4. Conclusion

Thus, serious complications are observed in the facial area due to Covid-19 disease and/or its treatment. Most of them are directly or indirectly related to drugs that occur during treatment. The individual approach to each patient in the treatment of such conditions, the choice of optimal drugs by doctors leads to the prevention of many complications. From small changes in the oral cavity to osteonecrosis of the face and jaw and other changes in the body require long-term follow-up and thorough scientific examination. Of course, this short period of 1 or 2 years is not enough for long-term follow-up of some facial-jaw area complications — such as osteonecrosis or osteomyelitis — so this analysis should be continued and cohort, randomized trials should be carried out.

Financial support

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The authors declare that they have no competing or financial interests, either directly or indirectly, in the products listed in the study.

Acknowledgments

All authors participated in the research process and data collection. All authors performed all tissue analyses and participated equally in the revisions of this work and the writing and review of this article.

References

[1] Zheng J. SARS-CoV-2: An emerging Coronavirus that causes a global threat. Int J Biol Sci 2020;16(10):1678–85.
[2] Shi Q, Zhang X, Jiang F, et al. Clinical characteristics and risk factors for mortality of COVID-19 patients with diabetes in Wuhan, China: a two-center, retrospective study. Diabetes Care 2020;43:1382–91.
[3] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020 Feb;395(10223):507–13.
[4] Jose RJ, Manuel A. COVID-19 cytokine storm: the interplay between inflammation and coagulation. Lancet Respir. Med. 2020 Jun;8(6):e46–7.
[5] Prezioso C, Marcocci ME, Palamara AT, Chiara G, Pietropaolo V. The "Three Italy" of the COVID-19 epidemic and the possible involvement of SARS-CoV-2 in triggering complications other than pneumonia. J Neurovirol 2020;26:311–23. https://doi.org/10.1007/s13365-020-00862-z.
[6] Ahmad I, Rathore FA. Neurological manifestations and complications of COVID-19: a literature review. J Clin Neurosci 2020. https://doi.org/10.1016/j.jocn.2020.05.045.
[7] Long B, BradyWJ, Koyfman A, GottliebM. Cardiovascular complications in COVID-19. Am J Emerg Med 2020;S0735–6757(20):30271–7. https://doi.org/10.1016/j.ajem.2020.04.048. pii.
[8] Halboub E, Al-Maweri SA, Alanazi RH, Qaid NM, Abdulrab S. Orofacial manifestations of COVID-19: a brief review of the published literature. Braz Oral Res 2020;34:e124. https://doi.org/10.1590/1807-3107bor-2020.vol34.0124.
[9] Boymuradov ShA, Qurbanov YoX, Bobamuratova DT. Clinical analysis of complications of cavernous sinus thrombosis in patients undergoing COVID-19. Materials of the conference "Modern technologies in facial and maxillofacial surgery. March 12. 2021. p. 43–4.
[10] Abdumalikova R. Dildora,Yokubjon Kh. Kurbonov, Shukhrat A. Boymuradov, Bobamuratova T. Dilnoza, Shokhrukh Yusupov, Bakhriddin I. Karimberdiev, "COVID-19 associated cavernous sinus thrombosis: a case report of patient presented with necrosis of hard palate and glabella region of the face following by acute stroke", IJMSIR- April - 2021, Vol 6, Issue - 2, P. No. 250 – 256.
[11] Maciel PP, MartelliJúnior H, Martelli DRB, Machado RA, Andrade PV, Perez DEC, et al. COVID-19 pandemic: oral repercussions and its possible impact on oral health. Pesqui Bras OdontopediatriaClínIntegr. 2020;20:e0138. https://doi.org/10.1590/pboci.2020.135.
