



Literature review

Coronavirus-Associated Mucormycosis in the Stomatognathic System: Exploratory Systematic Review

José Eduardo Orellana-Centeno¹,
Roxana Nayeli Guerrero-Sotelo²

¹ Universidad de la Sierra Sur, Instituto de Investigación Sobre la Salud Pública, Licenciatura de Odontología
ORCID: 0000-0002-9518-7319

² Universidad de la Sierra Sur, Instituto de Investigación Sobre la Salud Pública, Licenciatura de Enfermería
ORCID: 0000-0002-4503-7478

Corresponding author:

José Eduardo Orellana Centeno
E-mail: jeorellano@unsis.edu.mx

Received: October 2021

Accepted: September 2022

Cite as:

Orellana-Centeno J, Guerrero-Sotelo R. Coronavirus asociado a mucormicosis en el sistema estomatognático: Revisión sistemática exploratoria. [Coronavirus-Associated Mucormycosis in the Stomatognathic System: Exploratory Systematic Review]. *Rev Odont Mex.* 2022; 26(4): 21-30. DOI: 10.22201/fo.1870199xp.2022.26.4.81081

Abstract

Introduction: Since the end of 2020, mucormycosis began to be reported in patients who were or had suffered from SARS-CoV-2 (COVID-19). The areas affected by this condition are diverse, including lung, nose, eye, mouth. **Objective:** To synthesize and systematize the existing information on the relationship between: mucormycosis, COVID-19 and the stomatognathic system. **Material and methods:** The search was carried out in the bibliographic databases: PubMed-MedLine, NCBI, Scopus, Springer and Google Scholar. The process was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. To control the risk of bias,

the template “understanding a Systematic Review” of the *Critical Appraisal Skills Programme - Español* (CASPe) was applied. Finally, the tool SPIDER (Sample, Phenomenon of interest, Design, Evaluation, Research type) was used to collect the information, including sample, phenomenon, design, evaluation and type of research. **Results:** 11 manuscripts were selected: 3 research articles, 4 case reports, and 3 literature reviews which describe the diagnosis, causes of presentation, treatments and pre- and post-operative management protocols of the cases. **Conclusions:** Although the articles found are not in large number, there is currently a description of this disease, and some considerations that dentists should make when finding patients with this infection.

Keywords: Mucormycosis, Coronavirus, Stomatognathic system, Oral Pathology, Oral Surgery

INTRODUCTION

The appearance of SARS-CoV-2 (COVID-19) in Wuhan, China in 2019 caused many innovations in various areas such as political, legal and economic, but the most decisive is in the medical field¹. In this area, the chronology and typologies of the challenges have changed: first, was the need for the production and distribution of masks; second, the genetic sequencing of the virus; third, the development of vaccines, as well as the challenges of their production, distribution and application; fourth, to identify the logarithms of treatment and drug development; and fifth, the emergence of the need to study certain pathologies associated with COVID-19, such as: cardiovascular diseases, thrombosis, renal failure, cardiomyopathy, coronary and systemic vasculitis².

Our study is located in this last phase, since so far in 2021, various countries, including India, Pakistan, the United States, Brazil, and Italy, have reported cases of Invasive Fungal Infections (IFI) associated with COVID-19, specifically: mucormycosis and aspergillosis³. In India, COVID-19 cases increased to almost 4,000 in the first week of June, which is why on 11 June, 2021, the WHO-PAHO issued “Epidemiological alert: COVID-19-associated mucormycosis (CAM)”⁴. This alert was supported by a retrospective multicentric study supported in India from September to December 2020, as it was found that of 287 patients with mucormycosis, 187 (65.2%) presented CAM. On the other hand, in America, the reported CAM cases covered a total of 7 countries: Brazil, Chile, Honduras, Uruguay, Paraguay, Mexico and the United States⁴.

Mucormycosis belongs to the Order *Mucorales* and the Family *Mucoraceae*², and the reported cases are rhino-cerebral, rhino-orbital, rhino-orbital cerebral, pulmonary, and gastrointestinal or disseminated⁵. Studies so far associate cases of black fungus not only with COVID-19, but with the pre-existence of diseases in immunocompromised patients such as diabetes, kidney failure, HIV, hypertension, among others⁵, and the administration of steroids and glucocorticoids as treatment of COVID-19 patients⁵ and less frequent events such as: organ transplants and burns².

Chronic diseases are a global public health problem, due to circumstances that complicate the international panorama. The World Health Organization (WHO)² estimates that, in the world, about 80% of people with these conditions are located in low-income countries such as India, Pakistan, Bhutan, Sri Lanka, the Philippines and Indonesia². In the case of Mexico, according to

the National Health and Nutrition Survey (*ENSANUT* for its acronym in Spanish) in 2018, 10.3% of the population aged 20 years or older had a previous diagnosis of diabetes, which is equivalent to 8.6 million people, meanwhile, the prevalence of hypertension was estimated at 18.4%, equivalent to 15.2 million people⁶.

