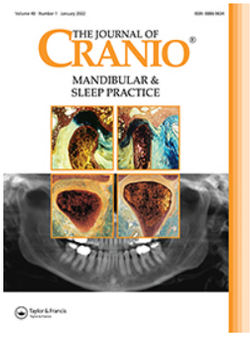

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The Journal of Craniomandibular & Sleep Practice

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ycra20

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To cite this article: Najla Dar-Odeh, Dilnoza Turdikulovna Bobamuratova, Ahmad Alnazzawi, Hamzah Babkair, Safa Jambi, Abdalla Abu-Hammad & Osama Abu-Hammad (2022): Jaw-related complications in COVID-19 patients; a systematic review, CRANIO®, DOI: 10.1080/08869634.2022.2031438

To link to this article: https://doi.org/10.1080/08869634.2022.2031438

Published online: 27 Jan 2022.

CRANIO®: THE JOURNAL OF CRANIOMANDIBULAR & SLEEP PRACTICE
https://doi.org/10.1080/08869634.2022.2031438

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LITERATURE REVIEW

Jaw-related complications in COVID-19 patients; a systematic review

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ABSTRACT

Objective: The aim of this review was to highlight jaw-related complications in COVID-19 manifestations, their etiology, and prevention methods.

Methods: A systematic review of literature was conducted. MEDLINE/PubMed, and Google Scholar were searched for the following keywords: "COVID-19" "Oral manifestations", "Musculoskeletal patients", "Mandible", "Jaw", "Osteonecrosis", "MRONJ", and "dry socket".

Results: Only nine articles were included in this review. Jaw-related disorders associated with COVID-19 were dry socket, osteonecrosis, and orofacial pain related to temporomandibular joint disorders (TMD) and giant cell arteritis (GCA).

Conclusion: COVID-19 potentially predisposes to osteonecrosis due to thrombotic inflammatory phenomena caused by the disease itself or its therapeutic modalities. All jaw osteonecrosis cases reported so far in relation to COVID-19 affected the upper jaw. Orofacial pain in COVID-19 patients was related to TMD and GCA. Clinical evidence-based studies are required to investigate the actual prevalence and possible correlation between COVID-19 and jaw-related disorders.

KEYWORDS

Jaw disorders; COVID-19; temporomandibular joint; orofacial pain; giant cell arteritis; osteonecrosis

Introduction

Since the declaration of COVID-19 as a pandemic in early 2020 by the World Health Organization, it was obvious that the disease is associated with high morbidity and mortality rates [1]. The disease is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which belongs to the coronavirus family of positive sense, single-stranded RNA viruses known to infect humans, including SARS-CoV responsible for SARS (severe acute respiratory syndrome), and MERS-CoV responsible for MERS (Middle East respiratory syndrome) [2].

While some infected patients experience asymptomatic or mild infections, other patients suffer severe symptoms that include respiratory as well as systemic acute and chronic symptoms. Clinicians and scientists worldwide have intensified their efforts to design the ideal treatment strategies and manufacture effective vaccines. They are also continuously working to understand the full diagnostic picture of the disease and identify its spectrum of manifestations and complications. These manifestations and complications can be related to the causative virus itself or to the various therapeutic modalities used to manage the disease or its complications.

Several extrapulmonary manifestations and complications were identified in the orofacial region [3] as well as other body systems [4]. Of particular interest is the musculoskeletal burden, which has been reported in patients with moderate and severe SARS infections, including muscular, neurological, bony, and joint disorders [5,6]. A recent study indicated that skeletal muscles, synovium, and cortical bone could be potential sites of direct SARS-CoV-2 infection [7]. Further, atypical manifestations of COVID-19 resembling rheumatic musculoskeletal diseases are being reported [8]. There is more data on disorders of skeletal muscle than bone and joint disorders in patients with COVID-19. Arthralgias are commonly reported in patients with COVID-19 but are often combined with myalgia [9–11], making it challenging to specifically identify prevalence of arthralgia. Moreover, arthralgias and reduced bone mineral density have been previously reported in other coronavirus infections, such as SARS, which was largely attributed to the extent and duration of treatment with corticosteroids [6,12].

Within the context of the jaw region, certain disorders have been mentioned in literature among COVID-

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19 patients, including osteonecrosis, dry socket, and orofacial pain. These manifestations appear to be a less understood category with more research needed to identify their exact etiology and evaluate their actual impact. Dysfunction of the dental-masticatory system has a great impact on quality of life [13], and post-COVID-19 jaw-related complications might become a major problem in dental practice that warrant special attention by oral healthcare providers.