[12] Martín Carreras-Presas C, Amaro Sánchez J, López-Sánchez AF, Jané-Salas E, Somacarrera Pérez ML. Oral vesiculobullous lesions associated with SARS-CoV-2 infection. Oral Dis 2020 May. https://doi.org/10.1111/odi.13382. odi.13382.
[13] Putra BE, Adiarto S, Dewayanti SR, Juzar DA. Viral exanthem with "spins and needles sensation" on extremities of a covid-19 patient: a self-reported case from an Indonesian medical frontliner. Int J Infect Dis 2020 Jul;96:355–8. https://doi.org/10.1016/j.ijid.2020.05.020.
[14] CebeciKahraman F, Çaşkurlu H. Mucosal involvement in a COVID-19-positive patient: a case report. Dermatol Ther 2020 Jun:e13797. https://doi.org/10.1111/dth.13797.
[15] Chaux-Bodard AG, Deneuve S, Desoutter A. Oral manifestation of covid-19 as an inaugural symptom? J. Oral Med. Oral Surg. 2020;26(2):18. https://doi.org/10.1051/mbcb/2020011.
[16] Ciccarese G, Drago F, Boatti M, Porro A, Muzic SI, Parodi A. Oral erosions and petechiae during SARS-CoV-2 infection. J Med Virol 2020 Jun:26221. https://doi.org/10.1002/jmv.26221.
[17] A. Nunõ González, K. Magaletskyy, P. Martín Carrillo et al., ¿Son las alteraciones en la mucosa oral un signo de COVID-19? Estudio transversal en un Hospital de Campana, ~ ACTAS Dermo-Sifiliográficas, https://doi.org/10.1016/j.ad.2021.02.007.
[18] Amorim Dos Santos J, Normando AGC, Carvalho da Silva RL, et al. Oral mucosal lesions in a COVID-19 patient: new signs or secondary manifestations? Int J Infect Dis 2020;97:326–8. https://doi.org/10.1016/j.ijid.2020.06.012.
[19] Brandão TB, Gueiros LA, Melo TS, Prado-Ribeiro AC, Nesrallah ACFA, Prado GVB, Santos-Silva AR, Migliorati CA. Oral lesions in patients with SARS-CoV-2 infection: could the oral cavity be a target organ? Oral Surg Oral Med Oral Pathol Oral Radiol 2020 Aug 18;(20):S2212–4403. https://doi.org/10.1016/j.oooo.2020.07.014.
[20] La Rosa GRM, Libra M, De Pasquale R, Ferlito S, Pedullà E. Association of viral infections with oral cavity lesions: role of SARS-CoV-2 infection. Front Med 2021; 7:571214. https://doi.org/10.3389/fmed.2020.571214.
[21] Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, Li T, Chen Q. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci 2020 Feb 24;12(1):1–5.
[22] Jimenez-Cauhe J, Ortega-Quijano D, de Perosanz-Lobo D, et al. Enanthem in patients with COVID-19 and skin rash. JAMA Dermatol 2020;156(10):1134–6. https://doi.org/10.1001/jamadermatol.2020.2550.
[23] Soares CD, Mosqueda-Taylor A, de Carvalho MGF, de Almeida OP. Oral vesiculobullous lesions as an early sign of COVID-19: immunohistochemical detection of SARS-CoV-2 spike protein. Br J Dermatol November 2020. https://doi.org/10.1111/bjd.19569.
[24] de Sousa FACG, Paradella TC. Considerations on oral manifestations of COVID-19. J Med Virol 2020. https://doi.org/10.1002/jmv.26451.
[25] Amorim Dos Santos J, Normando AGC, Carvalho da Silva RL, Acevedo AC, De Luca Canto G, Sugaya N, et al. Oral manifestations in patients with COVID-19: a living systematic review. J Dent Res 2020. https://doi.org/10.1177/0022034520957289 [Epub ahead of print].
[26] Santos JAD, Normando AGC, Silva RLCD, Paula RM, Cembranel AC, Santos-Silva AR, et al. Oral mucosal lesions in a COVID-19 patient: new signs or secondary manifestations? Int J Infect Dis 2020; 97:326-8. Pesqui. Bras. OdontopediatriaClín. Integr. 2020. https://doi.org/10.1016/j.ijid.2020.06.012. 20(supp1):e0112 6.