Therefore, it is necessary to carry out an exploratory systematic review that identifies and systematizes the existing data on the relationship between COVID-19 and mucormycosis. Thus, the objective of the exploratory systematic review is to synthesize and systematize the existing information regarding the relationship between: mucormycosis, COVID-19 and the stomatognathic system.

MATERIAL AND METHODS

Exploratory Systematic Review (ESR) was used to investigate mucormycosis in the stomatognathic system and its relationship with COVID-19. It was conducted to synthesize and communicate the findings of existing evidence, identify knowledge gaps, and map both the scientific evidence and the reports that guide clinical practice in a particular area⁷. The above were implemented out in five stages or phases: research question, systematized search, study selection, data extraction and compilation, synthesis and dissemination of the results⁷. Methodologically, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)⁸ was applied. The research is registered at the Universidad de la Sierra Sur before the Research Committee with registration number 02/2020 and before the Research Ethics Committee with registration number CEI-04A/2020.

Within the selection criteria, the inclusion of articles were to be complete texts in English, Portuguese and Spanish languages, journal texts published from January 1, 2020 to May 31, 2021. The elimination criteria were texts that were not complete and in languages other than English, Portuguese and Spanish, of not published status, where the term mucormycosis appeared within the text in a site other than the stomatognathic system, and where the design of study was different from that of clinical case, case report, multicentric retrospective observational, retrospective observational and observational. The data search was performed in the PubMed-Medline, NCBI, Scopus, Springer and Google Scholar databases from May 1 to 31, 2021, with the following words and Boolean operators: (COVID-19) and (mucormycosis) OR (mucormycosis) AND (palate) OR (oral). These criteria were applied to the title, summary and keywords, obtaining a total of 345 texts in all databases together. Subsequently, the search results were manually cross-referenced with Microsoft® Excel® and duplicates were eliminated, so 230 texts were eliminated. Subsequently, all the summaries of the 115 resulting articles were read and the reasons and criteria were applied.

The data extraction process was carried out manually using Microsoft® Excel® and the list of data was collected according to the categories corresponding to the SPIDER tool (Sample, Phenomenon of Interest, Design, Evaluation and Research Type) (Table 1 and Table 2)⁹. To control the risk of bias in the selected studies, the *Critical Appraisal Skills Programme - Español* (CASPE) was applied, specifically the "understanding a Systematic Review" template¹⁰. The application of the templates to the articles was carried out on each of the texts, then the results of the evaluations were discussed and there was no disagreement between the two reviewers.

Table 1. COVID-19-associated mucormycosis (CAM) in the stomatognathic system: SPIDER

COVID-19-associated mucormycosis (CAM) in the stomatognathic system: SPIDER	
S (Sample)	COVID-19 patients Post-COVID-19 patients
PI (Phenomenon of Interest)	COVID-19-associated mucormycosis in the stomatognathic system
D (Design)	Clinical case Case report Multicenter retrospective observational Retrospective observational and Observational
E (Evaluation)	Causes Signs Symptoms Type of diagnostic tests Treatment Prevention protocols for dental practice
R (Research Type)	Quantitative

Table 2. Synthesis of SPIDER in Mucormycosis and COVID-19.

