Review Article

Evaluating the role of local host factors in the candidal colonization of oral cavity: A review update

ABSTRACT

Human oral cavity is home to a number of organisms, *Candida albicans* being one of them. This review article aims at understanding the correlation between the oral candidal colonization and the local host factors that may influence it with special emphasis on congenital craniofacial anomalies such as cleft lip and palate (CLP). Various scientific databases were searched online and relevant articles were selected based on the inclusion criteria. A comparative study was done to understand the interdependence of various factors (including CLP) and oral candidal colonization. The results revealed a strong association of certain local host factors which may influence the oral colonization of *Candida* species. Factors such as mucosal barrier, salivary constituents and quantity of saliva, congenital deformities like CLP, oral prostheses such as dentures/palatal obturators and fixed orthodontic appliances (FOAs) were identified. All these factors may directly affect the growth of *Candida* in the oral cavity. Although numerous studies have pointed a positive correlation between Oral Candidal colonization and local host factors such as oral prostheses, FOA, and oral mucosal barrier only one study has been done, in the Indian subcontinent with respect to the correlation of candidal colonization and CLP. After the evaluation of all the factors mentioned in various case studies, it can be concluded that the presence of local host factors such as orofacial clefts, dental prostheses, FOA, xerostomia, and atrophy of the oral mucous membrane lead to significant increase in candidal colonization, but since very few studies in regard to CLP have been done worldwide and in India, in particular, further studies are warranted.

Keywords: *Candida albicans,* candidal carriage, cleft lip and palate, orofacial clefts

INTRODUCTION

The oral cavity is home to more than 700 different species of microorganisms making it the second most diversely inhabited cavity in the human body, gut being the first.[1] Humans inheritably do not have any microorganisms in their oral cavity but the process of acquisition of microbes starts right at the time of birth. In a matter of minutes, the oral cavity becomes home to various microorganisms depending on the type of birth, intimacy with people around and the external environment. The oral cavity harbors numerous *Candida* species right from the 1st day of a newborn's life.[2]

Candida is a dimorphic fungus comprising of more than 150 species. It normally resides as a commensal and is harmless which may become pathogenic owing to factors such as any change in the normal oral flora, altered anatomy as in congenital deformities like cleft lip and palate (CLP) or debilitation of the host immune system. *Candida albicans* is the most common species of *Candida* found in the oral cavity, being present in 30%–50% of the people with varying carriage.[3,4] The oral carriage of *Candida* ranges from 3%–75%

Imran Khan[1,2], Tanveer Ahmad[2,3], Nikhat Manzoor[2], Moshahid Alam Rizvi[2], Uqba Raza[1], Shubhangi Premchandani[1]

[1]Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, [3]Department of Human Anatomy, Faculty of Dentistry, [2]Department of Biosciences, Faculty of Natural Sciences, Jamia Millia Islamia, New Delhi, India

Address for correspondence: Prof. Nikhat Manzoor, Medical Mycology Lab, Department of Biosciences, Faculty of Natural Sciences, Jamia Millia Islamia, New Delhi-110 025, India. E-mail: nmanzoor@jmi.ac.in

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owing to factors such as age, smoking, gender, oral hygiene status, and association of systemic diseases[5] to name a few.

CLP is the most common form of orofacial clefts with its incidence rate being as high as 1/700 births worldwide. In India, approximately 35,000 cases of cleft are seen annually.[6,7]

This literature review aims at understanding the correlation between oral candidal colonization with orofacial clefts as well as other local host factors.

MATERIALS AND METHODS

An English language systematic search was carried out at PubMed, ResearchGate, Scopus, and Google Scholar databases for articles published between 2000 and 2020 with the keywords Oral Candidiasis, *Candida* species, *C. albicans*, Candidal colonization, Candidal carriage, Host factors, Local factors, Risk factors, Host pathogen interaction, CLP, orofacial clefts, obturators, denture stomatitis, and orthodontic appliance. Apart from that, cross references were also searched.

Inclusion criteria

1. Studies containing data suggestive of correlation between orofacial clefts and prevalence of candidiasis/carriage of *C. albicans*
2. Studies suggesting other local host factors that affect the oral colonization of *C. albicans*.

Exclusion criteria

1. Studies other than the ones in English language
2. Studies having no/inadequate data
3. Exclusively *in vitro* or animal studies.