[27] Patel J, Woolley J. Necrotizing periodontal disease: oral manifestation of COVID-19. Oral Dis 2020 Jun. https://doi.org/10.1111/odi.13462. odi.13462.

[28] Soares CD, Carvalho RA, Carvalho KA, Carvalho MG, Almeida OP. Letter to editor: oral lesions in a patient with Covid-19. Med Oral Patol Oral Cir Bucal 2020;25:e563–4. https://doi.org/10.4317/medoral.24044.

[29] Cruz Tapia RO, Peraza Labrador AJ, Guimaraes DM, Matos Valdez LH. Oral mucosal lesions in patients with SARS-CoV-2 infection. Report of four cases. Are they a true sign of COVID-19 disease? Spec Care Dent 2020;40:555–60. https://doi.org/10.1111/scd.12520.

[30] Ansari R, Gheitani M, Heidari F, Heidari F. Oral cavity lesions as a manifestation of the novel virus (COVID-19): a letter-to-editor. Oral Dis 2020:13465. https://doi.org/10.1111/odi.13465.

[31] Favia G, Tempesta A, Barile G, Brienza N, Capodiferro S, Vestito MC, Crudele L, Procacci V, Ingravallo G, Maiorano E, et al. Covid-19 symptomatic patients with oral lesions: clinical and histopathological study on 123 cases of the university hospital policlinic of bari with a purpose of a new classification. J Clin Med 2021; 10:757. https://doi.org/10.3390/jcm10040757.

[32] Capaccio P, Pignataro L, Corbellino M, Popescu-Dutruit S, Torretta S. Acute parotitis: a possible precocious clinical manifestation of sars-cov-2 infection? Otolaryngol Head Neck Surg 2020 Jul;163(1):182–3. https://doi.org/10.1177/0194599820926992.

[33] Wang C, Wu H, Ding X, Ji H, Jiao P, Song H, et al. Does infection of 2019 novel coronavirus cause acute and/or chronic sialadenitis? Med Hypotheses 2020 Apr 24:109789.

[34] Lechien JR, Chetrit A, Chekkoury-Idrissi Y, Distinguin L, Circiu M, Saussez S, et al. Parotitis-like symptoms associated with covid-19,France, march-april 2020. Emerg Infect Dis 2020 Sep;26(9):26. https://doi.org/10.3201/eid2609.202059.

[35] Fisher J, Monette DL, Patel KR, Kelley BP, Kennedy M. COVID-19 associated parotitis: a case report. Am J Emerg Med 2020 Jun 20;S0735–6757. https://doi.org/10.1016/j.ajem.2020.06.059. 30549-0.

[36] Chen L, Zhao J, Peng J, Li X, Deng X, Geng Z, et al. Detection of 2019-ncov in saliva and characterization of oral symptoms in covid-19 patients. SSRN 2020 Mar 19. https://doi.org/10.2139/ssrn.3557140.

[37] Khurshid Z, Asiri FYI, Wadaani HA. Human saliva: non-invasive fluid for detecting novel coronavirus (2019-nCoV). Int J Environ Res Publ Health 2020;17: 2225.

[38] To KK, TsangOT, Chik-Yan YC, et al. Consistent detection of 2019 novel coronavirus in saliva. Clin Infect Dis 2020;71:841.

[39] Seirafianpour F, Sodagar S, Pour Mohammad A, Panahi P, Mozafarpoor S, Almasi S, Goodarzi A. Cutaneous manifestations and considerations in COVID-19 pandemic: a systematic review. Dermatol Ther 2020;33:e13986.

[40] Sai Krishna D, Raj H, Kurup P, Juneja M. Maxillofacial infections in covid-19 era-actuality or the unforeseen: 2 case reports [published online ahead of print, 2021 may 17]. Indian J Otolaryngol Head Neck Surg 2021:1–4. https://doi.org/10.1007/s12070-021-02618-5.

[41] Boymuradov Shukhrat A, Dildora Abdumalikova R, Dilnoza Bobamuratova T, Yokubjon Kh Kurbanov, et al. Complications of COVID-19 in the maxillo-facial region: clinical case and review of the literature. Adv Oral Maxillofac Surg 2021; 3:100091. https://doi.org/10.1016/j.adoms.2021.100091.