Author Location Year	Title	Sample	Phenomenon of interest	Design	Evaluation	Research type	Objectives	Results	Conclusions
Moorthy et al. Bengaluru, India 2021	SARS-CoV-2, uncontrolled diabetes and corticosteroids—An unholy trinity in invasive fungal infections of the maxillofacial region? A retrospective, multi-centric analysis	18 patients	CAM	Multicenter retrospective observational. Analysed clinical data of patients belonging to different specialties in Bengaluru, India	Presentation and treatment of patients. Relationship between aggressive maxillofacial and rhino-orbital cerebral fungal infections and COVID-19, administration of corticosteroids and uncontrolled diabetes mellitus	Quantitative (Research Article)	To collect and analyse data on maxillofacial/rhino-orbital cerebral fungal infections reported during the time of the COVID-19 pandemic. To investigate the common factors that contribute to these infections and highlight the importance of its increase observed in patients infected by COVID-19	Type of mycosis: 16 cases of mucormycosis, 1 of aspergillosis and 1 mixed fungal infection. 11 patients survived, 6 died, and 1 was lost to follow-up. There was a significantly higher incidence of diabetes (p=0.03) among this cohort of COVID-19 positive patients with mucormycosis. A significantly greater number (p=0.0013) of patients received steroids at some point during treatment	There is a significant increase in the incidence of angioinvasive maxillofacial fungal infections in diabetic patients treated for COVID-19 with a strong association with the administration of corticosteroids
Pauli et al. Brazil 2021	Painful palatal lesion in a patient with COVID-19	1 patient	CAM	Clinical descriptive case	The differential diagnosis was based on inflammatory conditions, malignant neoplasms, soft tissue infections, bone infections, and oral lesions related to COVID-19 infection	Quantitative (Case report)	To provide descriptive information and study the relationship between Mucormycosis, COVID-19 and uncontrolled diabetes	Confirms diagnosis of oral lesions related to COVID-19 infection caused by mucormycosis	There is a coinfection relationship since the patient with mucormycosis simultaneously had COVID-19 and uncontrolled diabetes
Sai Krishna et al. Karnataka, India 2022	Maxillofacial infections in COVID-19 era—Actuality or the unforeseen: 2 case Reports	2 patients	CAM	Clinical descriptive case	Relationship between oral and maxillofacial fungal pathologies associated with COVID-19 infection.	Quantitative (Case report)	To document cases of oral and maxillofacial pathologies that are associated with COVID-19 infection.	The pathophysiology of diabetes mellitus and the host response to COVID-19 have similarities that could be adding to the situation and resulting in a higher incidence of oral and mandible pathologies caused by fungi.	With very little information on the correlation between COVID-19, uncontrolled diabetes and mucormycosis, it is difficult to recognize whether patients after becoming infected with COVID-19 have a significant contribution to the development of these pathologies. More and larger multicenter studies are required to provide a better understanding of the pathophysiology in patients following COVID-19 infection.
Verma & Bati Bilaspur, India 2021	COVID-19 and mucormycosis of the craniofacial skeleton: Causal, contributory or coincidental?	16 articles	CAM	Literature review in the PubMed database	In this base, the relationship (maxillary osteomyelitis or craniofacial osteomyelitis) AND (COVID-19 OR Coronavirus OR SARS-CoV-2) surprisingly did not yield results. The search with terms (mucormycosis or zygomycosis or fungal osteomyelitis) AND (COVID-19 OR Coronavirus OR SARS-CoV-2) returned 16 results	Quantitative (Literature Review)	To collect information about a) the relationship between COVID-19 and osteomyelitis of the craniofacial and/or maxillary skeleton, and b) the relationship between COVID-19 with respect to mucormycosis, zygomycosis and fungal osteomyelitis	Strong association between the presence of a history of COVID-19 and mucormycosis, the presence of two factors was also observed: diabetes and other comorbid conditions. Diabetes has been identified as an independent variable associated with the severity of COVID-19 infection and hospitalization. Additionally, current guidelines suggest the use of steroids in hospitalized patients requiring oxygen support	A combination of these factors makes patients hospitalized with COVID-19 a high-risk group for fungal infections such as aspergillosis (associated with fungal balls of the paranasal sinuses without tissue invasion) and mucormycosis (angioinvasive fungal infection that causes ischemic necrosis of the areas involved), the clinical course has a fatality rate of 46%. Clinicians should have a high index of suspicion in immunocompromised patients and COVID-19 patients, with a history of hospital admission for oxygen support, as this category frequently has comorbid conditions such as diabetes, renal failure and are usually administered steroids/antibiotics as part of the COVID-19 management protocol. Diagnosis of fungal infections is based on direct microscopy with KOH-mounted slides and confirmatory diagnosis is based on definitive histological evidence of invasion and tissue culture

Table 2. Continued.