Therefore, the authors critically reviewed literature to report jaw-related disorders associated with COVID-19 or its therapeutic modalities with the main aim to highlight these manifestations and to outline their possible etiology and recommended methods of prevention.

Materials and methods

This systematic review followed the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline [14].

Eligibility criteria

The following inclusion criteria were used:

1. Papers published in English
2. SARS-CoV-2 literature published since the appearance of the disease (December 2019 until August 17 2021)
3. Clinical trials
4. Case reports and series
5. Reviews
6. Expert opinions and letters to the editor
7. Patients: Adult and pediatric patients affected by COVID-19 infection
8. Intervention: Therapeutic measures of COVID-19.

The study excluded articles that exclusively discussed the following:

1. In vitro and animal studies
2. Non-musculoskeletal orofacial manifestations (soft tissue, oral mucosa, salivary glands, thyroid)
3. Systemic extraoral manifestations, including arthralgia and myalgia
4. Operative jaw procedures reported for cross-infection control or surgical reconstruction of the mandible in COVID-19 patients
5. Non-COVID-19 literature
6. Vaccine-related manifestations
7. Specific patient categories, such as patients with blood diseases.

Information sources

A literature search was conducted in MEDLINE/PubMed, and Google Scholar data sources using the combinations of "COVID-19" and the following key words: "Oral manifestations", "Musculoskeletal manifestations", "Mandible", "Jaw", "Osteonecrosis", "MRONJ", and "dry socket". Reference lists in retrieved articles were also screened for the same keywords.

Selection process

The Mendeley Reference Manager was used to select studies. Two reviewers (N.D-O and O. A-H) independently selected the eligible studies. Any disagreement between reviewers was resolved by consensus or by a third reviewer (D.B.). The Joanna Briggs Institute (JBI) critical appraisal tool was used to assess articles for this review [15].

Results

Study selection

A total of nine articles were determined to be appropriate and were included in the review. The flowchart that describes the process of selection is presented as Figure 1.

Study characteristics

Musculoskeletal manifestations described in the included articles are presented in Table 1.

Jaw-related disorders in COVID-19 patients

Osteonecrosis

The most severe jaw-related morbidity reported so far in COVID-19 patients is osteonecrosis of the jaw (ONJ). It occurs when there is an exposed jaw bone that persists despite appropriate therapy [25]. Its importance as a comorbidity was first described in 2003 when it was recognized in cancer patients treated with high doses of antiresorptive agents such as bisphosphonates, which constitute the most important example of medication-related osteonecrosis of the jaw (MRONJ) [25]. ONJ can also be detected in benign diseases, such as osteoporosis and Paget's disease of bone [25]. However, a nonexposed variant of bisphosphonate-associated osteonecrosis of the jaw was described, whereby a variety of non-specific features exist, including jaw pain, bone or gingival swelling, and the development of sinus tracts [26]. Medications other than bisphosphonates could be involved in MRONJ, such as denosumab. The underlying mechanism was attributed to trauma, which could lead to microbial access to bone surface. Another mechanism involves drugs, which could have