[42] Boymuradov ShA, Qurbanov YoX, Bobamuratova DT. Features of the clinical course of osteomyelitis of the upper jaw in patients undergoing Covid-19. Materials of the conference "Modern technologies in facial and maxillofacial surgery. March 12. 2021. p. 35–6.

[43] Boymuradov Shukhrat A, Dildora Abdumalikova R, Kurbonov Yokubjon Kh, Dilnoza Bobamuratova T, Yusupov Shokhrukh, Bakhriddin I, Karimberdiev. Aspects of Maxillar osteomyelitis in patients Who had COVID-19 in Uzbekistan. Ann Oral Maxillofac Surg 2021;4:100106.

[44] Turbin RE, Wawrzusin PJ, Sakla NM, et al. Orbital cellulitis, sinusitis and intracranial abnormalities in two adolescents with COVID-19. Orbit 2020;39: 305–10.

[45] Acharya S, Diamond M, Anwar S, Glaser A, Tyagi P. Unique case of central retinal artery occlusion secondary to COVID-19 disease. IDCases 2020;21:e00867. https://doi.org/10.1016/j.idcr.2020.e00867.

[46] Dumitrascu OM, Volod O, Bose S, Wang Y, Biousse V, Lyden PD. Acute ophthalmic artery occlusion in a COVID-19 patient on apixaban. J Stroke Cerebrovasc Dis 2020;29:2–4.

[47] Chen L, Deng C, Chen X, Zang X, Chen B, Yu H, et al. Ocular manifestations and clinical characteristics of 534 cases of COVID-19 in China: a cross-sectional study. medRxiv 2020 March 16. https://doi.org/10.1101/2020.03.12.20034678.

[48] Gangneux JP, Bougnoux ME, Dannaoui E, Cornet M, Zahar JR. Invasive fungal diseases during COVID-19: we should be prepared. J Mycol Med 2020;30:100971. https://doi.org/10.1016/j.mycmed.2020.100.

[49] Balaji SM. Post COVID-19 fungal and microbial infections. Indian J Dent Res 2020 [cited 2021 May 15];31:669. Available from: https://www.ijdr.in/text.asp?2020/31/5/669/306440.

[50] Song G, Liang G, Liu W. Fungal co-infections associated with global COVID-19 pandemic: a clinical and diagnostic perspective from China. Mycopathologia 2020;185:599–606.

[51] Arani Rajesh, Afsar Shareef SNH, Khanam H M Khuthija. Mucormycotic osteomyelitis involving the maxilla: a rare case report and review of the literature. Case Rep Infect Dis 2019;6. https://doi.org/10.1155/2019/8459296. 2019.

[52] Gonzalez BDG, Garaa R, Gil F, et al. Mucormycosis of head and neck Report of five cases with different presentations. J Cranio-Maxillofacial Surg 2012;40: 584–91.

[53] Moorthy A, Gaikwad R, Krishna S, et al. SARS-CoV-2, uncontrolled diabetes and corticosteroids—an unholy trinity in invasive fungal infections of the maxillofacial region? A retrospective, multi-centric analysis. J Maxillofac Oral Surg 2021. https://doi.org/10.1007/s12663-021-01532-1.

[54] Waizel-Haiat S, Guerrero-Paz JA, Sanchez-Hurtado L, Calleja-Alarcon S, Romero-Gutierrez L. A case of fatal rhino-orbital mucormycosis associated with new onset diabetic ketoacidosis and COVID-19. Cureus 2021 Feb 5;13(2):e13163. https://doi.org/10.7759/cureus.13163. PMID: 33575155; PMCID: PMC7870113.

[55] Werthman-Ehrenreich A. Mucormycosis with orbital compartment syndrome in a patient with COVID-19. Am J Emerg Med 2021;42 264. e5-264.e8.