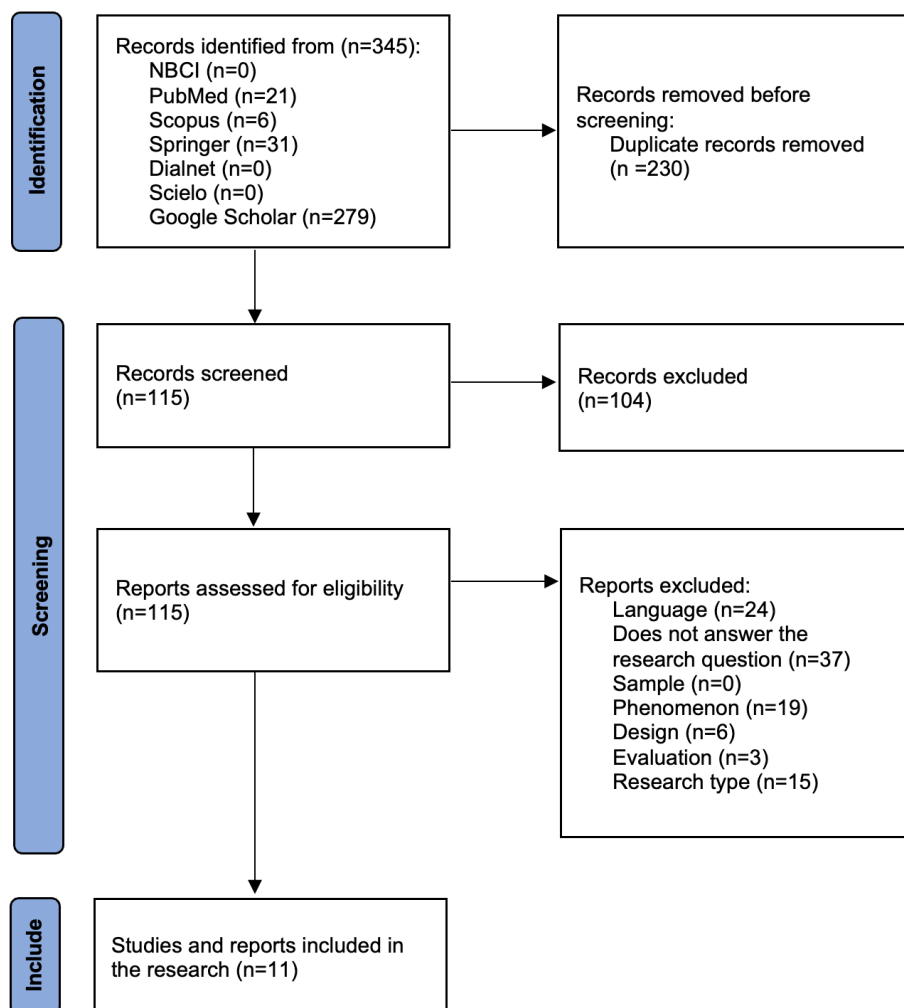
Author Location Year	Title	Sample	Phenomenon of interest	Design	Evaluation	Research type	Objectives	Results	Conclusions
Rajendra Santosh et al. Mona, Jamaica 2021	<i>Fungal infections of oral cavity: diagnosis, management, and association with covid-19.</i>	88 articles in general and 7 articles for covid-19.	CAM	Literature review	Relationship of oral fungal infections with covid-19	Quantitative (Literature Review)	To review information on the diagnosis and therapeutic management of candidiasis, aspergillosis, cryptococcosis, histoplasmosis, blastomycosis, mucormycosis and geotrichosis, as well as analysis of oral fungal infections associated with covid-19	High-risk covid-19 patients, including those with a history of respiratory distress syndrome, admitted to intensive care units, and who used immunosuppressive drugs or corticosteroids are more likely to develop oral candidiasis. This pathology was also found in asymptomatic covid-19 patients and in patients without risk factors	The clinical presentation of oral mycosis may vary depending on the pathogen. Oral mycosis may present clinically with a benign appearance with a colour change (white), swelling, or an invasive picture of ulcerated swelling or ulcerative perforation with deep bone exposure. Oral mycosis should be suspected when the clinical presentations mentioned above are found in immunosuppressed patients or under immunosuppressive treatment. Preliminary diagnosis of oral mycosis can be achieved by salivary rinsing or cytological methods. Therefore, collecting tissue samples for oral mycosis is minimally invasive. Critical evaluation of clinical data will help dental surgeons achieve a valid clinical diagnosis
Rashid et al. Pakistan 2021	<i>Taking a step down on the reconstruction ladder for head and neck reconstruction during the covid-19 pandemic.</i>	31 patients	CAM	Retrospective study, from April 1 to July 1, 2020	Relationship of covid-19 infection in patients who required reconstruction of post-ablative head and/or neck defects. All underwent preoperative screening with covid-19 PCR nasal swabs and high-resolution CT of the chest	Quantitative (Research Article)	The measures were: patients with negative results were operated. During the surgery, all medical staff wore a particulate respirator mask, protective glasses, disposable surgical gowns, and gloves	With modification of the protocol: preoperative, operative and postoperative, no one tested positive for covid-19. Including dental care personnel in surgery, neither health personnel, nor patients	The careful use of appropriate personal protective equipment and compliance with ethical principles turns out to be the only shield that will benefit patients, healthcare personnel and the healthcare system
Pitak-Arnoop et al. Thailand-Germany 2022	<i>A German AWMFs S2e/realist synthesis and meta-narrative snapshot of craniomaxillofacial manifestations in covid-19 patients: Rapid living update on 1 January 2021</i>	64 articles	CAM	A realist synthesis and a meta-narrative review were performed by extracting data in English, French, German and Thai from PubMed-Medline, Embase, Biomed Central, Cochrane Library and Thai Journals Online, up to 1 January, 2021. The main variable of the result was the manifestation of MMC grouped into 5 categories: (1) mouth and throat, (2) nose, paranasal sinuses and skull base, (3) ocular/orbital and periorbital tissue, (4) ear and (5) skin craniofacial	Craniomaxillofacial (CMF) manifestations in patients with covid-19	Quantitative (Literature Review)	To run a review that answers the following question: Among the new diseases due to patients with covid-19, what are the CMF manifestations, according to the RAMESES and the German Association of Scientific Medical Societies (AWMF)'s S2e guidelines?	37 original articles that met the inclusion criteria were analysed. All were in English and indexed in PubMed-Medline. Manual searches of their references yielded a total of 101 articles for review. Most of the data had a low level of evidence and focused on alterations in smell, taste, and orofacial lesions. Iatrogenic complications can occur in this region of the body. Conservative measures were effective and generally sufficient for patient care	Because covid-19 infection is new and becomes the strictest global pandemic within a short period of time, most of the data on CMF symptoms are of low level of evidence. Apart from taste and smell dysfunctions, non-specific CMF lesions can be found and treated conservatively, complications are possible. Dentists and maxillofacial surgeons have the privilege of examining the orofacial region and working closely with colleagues in other specialties to combat the pandemic.