RESULTS

A total of 51 studies were searched and thirty nine were included while twelve studies were excluded. Out of the twelve excluded studies, two were in language other than English; four were *in vitro* or animal studies while six had insufficient or no data supporting the correlation between Candidal colonization and the local host factors.

The various host factors which may influence the colonization of *Candida* in the oral cavity, as derived from the various articles have summarized in Table 1.[8,9]

Table 1: Predisposing host factors and their effects on oral *Candidal* colonization

Factors	Effect on candidal colonization
Local factors	
Mucosal barrier	
Healthy oral mucosa (proteins)	Inhibits
Atrophy/hyperplasia/dysplasia	Promotes
Saliva	
Immunoglobulins	Inhibit
Enzymes	Inhibit
Acidic pH	Promotes
Xerostomia	Promotes
Coliforms	Promote
Orofacial abnormalities: Cleft lip/cleft palate	Promote
Dental appliances	Promote
Systemic factors	
Physiologic	
Extremes of age (infancy/old age)	Promote
Pregnancy	Promotes
Nutritional deficiencies	
Vitamin B12	Promotes
Folic acid	Promotes
Ferritin	Promotes
Endocrinopathies	
Diabetes mellitus	Promotes
Hypothyroidism	Promotes
Hypoparathyroidism	Promotes
Blood dyscrasias/malignancies	Promote
Immune suppression: HIV	Promotes
Iatrogenic factors	
Oral hygiene status	
Good oral hygiene	Inhibits
Poor oral hygiene	Promotes
Therapies	
Broad spectrum antibiotics	Promote
Corticosteroids	Promote
Chemotherapy/radiotherapy	Promotes
Smoking	Promotes

DISCUSSION

The ability of various microorganisms to colonize the oral mucosa and the type of infections caused may be determined by strain-specific features of that particular microorganism like invasiveness, ability to adhere to the mucosa and their ability to form biofilm[10] and *Candida,* being a ubiquitous fungus is no exception. Apart from these, there are some local host factors which may influence the oral candidal colonization in humans. The various local factors have been discussed below:

Mucosal barrier

The defense of the host includes mechanical barriers to the penetration of the fungus like the epithelium, antimicrobial factors as well as the innate and the adaptive cellular immunity.[11]

The first line of defense against the microorganisms (in this case, *Candida* species) is the mucosa. Earlier it

was believed that the role of the oral mucosa is passive in restraining the invasion of underlying tissues by *Candida* species. Recent researches, however, indicate a very active role of the cells of the epithelium in triggering the immune responses.[12,13]

For establishing infection, the *Candida* species must be adherent to the epithelium, proliferate and be able to penetrate the oral epithelium (non-keratinized or keratinized). Proteins present in the cells of the oral mucosa might cause retardation of *Candida* invasion.[14] Pathogen detection at the epithelial surface is mainly immune mediated process which involves pathogen-associated molecular pattern recognition by a receptor group named pattern recognition receptors (PRRs). The PRRs include Nod-like receptors, Toll-like receptors and C-type lectin receptors.[15-18]

Various cell types are involved in innate immunity: monocytes, neutrophils, dendritic cells, Natural Killer cells, CD8+ and CD4+ T cells, epithelial cells, non-MHC restricted T cells, keratinocytes, and stromal cells. These cells play a significant role in protection through direct effects by either phagocytosis or secretion of antimicrobial compounds that neutralize the fungal components.[19]

Any alteration in the oral epithelium, i.e., atrophy, dysplasia or hyperplasia affects the mucosal barrier's efficiency. The oral mucosal constant desquamation occurring at a much faster rate in comparison to the growth of *Candida* species helps protect the host against Candidiasis to some extent.[8]

Saliva

Salivary role in Candidal Colonization is not very clear.[20-23] A continuous salivary flow removes loosely adhered *Candida*, thereby, preventing its colonization into the oral cavity. Moreover, while some salivary proteins like lactoferrin, lysozyme, defensins, histatins, calprotectins, and IgA antibodies help keep a check on the growth of *Candida*,[19-21] others like statherins and mucines might enhance adhesion of *Candida* species by acting as receptors of mannoproteins in the various species of *Candida*.[21-24] Xerostomia creates an imbalance in the normal oral microflora, favoring the growth of some bacteria such as *Staphylococcus aureus, Lactobacillus* as well as fungi such as *Candida*.[20] Studies have shown a positive correlation between patients of Sjogren's Syndrome (both Primary and Secondary), Chronic Hepatitis C virus infection and oral candidiasis. Diabetes Mellitus, Sialadenosis and other such disorders which cause xerostomia too predispose to candidiasis.[24]