[56] Alekseyev K, Didenko L, Chaudhry B. Rhinocerebral mucormycosis and COVID-19 pneumonia. J Med Cases 2021;12(3):85–9. https://doi.org/10.14740/jmc3637.

[57] Auluck A. Maxillary necrosis by mucormycosis. A case report and literature review. Med Oral Patol Oral Cir Bucal 2007;12:E360–4.

[58] Mehta S, Pandey A. Rhino-orbital mucormycosis associated with COVID 19. Cureus 2020;12:10–4. https://doi.org/10.7759/cureus.10726.

[59] Mekonnen ZK, Ashraf DC, Jankowski T, et al. Acute invasive rhino-orbital mucormycosis in a patient with COVID-19-associated acute respiratory distress syndrome. Ophthalmic Plast Reconstr Surg 2021;37(2):e40–80. https://doi.org/10.1097/IOP.0000000000001889. PMID: 33229953.

[60] Gupta Gaurav. Osteonecrosis of jaw as an oral manifestation of COVID-19: a case report. Acta Sci Dental Sci 2021;5:21–5.

[61] Urs A, Singh H, Mohanty S, Sharma P. Fungal osteomyelitis of maxillofacial bones: rare presentation. J Oral Maxillofac Pathol 2016;20(3):546.

[62] Kumar JA, Babu P, Prabu K, Kumar P. Mucormycosis in maxilla: rehabilitation of facial defects using interim removable prostheses: a clinical case report. J Pharm BioAllied Sci 2013;5(2):S163.

[63] Saqulain G, Khan MM, Nasir S, Muhammad S, Ramzan MH. Fungal osteomyelitis of zygomaticomaxillary complex: a case report highlighting clinicopathological approach to diabetic patients. Gomal J Med Sci 2015;13(2).

[64] Rai A, Jain A, Thukral R. Osteomyelitis of frontal sinus, zygomatic bone and maxilla. BMJ Case Rep 2020 Sep 14;13(9):e236163. https://doi.org/10.1136/bcr-2020-236163. PMID: 32928834; PMCID: PMC7490959.

[65] Hasan A, Alraisi S. MRONJ and COVID-19 caution. Br Dent J 2021;230:59–60. https://doi.org/10.1038/s41415-021-2616-9.

[66] D. Patel, V. Patel, MRONJ risk factor DOI: 10.1038/sj.bdj.2018.132.

[67] REMAP-CAP Trial. REMAP-CAP response to the COVID19 pandemic (accessed January 2021), https://www.remapcap.org/coronavirus.

[68] Sakkas A, Heil S, Kargus S, Rebel M, Mischkowski RA, Thiele OC. Tocilizumab: another medication related to osteonecrosis of the jaws? A case report and literature review. GMS Interdiscip Plast Reconstr Surg DGPW 2021;10:Doc03. https://doi.org/10.3205/iprs000153. URN: urn:nbn:de:0183-iprs0001537.

[69] Ruggiero SL, Dodson TB, Fantasia J, Goodday R, Aghaloo T, Mehrotra B, et al. American association of oral and maxillofacial surgeons position paper on medication related osteonecrosis of the jaw-2014 update. J Oral Maxillofac Surg 2014;72(10). 1938–56. [PUBMED: 25683041].

[70] Bindakhil MA, Mupparapu M. Osteomyelitis of the mandible exhibiting features of medication-related osteonecrosis in a patient with history of tocilizumab treatment. J Orofac Sci 2018;10:53–5.

[71] Bennardo F, Buffone C, Giudice A. New therapeutic opportunities for COVID-19 patients with Tocilizumab: possible correlation of interleukin-6 receptor inhibitors with osteonecrosis of the jaws. Oral Oncol 2020;*106*. https://doi.org/10.1016/j.oraloncology.2020.104659.

[72] Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci U S A 2020;117:10970–5.

[73] Beth-Tasdogan NH, Mayer B, Hussein H, Zolk O. Interventions for managing medication-related osteonecrosis of the jaw. Cochrane Database Syst Rev 2017; 10. https://doi.org/10.1002/14651858.CD012432.pub2. Art. No.: CD012432.