Ahmad et al. Lahore, India 2020	<i>Emergent aerosols generating procedures in oral and maxillofacial surgery in covid-19 pandemic</i>	542 patients	CAM	Retrospective observational study at the Department of Oral and Maxillofacial Surgery, Mayo Hospital, Lahore, India	Diagnosis, type of emergency, procedures, duration of the procedure, type of anaesthesia, precautionary measures were followed according to recommended guidelines and modifications were recorded	Quantitative (Case report)	To study and analyse the aerosol-generating emergency procedures used and modifications made according to the current situation, duration of procedures and recommended precautionary measures	542 patients were included. Of them, 358 presented trauma and closed reduction was performed in 160 cases, open reduction and internal fixation in 49 cases, incision and drainage in 19 cases, debridement in 5 cases, wound irrigation in 76 cases, tracheostomies in 7 cases, resections with or without neck dissections in 10 cases, repair of lacerations in 151 cases, flap divisions in 3 cases, extractions in 32 cases and resections of the lesions along with tracheostomy in 2 cases	During this pandemic, there is a great chance of airborne transmission of virus during aerosol generating procedures. The best possible treatment and care must be provided to the patient, while ensuring protection of the patient and hospital staff by modifying procedural techniques and following recommended safety protocols
Passarelli et al. Italy 2020	<i>covid-19 and oral diseases: How can we manage hospitalized and quarantined patients while reducing risks?</i>	N/A	CAM	N/A	N/A	N/A	N/A	N/A	We must be aware of the high risk of covid-19 infection in healthcare workers, even more so in dentists. On the other hand, many people may currently need dental treatments and the dental professional must have practical and easy-to-perform protocols to avoid possible cross infections
Gowda et al. Maharashtra, India 2021	<i>Rehabilitation of a defect secondary to sino-orbital mucormycosis -A prosthodontic challenge</i>	1 patient	CAM	Clinical descriptive case	Prosthetic rehabilitation of a patient with residual maxillary and orbital defects, residual orbital after surgical treatment of sino-orbital mucormycosis	Quantitative (Case report)	To prepare a clinical report that describes rehabilitation with a combined prosthesis composed of orbital and obturator using an innovative method to achieve retention between both. Providing complete functional and aesthetic rehabilitation of the patient	Patient recovery	Prosthetic rehabilitation of residual maxillary and secondary orbital defects damaged by mucormycosis is described with an innovative method to achieve retention for orbital prosthesis of the obturator bulb in a complex defect
Chitguppi India 2021	<i>covid-19 and risk factors for fungal osteomyelitis of jawbones: Insights from oral and maxillofacial surgeons</i>	33 respondents (oral and maxillofacial surgeons who have treated cases of fungal infections in recovered covid-19 patients)	CAM	Observational, Transversal. With a total of 33 maxillofacial surgeons who participated by answering a Google Form survey. The survey had 12 questions designed to gather knowledge from oral surgeons who had treated cases of mandibular complications in patients after recovery from covid-19	Risk factors, medication for covid-19, dosage and duration of medications	Quantitative (Research Article)	To reduce risk factors and invite some suggestions to minimize complications	Clinically, 73.5% of respondents said that tooth mobility was the most common finding, followed by dental mobility and bone fragments (70.6%). Mucormycosis was the most diagnosed (64.7%). Most respondents (73.5%) said covid-19 medications increase the risk of complications with 94.1% being steroids the most common medication. Poor oral hygiene could be a causal factor (35.3%)	Immunocompromised host, comorbidities (especially diabetes) and medications (indiscriminate use of steroids) make the three key risk factors responsible for the development of fungal infections in the mandible bones. The need for good oral hygiene appears to be a key factor in patients hospitalized with covid-19