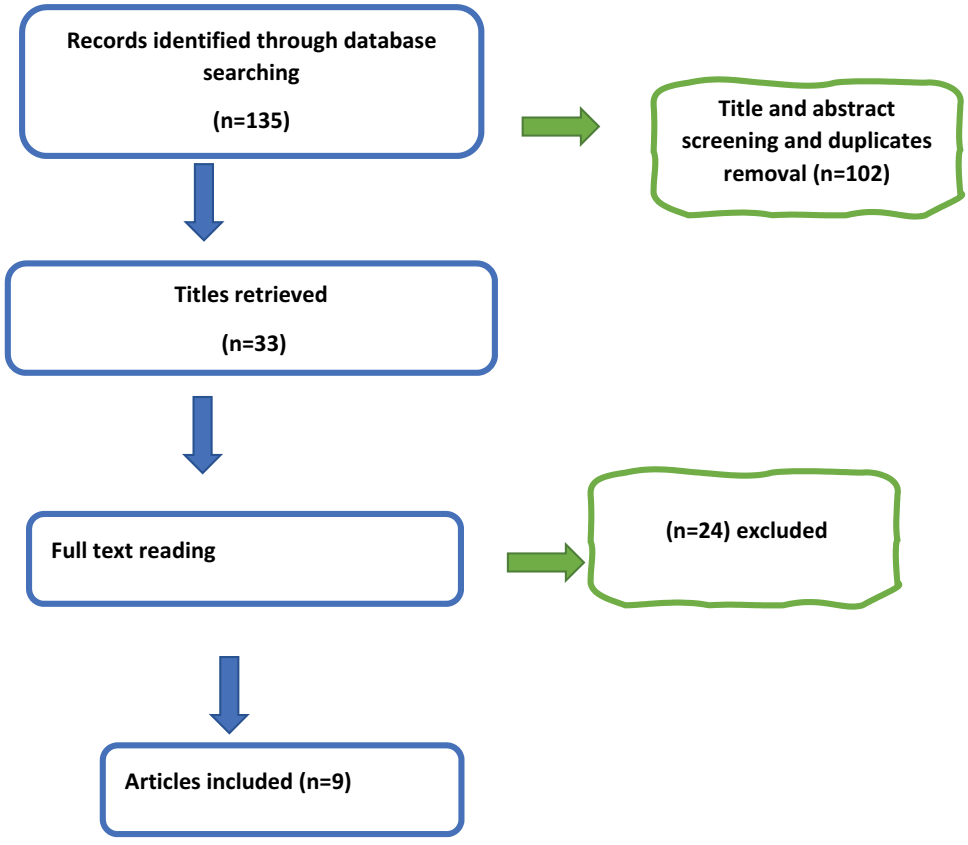

Figure 1. Study flowchart adopted and modified from the original PRISMA statement to identify eligible studies for musculoskeletal manifestations in COVID-19 patients.

an effect directly or indirectly through reduced bone turnover, disrupting epithelial repair, and macrophage function with the end result of bone necrosis, bone resorption, or exposed bone intraorally [25]. A recent review on MRONJ reported that a wide range of medications unrelated to bisphosphonates and denosumab are implicated in MRONJ, including tyrosine kinase inhibitors, monoclonal antibodies, mammalian target of rapamycin inhibitors, radiopharmaceuticals, selective estrogen receptor modulators, and immunosuppressants [27]. Medications involved in MRONJ that have attracted attention lately in treatment of COVID-19 include tocilizumab and corticosteroids [19]. Corticosteroids, including dexamethasone and methylprednisolone, are used due to their anti-inflammatory properties [28]. Tocilizumab, on the other hand, is humanized monoclonal antibody that binds to interleukin-6 (IL-6) receptors, thus inhibiting the IL-6-mediated inflammatory reaction. It is also being used as treatment in autoimmune diseases such as rheumatoid arthritis and giant cell arteritis. Its use in the treatment of COVID-19 is controversial since the results of the investigating clinical trials and observational studies may not be consistent [29]. This literature search identified six articles that describe osteonecrosis as a possible complication of COVID-19 in the form of letters to the editor [17,21,22], reviews, and case reports [18,19,30].

The letter of Bennardo et al. [17] was published in March, 2020, i.e., at the beginning of the COVID-19 pandemic, when tocilizumab use in COVID-19 patients was still in the trial phase. In their letter, they referred to a review and a case report published in the pre-COVID -19 era on the association of MRONJ and tocilizumab [27,31]. The second letter, written by Hasan and Alraisi [21], was published in early 2021 and referred to the same case report [31] and an editorial [32]. In the third letter, which was published in July 2021 [22], the author also referred to the same case report [31]. On the other hand, case reports clearly show that ONJ develop in COVID-19 patients who have multiple comorbidities such as diabetes mellitus and ischemic heart disease. Although medications taken by these patients were not clearly described as corticosteroids or other immune suppressants, this cannot be ruled out [18,20].

It seems that no widescale clinical studies have been done on COVID-19 patients to investigate the association of the disease itself or its therapeutic modalities

Table 1. Articles that discussed jaw-related manifestations in COVID-19 patients.

Musculoskeletal manifestation	Author(s)/year	Study type	Possible mechanisms
Dry socket	Shetty et al. (2021) [16]	Letter	-Avascular necrosis associated with corticosteroids. -Endothelial dysfunction and hypercoagulability associated with SARS-CoV-2.
Osteonecrosis of the jaw	Bennardo et al. (2020) [17]	Letter	-MRONJ associated with Tocilizumab used in the treatment of COVID-19.
	Boymuradov et al. (2021) [18]	Case series	-Post-COVID upper jaw osteomyelitis in four patients older than 60 years with multiple comorbidities, namely diabetes mellitus and ischemic heart disease. -Medications used in treatment of COVID-19 prior to development of osteomyelitis were not clearly stated.
	Bobamuratova et al. (2021) [19]	Review	-Coagulopathy and microthrombi attributed to COVID-19 were presumed to hinder microcirculation, resulting in a local ischemic state, causing ONJ.
	Krishna et al. (2021) [20]	Case report	–34- year old man with diabetes and hypertension developed post-COVID upper jaw fungal osteomyelitis.
	Hasan and Alraisi (2021) [21]	Letter	-MRONJ associated with tocilizumab and sarilumab used in the treatment of COVID-19.
	Asim (2021) [22]	Letter	-MRONJ associated with Tocilizumab used in the treatment of COVID-19.
Orofacial pain	Abubaker et al. (2021) [23]	Cross-sectional survey	-Patients with mild-moderate disease. -12% of 573 patients had jaw/joint pain. -Significantly associated with females. -Muscle pain is attributed to reduced protein synthesis and increased muscle fiber proteolysis. -Joint pain was attributed to emotional stress
	Luther et al. (2020) [24]	Case series	-Increased number of GCA diagnoses during COVID-19 pandemic. -Potential predisposing factors included COVID-19. -None of the patients diagnosed with GCA had symptoms suggestive of COVID-19. -Asymptomatic patients were not tested for the infection.