Low salivary pH also increases the chances of adhesion and proliferation of *Candida* species by increasing the enzymatic activities of lipases and proteinases which are significant for the virulence of *Candida* species.[20,25]

Congenital craniofacial anomalies like cleft lip and palate

CLP patients present with an abnormal oronasal communication which may be a cause of altered flora in the oral cavity and such patients often require intervention at the early stages of their lives, the mainstay of the treatment being surgical therapy. Maintaining proper oral hygiene is often a challenge in such patients which may render them susceptible to oral infections, such as candidiasis. Immaturity of the immune system and poor oral hygiene play a significant role in the same. Surgical intervention often requires the administration of prophylactic antibiotics in such cases which further increase their chances of acquiring candidiasis.[26] Table 2 summarizes the work of various researchers in establishing a correlation between orofacial clefts and prevalence of *Candida* species.

Dental prosthesis

The oral microbiota changes and favors the growth of *Candida* species and other microorganisms when an individual starts wearing a dental prosthesis, be it a complete denture or a partial denture, eventually leading to denture stomatitis.[32]

An inflammatory mycotic infection, denture stomatitis presents mainly as oral mucosal inflammation below the tissue surface (intaglio surface) of maxillary dental prosthesis.[33] The maxillary denture covers a larger area of the palate thus making it devoid of the protective action of saliva, whereas, the mandibular denture being relatively loose ensures an adequate flow of saliva beneath it.

Denture stomatitis is multifactorial with candidal colonization and age related immune suppression acting as major risk factors.[34-36] Earlier, studies reported that about 54%–74% of denture stomatitis cases were due to *C. albicans*[35,37-39] but now there are reports of cases demonstrating non-albicans species in denture stomatitis.

Newton in 1962,[40] proposed a classification based on the clinical presentation of the denture stomatitis:

- Type I: Localized inflammation or pinpoint hyperemia
- Type II: Diffuse erythema
- Type III: Inflammatory papillary hyperplasia.

The findings of various researchers in this regard have summarized in Table 3.

Fixed orthodontic appliance

FOAs increase the area for plaque retention as well as make it difficult for the patient to maintain a proper oral

Table 2: Various studies showing correlation of orofacial clefts with prevalence of *Candida albicans*

Author	Country and year of study	Number of subjects	Age group targeted (years)	Control (if present)	Type of cleft	Results and conclusions
Mÿburgh.[27]	South Africa 2009	100	-	-	Soft palate cleft - had undergone repair	Swabs taken from 100 patients on day 0,2, 4 and 6 post cleft repair surgery showed that 9, 28,19, and 27 patients had presence of *C. albicans* respectively on the above-mentioned days
Rawashdeh *et al*.[28]	Jordan 2011	60	≤5 6- 16 ≥17	60	Both bilateral and unilateral CLP	Candidal carriage increased with age It was the maximum in patients who had undergone 3 surgeries - 78.2% More in bilateral cases - 77.7%
Chopra *et al*.[29]	India 2014	48	4- 6	Present	-	Patients with cleft presented with higher incidence of oral mucosal lesions (20.6% - including candidiasis, coated tongue, and ulcers) compared to the control group (8.2%)
Machorowska-Pieniążek *et al*.[30]	Poland 2017	30+25	0- 1	-	Complete CLP (30) CSP (25)	*C. albicans* was found to be present only in the CLP cases (30/55) in the gum pad stage Prevalence - 6.6%
Silva *et al*.[31]	Brazil 2018	46	0- 12	-	-	*C. albicans* isolated from 18 patients (39.1%) prior to asepsis More prevalent in bilateral CLP (77.7%) as compared to unilateral CLP and CP cases (57.1%)

C. albicans: Candida albicans, CP: Cleft palate, CLP: Cleft lip and palate, CSP: Cleft soft palate

Table 3: Various studies showing the prevalence of denture stomatitis among denture users