RESULTS

A total of 11 manuscripts were selected, of which 3 were research articles^{1-2, 11}, 4 case reports¹²⁻¹⁵, and 3 literature reviews^{5,11,16}. As for the places of study: 6 of the manuscripts were from India^{2,5,11,12,14,17}, 1 from India-Jamaica¹¹, 1 from Thailand-Germany¹⁶, 1 from Brazil¹⁵, 1 from Pakistan¹ and 1 from Italy¹³. Regarding the publication date, only one manuscript dates from 2020, while the remaining 10 were published in 2021.

Within the articles reviewed, different sample sizes were found; in some studies, it was a single case report such as those presented by Gowda *et al.*¹⁴ and Pauli *et al.*¹⁵, or a series of cases, those with the highest number, such as Chitguppi¹¹ with 33 cases and Rashid *et al.*¹ with 31 cases. It was also observed that the age variable presented a very wide range, from 31 years to 73 years (Table 3).

Among the main causes of mucormycosis found are: uncontrolled diabetes mellitus (9%) reported by Moorthy *et al.*², the use of medications, mainly steroids (36%) reported by Chitguppi¹¹, Moothy *et al.*², and Verma *et al.*⁵, patients with some type of immunosuppression (24%) such as renal failure, acquired immunodeficiency virus and malignant neoplasms according



to Pitak-Arnnop *et al.*¹⁶, Sai Krishna *et al.*¹⁸, and Pauli *et al.*¹⁵, transplantation of organs (18%) according to Chitguppi¹¹ and Gowda *et al.*¹⁴, and poor hygiene in general (9%) reported by Chitguppi¹¹.

Table 3.
Authors, sample and age

Author	Sample	Age
Moorthy <i>et al.</i>	18	37 to 73
Pauli <i>et al.</i>	1	50
Sai Krishna, <i>et al.</i>	2	34 and 50
Rashid <i>et al.</i>	31	52
Gowda <i>et al.</i>	1	60
Chitguppi	33	31-60

DISCUSSION

Mucormycosis is an acute fungal disease caused by different genera, mainly *Mucor*, *Rhizopus*, *Ab-sidia*, *Cunninghamella*, *Rhizomucor*, *Saksenaea*, *Apophysomyces* and *Lichtheimia*¹². The condition is rare and occurs in different parts of the body such as: head, neck, organs of the respiratory and central nervous systems. It is associated with immunosuppressed patients (leukaemia, un-controlled diabetes mellitus, etc.). Commonly its starting site is the nose, since it is the entry route. Dental pain and tooth extraction are associated with the appearance of mucormycosis symptoms¹⁸. Most fungal infections in the mouth (oral mycosis) are the result of systemic conditions of the host that are exploited by opportunistic microorganisms. The host has a decrease or deterioration in its immune system, which favours these pathogenic microorganisms to have the appropriate conditions to colonize the oral cavity. Mucormycosis is an angioinvasive fungal infection that causes ischemic necrosis of the affected areas, with a fatality rate of 46%⁵. Fungi of the genus *Rhizopus* are the main agent in cases of rhino cerebral mucormycosis, which affects the oral cavity¹². Germination and invasive growth of fungal spores are facilitated by high levels of glucose, excessive levels of ketone bodies, reduced levels of oxygen, low pH, and high levels of iron. In addition, fungal hyphae have the ability to produce rhizoferrin, complexes formed by iron and hyphae. Thrombus formation caused by ischemic strokes has also been detected, a situation that causes necrosis of adjacent tissues¹⁸. It should be noted that associated with mucormycosis, osteomyelitis has occurred, which is an inflammatory condition in the bones and that begins its presentation in the medullary cavity and extends into the periosteum¹⁸.

There are currently six well-recognized clinical forms of mucormycosis that are named according to their site of manifestation: pulmonary, cutaneous, gastrointestinal, rhino cerebral, central nervous system, and the disseminated variety. Mucormycosis that affects the oral cavity is associated with the rhino cerebral variety, given its relationship with the nasal areas and paranasal sinuses. Likewise, they present in an ulcerative and/or necrotic manner in the palatal region¹². Hyphae are responsible for the initial symptoms of defective phagocytic function; in blood vessels they cause ischemia, thrombosis, tissue necrosis and infarction¹².