ONJ: Osteonecrosis of the jaw; MRONJ: Medication-related osteonecrosis of the jaw; GCA: Giant cell arteritis.

with ONJ. More evidence is needed to elucidate the possible correlation between tocilizumab and MRONJ; however, the scientific community should be aware of this potential risk, and clinicians should take this into consideration while planning for surgical and other operative procedures in the jaw region [17].

Dry socket

Dry socket (alveolar osteitis) occurs after tooth extraction when the extraction socket fails to heal, leaving the alveolar bone exposed for days postoperatively. This complication is associated with severe pain in most cases, and management can be difficult [33]. Factors that reduce blood flow to the extraction area are speculated to predispose to dry socket. These include smoking, intake of oral contraceptives, and excessive trauma during extraction procedures [34], especially for lower wisdom teeth [35]. This lesion is listed under inflammatory lesions; however, antibiotics are contraindicated and management mainly relies on topical operative measures that enhance healing [36].

The potential susceptibility of COVID-19 patients to dry socket may exist particularly in patients treated with corticosteroids [16]. In the letter included in this study, the author links glucocorticoids use to increased plasma levels of von Willebrand factor as a result of endothelial cell damage, increasing the risk to thrombosis and avascular necrosis [16]. Furthermore, the pathogenic role of SARS-COV-2 is highlighted in terms of inducing endothelial dysfunction and producing excess thrombin and fibrinolysis shutdown. This results in a state of hypercoagulability, which in association with hypoxia, increases blood viscosity and activates the hypoxia-induced transcription factor-dependent signaling, thereby further increasing the risk of thrombosis and osteonecrosis [37]. Due to the possible association between COVID-19 and/or its treatment using glucocorticoids, some authors recommend that magnetic resonance imaging is used preoperatively in recovered COVID-19 patients for screening of suspected avascular necrosis [16].

Myofascial and vascular pain disorders

Two forms of jaw pain were described in COVID-19 patients: myofascial pain and giant cell arteritis. In their cross-sectional study, Abubakr et al. [23] reported that approximately 12% of surveyed COVID-19 patients had jaw pain, particularly females. The authors explained that this pain is probably muscular in origin [7], emanating from emotional distress and muscle spasm associated with the disease rather than mechanical or physical trauma [23].

Another important finding was the notion of the five-fold increase in cases of giant cell arteritis (GCA) in the period following the peak of the COVID-19 pandemic in the UK [24]. GCA, a common primary granulomatous systemic vasculitis affecting medium and large vessels, presents acutely as a medical emergency and

requires rapid specialist management to prevent irreversible vision loss [38]. Cranial GCA is the classic pattern and involves extracranial branches of the carotid artery, with predilection for the temporal artery and women older than 50 years [39]. The basic pathology is persistent vasculitis that may lead to vascular damage and, consequently, result in partial or complete stenosis and produce headache, scalp pain, and tongue or jaw claudication [40]. The etiology is unclear so far; however, considering that GCA occurs almost exclusively in subjects older than 50 years and that the incidence increases progressively after that, it would appear that age-related immune changes, in genetically susceptible subjects, are important in the development of the disease [41]. While psychological stress and shifts in previously identified seasonality are considered potential factors in the increased incidence of GCA during the COVID-19 era, viral etiopathogenesis hypothesis for GCA cannot be ruled out [24]. The theory of infectious etiology as a trigger of GCA is based on the fact that certain infectious agents have been detected in temporal artery specimens of GCA patients. These are mainly viruses of the herpes family, including herpes simplex virus, Epstein–Barr virus [42], and varicella zoster virus (VZV) [43]. However, to date, no clear conclusions can be drawn, as viruses such as VZV are ubiquitous, and the data are currently conflicting.