[74] Zhang X, Hamadeh IS, Song S, Katz J, Moreb JS, Langaee TY, et al. Osteonecrosis of the jaw in the United States food and drug administration's adverse event reporting system (FAERS). J Bone Miner Res 2010;31(2):336–40. https://doi.org/10.1002/jbmr.2693. PUBMED: 26288087.

[75] Denien M, Carey B, Hullah E, Sproat C, Patel V. Methotrexate-associated osteonecrosis of the jaw: a report of two cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2017;124:e283–7.

[76] Mupparapu M, Akintoye S. New groups of drugs suspected in the medication-related osteonecrosis of the jaws (MRONJ). J Orofac Sci 2017;9:67.

[77] Baur DA, Altay MA, Teich S, Schmitt OM, Quereshy FA. Osteonecrosis of the jaw in a patient on raloxifene: a casereport. Quintessence Int 2015;46:423–8.

[78] Cheung Ada, Ego Seeman. Teriparatide therapy for alendronate-associated osteonecrosis of the jaw. N Engl J Med 2010;363:2473–4.

[79] Pires FR, Miranda A, Cardoso ES, et al. Oral avascular bone necrosis associated with chemotherapy and biphosphonate therapy. Oral Dis 2005;11:365–9.

[80] Lee LW, Hsiao SH, Chen LK. Clinical treatment outcomes for 40 patients with bisphosphonates-related osteonecrosis of the jaws. J Formos Med Assoc 2014;113 (3):166–72.

[81] Boonyapakorn T, Schirmer I, Reichart PA, et al. Bisphosphonate-induced osteonecrosis of the jaws: prospective study of 80 patients with multiple myeloma and other malignancies. Oral Oncol 2008;44:857–69.

[82] Mozzati M, Arata V, Gallesio G. Tooth extraction in osteoporotic patients taking oral bisphosphonates. 1707–1 Osteoporos Int 2013;24(5). https://doi.org/10.1007/s00198-012-2239-8. PUBMED: 23288026.

[83] Davis N. Arthritis drugs could help save lives of Covid patients, research fnds. The Guardian (London) 2021 January 7. (accessed January 2021).