Due to COVID-19, the palate is altered by the viral interaction with mucormycosis, causing alterations such as dysgeusia (38%), hypogeusia (35%) and ageusia (24%). In addition to the

deterioration in the nervous system, COVID-19 binds to components of salivary mucin, accelerating the degradation of taste buds and, therefore, can alter and/or modify the sense of taste. The alteration in the taste response is temporary (approximately 15 days) linked to rhinitis due to location and affects more frequently both Caucasian people and females. Another alteration present in the oral cavity is recurrent aphthous stomatitis due to an increase in granulocyte chemotaxis that arises from an increase in tumour necrosis factor (TNF), together with stress or immunosuppression. Oral submucosal fibrosis is due to increased levels of angiotensin II, because there is an increase of vasoconstriction in the area as well as the presence of transforming growth factor (TGF)¹⁶. Oral lesions appear such as necrotic, painful and aphthous ulcers. These lesions are grouped and can measure 1 to 1.5 cm in diameter, covered with scabs and even necrotic areas. One of the most worrying aspects of these injuries is the presence of infections¹⁵.

On the other hand, among the factors that predispose mucormycosis we can list the following: the increased use of immunosuppressive drugs and immunodeficiency cause proliferation of fungal infections in oral tissues¹², uncontrolled diabetes mellitus, immunosuppressed patients with immunological dysfunction (damage to the function of the neutrophils, weakening of the antioxidant system and humoral immunity)¹⁹. In this case, the host is more likely to suffer complications. When combined with COVID-19 and the administration of steroids, they enhance the deregulation problem, causing fungal invasion (mucormycosis and aspergillosis)². Specifically, the use of glucocorticoids such as dexamethasone and methylprednisolone have been increased in patients with COVID-19 to reduce hospital stay and patient mortality. Due to their immunosuppressive nature, they cause greater susceptibility in the host to secondary infections or infections caused by opportunistic microorganisms².

Regarding oral treatment, the prior use of mouthwash significantly reduces the oral viral load, as well as the contamination of the surrounding environment, reducing the risk of health professionals contracting COVID-19¹³. When the preventive part is not enough and the patient has mucormycosis, they must be treated with an antifungal, specifically with posaconazole and an antibiotic; amphotericin B is the drug of choice for this particular disease. Normally, only antifungal medications are required in the treatment of fungi, but since it is associated with other conditions, antibiotics are required to avoid infections¹². In patients who received a graft, fluconazole should be administered orally, although itraconazole and voriconazole, commonly used antifungals, administered prophylactically are also recommended²⁰. In very extreme cases, surgery is required in the head region, such as: exenteration of the affected eye, partial or total maxillectomy. Repeated debridement may be necessary for local control of the disease and an aggressive surgical approach may give better patient outcomes²¹.

CONCLUSIONS

After carrying out the systematic and exploratory review of mucormycosis, we found that it is an infection that develops in the oral cavity like most opportunistic fungi, but we cannot establish a direct association between said infection and COVID-19.

The articles found in the search describe the infection, as well as characteristics, location in the stomatognathic system, etc. The information is sufficient for dentists to know about infections such as mucormycosis present in patients with COVID-19.

LIMITATIONS AND STRENGTHS

No previous systematic review was identified that explores the relationship between COVID-19 and mucormycosis in the oral cavity; in this sense, the findings are novel. Possible biases are taken into account when ruling out other languages.

FINANCING

No funding was received for the development of this research.

CONFLICT OF INTERESTS

The co-authors declare that there is no type of conflict of interest.

BIBLIOGRAPHIC REFERENCES

1. Rashid HU, Rashid M, Khan N, Ansari SS, Bibi N. Taking a step down on the reconstruction ladder for head and neck reconstruction during the COVID-19 pandemic. *BMC Surg.* 2021; 21: a120. DOI: 10.1186/s12893-021-01134-1
2. Moorthy A, Gaikwad R, Krishna S, Hegde R, Tripathi KK, Kale PG, 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; 20(3): 418-25. DOI: 10.1007/s12663-021-01532-1
3. Garg D, Muthu V, Sehgal IS, Ramachandran R, Kaur H, Bhalla A, et al. Coronavirus disease (COVID-19) associated mucormycosis (CAM): Case report and systematic review of literature. *Mycopathologia.* 2021; 186(2): 289-298. DOI: 10.1007/s11046-021-00528-2
4. Organización Panamericana de la Salud (OPS). Epidemiological alert: COVID-19 associated mucormycosis. [Internet]. [Consultado 14 de junio del 2021]. https://iris.paho.org/bitstream/handle/10665.2/54284/EpiUpdate11June2021_eng.pdf?sequence=1&isAllowed=y
5. Verma DK, Bali RK. COVID 19 and mucormycosis of the craniofacial skeleton: Causal, contributory or coincidental? *J Maxillofac Oral Surg.* 2021; 20(2): 165-166. DOI: 10.1007/s12663-021-01547-8
6. INEGI, Instituto Nacional de Salud Pública, Secretaría de Salud. *Encuesta Nacional de Salud y Nutrición (ENSANUT). Presentación de Resultados 2018.* [Internet]. [Consultado 23 de mayo del 2021]. Disponible en: https://ensanut.insp.mx/encuestas/ensanut2018/doctos/informes/ensanut_2018_presentacion_resultados.pdf
7. Fernández-Sánchez H, King K, Enríquez-Hernández CB. Revisión Sistemática Exploratoria como metodología para la síntesis del conocimiento científico. *Enferm. univ.* 2020; 17(1): 87-94. DOI: 10.22201/eneo.23958421e.2020.1.697
8. Urrútia G, Bonfill X. Declaración PRISMA: una propuesta para mejorar la publicación de revisiones sistemáticas y metaanálisis. *Med. clín.* 2010; 135(11): 507-511. DOI: 10.1016/j.medcli.2010.01.015
9. Cooke A, Smith D, Booth A. Beyond PICO: the SPIDER tool for qualitative evidence synthesis. *Qual Health Res.* 2012; 22(10): 1435-1443. DOI: 10.1177/1049732312452938