In the included study [24], none of the GCA patients had symptoms of COVID-19 or were tested for SARS-CoV-2; however, COVID-19 infection cannot be ruled out [24]. Moreover, some researchers postulate that SARS-CoV-2 infection might directly induce GCA relapse via COVID-19-associated endothelial dysfunction [44,45].

Discussion

Several rheumatic musculoskeletal adverse effects have been reported in COVID-19 patients because of multiple mechanisms such as molecular mimicry, bystander killing, epitope spreading, viral persistence, formation of neutrophil extracellular traps, as well as the use of several antiviral drugs as a treatment modality in COVID-19 patients [8].

Osteonecrosis has been frequently reported in patients with severe SARS, with rates from 5% to 58% [6,46], which occurs mostly in the first year following the initiation of high-dose corticosteroid therapy, with patients who had a cumulative corticosteroid dose of 3,000 mg and were treated for 25 days being at the highest risk [47]. The majority of reported cases involved the femoral head, with less frequency in other anatomical areas like the knee, humeral head, talus, and calcaneus [6]. The combination of hypercoagulability, leukocyte aggregation, and vasculitis encountered in patients with SARS infections are thought to impair bone microvascular blood flow and contribute to the development of osteonecrosis. So far, five cases only of ONJ have been reported in COVID-19 patients in two Asian countries [18,20]. However, the critical location in the upper jaw and the severe disease outcomes necessitate further studies to investigate etiology, clinical outcomes, and ideal treatment strategies. Furthermore, other confounders should be investigated, such as the possible role of prone positioning, which was recommended in treatment of COVID-19 patients to improve ventilation. Pressure injuries are a well-recognized and a potentially preventable complication. Pressure necrosis is attributed to long-term obstruction of blood flow to tissues as a result of external compression. It, therefore, affects areas of dependent contact, necessitating careful attention to the face as well as other susceptible tissues [48].

Emotional stress and muscle spasm were reported in COVID-19 patients as predisposing factors to jaw pain [23]. In addition to psychological factors in initiating jaw pain, there could be other possible factors that were not mentioned previously in the COVID-19 literature, and these could contribute to muscular jaw disorders in the category of previously hospitalized COVID-19 patients. Orotracheal intubation in general anesthetic procedures has been described as a predisposing factor to temporomandibular joint disorders (TMJ) [49]. Prolonged intubation is also being used in critically ill patients, which could contribute to excessive mouth opening and strain on the masticatory musculoskeletal system. Furthermore, previous studies reported that prone positioning during sleep, which has been recommended in treatment of COVID-19 patients to improve ventilation, is associated with TMJ disc displacement [50,51]. Scarce data is available on TMJ disorders in COVID-19 patients; however, the multifactorial background of this disease in predisposing to TMJ disorders cannot be ruled out.

GCA was included in this review because of its potentially severe complications that may influence bony and muscular tissues in the orofacial region. The case series conducted by Luther et al. [24] complied with the required characteristics of case series [15]. However, there was no evidence to link COVID-19 with GCA, as patients included in this study did not have symptoms of COVID-19 and were not tested for the virus [24].

Limitations

The Joanna Briggs Institute (JBI) checklist was used to assess articles prior to inclusion in this study because

these were letters to the editor, case series, and a cross-sectional survey. The JBI has exclusively provided critical appraisal checklists for the assessment of expert opinion and case series [52]. There could be a high risk of bias in the included articles because they reflected either the opinions of their authors (letters) or the self-perceptions of patients (cross-sectional survey). The case studies reporting ONJ are interesting, but there needs to be a larger number of cases from other geographic areas. The inability to gauge the quality of evidence in this review is an important limitation for this study.

Conclusion

Literature describing serious musculoskeletal manifestations in the jaw region is expanding; however, they are not supported by evidence. More evidence-based research is required from the maxillofacial surgery community to collect accurate data on prevalence, predisposing factors, clinical disease course, and prognostic and therapeutic aspects. COVID-19 patients, whether those who are completely recovered or who still suffer long COVID, should be followed closely by their oral healthcare providers to monitor the possible consequences linked to the disease. Future research should be expanded to investigate serious or debilitating musculoskeletal complications of the disease or its therapies. These trends in research should be applicable to all patients, especially those who were hospitalized or critically ill. Studies should also be directed toward patients who received or are still receiving potent medications such as corticosteroids and immunomodulators.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

There was no financial support for this study.

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Availability of Data, Code and Other Materials

All included studies are available full-text on PubMed and Google Scholar databases.

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