[84] Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: a single center experience. J Med Virol 2020 Jul;92(7):814–8. https://doi.org/10.1002/jmv.25801.
[85] Ebker T, Rech J, von Wilmowsky C, Neukam FW, Stockmann P. Fulminant course of osteonecrosis of the jaw in a rheumatoid arthritis patient following oral bisphosphonate intake and biologic therapy. Rheumatology 2013 Jan;52(1):218–20. https://doi.org/10.1093/rheumatology/kes351.
[86] WHO TEAM. Corticosteroids for COVID-19. Living Guidance 2 September 2020 | COVID-19: Clinical care. https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1.
[87] Prescott HC, Rice TW. Corticosteroids in COVID-19 ARDS: evidence and hope during the pandemic. J Am Med Assoc 2020. https://doi.org/10.1001/jama.2020.16747.
[88] Yang Z, Liu J, Zhou Y, Zhao X, Zhao Q, Liu J. The effect of corticosteroid treatment on patients with coronavirus infection: a systematic review and meta-analysis. J Infect 2020.
[89] Daltro G, Silva ICF, Daltro PB, Silva ICF, Botelho VL. SARS-CoV-2/COVID-19 and its implications in the development of osteonecrosis. J Regen Biol Med 2020;2(4):1–19. https://doi.org/10.37191/Mapsci-2582-385X-2(4)-035.
[90] Hauzeur JP, Malaise M, Gangji V. Osteonecrosis in inflammatory bowel diseases: a literature review. Acta Gastroenterol Belg 2009;72(3):327–34.
[91] Hernigou P, Galacteros F, Bachir D, Goutallier D. Hip deformities in adults with sickle cell disease and a vascular necrosis in childhood. A natural history of fifty-two patients. J Bone Joint Surg Am 1991;73(1):81–92.
[92] Mishra Gyanshankar P, Mulani Jasmin. Corticosteroids for COVID-19: the search for an optimum duration of therapy. Lancet Respir Med 2021;9. https://doi.org/10.1016/S2213-2600(20)30530-0.
[93] Maiese A Manetti AC, La Russa R, et al. Autopsy findings in COVID-19-related deaths: a literature review. Forensic Sci Med Pathol 2020. https://doi.org/10.1007/s12024-020-00310-8.
[94] Shettya L, Naharb Sh, Domaha T, l RajcT A. COVID-19 patients could be at high risk for dry socket. Med Hypotheses 2021;146:11046. https://doi.org/10.1016/j.mehy.2020.110462.
[95] Mehta N, Mazer-Amirshahi M, Alkindi N, Pourmand A. Pharmacotherapy in COVID19; a narrative review for emergency providers. Am J Emerg Med 2020;38(7):1488–93. https://doi.org/10.1016/j.ajem.2020.04.035.
[96] Zhang B, Zhang S. Corticosteroid-induced osteonecrosis in COVID-19: a call for caution. J Bone Miner Res 2020;35(9):1828–9.
[97] Tang J. What can we learn about corticosteroid therapy as a treatment for COVID-19? Osteoporos Int 2020;31. 1595-1595.
[98] Yang Z, Liu J, Zhou Y, Zhao X, Zhao Q, Liu J. The effect of corticosteroid treatment on patients with coronavirus infection: a systematic review and meta-analysis. J Infect 2020;81(1):e13–20. https://doi.org/10.1016/j.jinf.2020.03.062.
[99] Xiong Y, Liu Y, Cao L, Wang D, Guo M, Jiang Ao, Guo D, Hu W, Yang J, Tang Z, Wu H, Lin Y, Zhang M, Zhang Qi, Shi M, Liu Y, Zhou Yu, Lan Ke, Chen Yu. Transcriptomic characteristics of bronchoalveolar lavage fluid and peripheral blood mononuclear cells in COVID-19 patients. Emerg Microb Infect 2020;9(1):761–70. https://doi.org/10.1080/22221751.2020.1747363.
[100] Law S, Leung AW, Xu C. Severe acute respiratory syndrome (SARS) and coronavirus disease-2019 (COVID-19): from causes to preventions in Hong Kong. Int J Infect Dis 2020;94:156–63. https://doi.org/10.1016/j.ijid.2020.03.059.
[101] Ebrahim Hazrati, Ramin Hamidi, Farahani Amir, Nezami Asl, et al. Acute transverse myelitis after SARS-CoV-2 infection: a rare complicated case of rapid onset paraplegia in a male veteran. 02 September 2020. PREPRINT (Version 1) available at Research Square.
[102] C Showers, Nuovo G, Lakhanpal A, Siegel C, et al. Covid-19 with complement-mediated coagulopathy and severe thrombosis. Pathobiology 2021;88:28–36. https://doi.org/10.1159/000512503.
[103] Shin L, Bowling LF, Armstrong DG, Boulton AJ. Saving the diabetic foot during the COVID-19 pandemic: a tale of two cities. Diabetes Care 2020;43:1704–9. https://doi.org/10.2337/dc20-1176.
[104] Disser NP, De Micheli AJ, Schonk MM, et al. Musculoskeletal consequences of COVID-19. J Bone Joint Surg Am 2020;102(14):1197–204.
[105] Huang Zeqing, et al. Chinese herbal Huo-Gu formula for the treatment of steroid-associated osteonecrosis of femoral head: a 14-year follow-up of convalescent SARS patients. J Orthop Transl 2020;23:122–31.
[106] McKee MD, Waddell JP, Kudo PA, Schemitsch EH, Richards RR. Osteonecrosis of the femoral head in men following short-course corticosteroid therapy: a report of 15 cases. CMAJ (Can Med Assoc J) 2001;23(2):164.
[107] Zhao R, Wang H, Feng F. Steroid therapy and the risk of osteonecrosis in SARS patients: a dose-response meta-analysis. Osteoporos Int 2017;28(3):1027–34.