10. Cabello, JB. Critical Appraisal Skills Programme Español (CASPE). Plantilla para ayudarte a entender una revisión sistemática. En: *CASPE. Guías de Lectura Crítica de la Literatura Médica*. Alicante: CASP, 2005. Cuaderno I. 13-17. [Internet]. [Consultado 15 de junio del 2021]. https://redcaspe.org/plan-tilla_revision.pdf
11. Chitguppi R. covid-19 and risk factors for fungal osteomyelitis of jawbones: Insights from oral and maxillofacial surgeons (April 27, 2021). SSRN 3834961: 1-8. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3834961
12. Rajendra Santosh AB, Muddana K, Bakki SR. Fungal infections of oral cavity: Diagnosis, management, and association with covid-19. *SN Compr Clin Med*. 2021; 3(6): 1373-1384. DOI: 10.1007/s42399-021-00873-9
13. Passarelli PC, Passarelli G, Charitos IA, Rella E, Santacroce L, D'Addona A. covid-19 and oral diseases: How can we manage hospitalized and quarantined patients while reducing risks? *Electron J Gen Med*. 2020; 17(6): em238. DOI: 10.29333/ejgm/7945
14. Gowda M, Sashidhar MP, Prakash P, Sahoo NK. Rehabilitation of a defect secondary to sino-orbital mucormycosis –A prosthodontic challenge. *IP Ann Prosthodont Restor Dent*. 2021; 7(1): 41-45. DOI: 10.18231/j.aprd.2021.008
15. Pauli MA, Pereira LM, Monteiro ML, de Camargo AR, Rabelo GD. Painful palatal lesion in a patient with covid-19. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2021; 131(6): 620-625. DOI: 10.1016/j.oooo.2021.03.010
16. Pitak-Arnnop P, Meningaud JP, Sirintawat N, Subbalekha K, Auychai P, Iamaroon A, et. al. A German AWMF's S2e/realist synthesis and meta-narrative snapshot of craniomaxillofacial manifestations in covid-19 patients: Rapid living update on 1 January 2021. *J Stomatol Oral Maxillofac Surg*. 2022; 123(1): 64-73. DOI: 10.1016/j.jormas.2021.01.012
17. Ahmad Z, Riaz N, Abid A, Shakir H, Mirza A, ul Haq E. Emergent aerosols generating procedures in oral & maxillofacial surgery in covid-19 pandemic. *Ann King Edw Med Univ*. 2020; 26(2): 330-335. DOI: 10.21649/akemu.v26i2.3922
18. Sai Krishna D, Raj H, Kurup P, Juneja M. Maxillofacial infections in covid-19 era -Actuality or the unforeseen: 2 case reports. *Indian J Otolaryngol Head Neck Surg*. 2022; 74(s2): 2959-2962. DOI: 10.1007/s12070-021-02618-5
19. Akash MSH, Rehman K, Fiayyaz F, Sabir S, Khurshid M. Diabetes-associated infections: development of antimicrobial resistance and possible treatment strategies. *Arch Microbiol*. 2020; 202(5): 953-965. DOI: 10.1007/s00203-020-01818-x
20. Cornely OA, Arikian-Akdagli S, Dannaoui E, Groll AH, Lagrou K, Chakrabarti A, et al. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of mucormycosis 2013. *Clin Microbiol Infect*. 2014; 20(s3): 5-26. DOI: 10.1111/1469-0691.12371
21. Patel NR, Patel PA. A case report of mucormycosis with palatal ulcer: a rare clinical dilemma. *J Coll Physicians Surg Pak*. 2018; 28(9): 721-723. DOI: 10.29271/jcpsp.2018.09.721