Author	Country and year of study	Number of denture wearers	DS	
			Individuals with DS	Prevalence of DS
Garcia-Pola Vallejo *et al*.[41]	Spain, 2002	102		19.6%
Kulak-Ozkan *et al*.[42]	Turkey, 2002	70	31	44%
Khasawneh and Al-Wahadni[43]	Jordan, 2002	321 203 males 118 females	94 45 males 49 females	29% 22.2% males 41.5% females
Espinoza *et al*.[44]	Chile, 2003	574 179 males 395 females	198 45 males 153 females	34.5% 25.1% males 38.7% females
Peltola *et al*.[45]	Finland, 2004	106 25 males 81 females		25%
Marchini *et al*.[46]	Brazil, 2004	236 59 males 177 females	100	42.4%
Mumcu *et al*.[47]	Turkey, 2005	178	33 14 males 19 females	18.5%
Triantos[48]	Greece, 2005	222	33	14.9%
Baena-Monroy *et al*.[49]	Mexico, 2005	105 43 males 62 females	50 21 males 29 females	47.6% 48.8% males 46.8% females
Marchini *et al*.[50]	Brazil, 2006	201	108	54%
Dikbas I. *et al*.[51]	Turkey, 2006	234	130	55.5%
Emami *et al*.[52]	Montreal, 2007	40 11 males 29 females	31	77.5%
Al-Dwairi[53]	Jordan, 2007	300 175 males 125 females	157 89 males 68 females	52% 50.9% males 54.4% females
Thiele *et al*.[54]	Brazil, 2008	59 24 males 35 females	26 11 males 15 females	44.1% 45.8% males 42.9% females
Freitas *et al*.[55]	Brazil, 2008	146		58.2%
Coco *et al*.[56]	Scotland, 2008	37	26	70.3%

Contd...

Table 3: Contd...

Author	Country and year of study	Number of denture wearers	DS	
			Individuals with DS	Prevalence of DS
Dağistan *et al*.[57]	Turkey, 2008	70 39 males 31 females	49 30 males 19 females	70% 76.9% males 61.3% females
Mathew *et al*.[58]	India, 2008	45	10	22.2%
Baran and Nalçacı *et al*.[59]	Turkey, 2009	310 159 males 151 females	111 56 males 55 females	35.8% 35.2% males 36.45% females
Marcos-Arias *et al*.[60]	Spain, 2009	100	45	45%
Naik and Pai[61]	India, 2011	100 86 males 14 females	70	70%
Bilhan *et al*.[62]	Turkey, 2012	64		8.3%
Bhat *et al*.[63]	India, 2012	55 34 males 21 females	27 21 males 6 females	50%
Khajehhosseini *et al*.[64]	Iran, 2014	100 69 males 31 females	53	53%
Patil *et al*.[65]	India, 2015	5100 3100 males 2000 females	1734	34%
Prakash *et al*.[66]	India, 2015	50 28 males 22 females	50	100%
Kimsa *et al*.[10]	Poland, 2020	72 13 males 59 females	46	63.8%

DS: Denture stomatitis

Table 4: Various studies showing the correlation between fixed orthodontic appliance and oral candidal carriage

Author	Year of publication	Number of subjects	Age group	Result
Hägg *et al*.[68]	2004	27	15.5±2.3 years	Significant increase in the oral candial carriage was noted after insertion of FOA However the prevalence remained same
Arslan *et al*.[69]	2008	72	Adolescents	Increase in CFU of *Candida* from pretreatment to 12 months after bonding was 51.85±5.44
Khanpayeh *et al*.[70]	2013	80	7- 18 years	Increased candidal carriage in patients with FOA compared to removable orthodontic appliance
Zheng *et al*.[71]	2014	50	10- 18 years	Increase in the number of patients with *Candida* as well as the number of CFU was seen within 2 months of FOA treatment
Shukla *et al*.[72]	2017	60	13- 18 years	Dramatic increase in the colonization of *Candida* was observed after FOA insertion

FOA: Fixed orthodontic appliance, CFU: Colony forming unit

hygiene. These factors contribute towards increased oral candidal colonization in patients undergoing fixed orthodontic therapy.[67] Table 4 displays some of the studies that prove the correlation between FOA and oral candidal carriage.

The results seen after carefully evaluating all the given studies suggest a strong correlation between increased number of Colony Forming Units of *Candida* species as well as increased prevalence in the presence of the above mentioned factors. There is extensive data that suggests association of *Candida* with denture prosthesis, FOA, etc., but very few studies have shown a possible correlation between congenital craniofacial anomalies like CLP and oral candidal colonization, therefore, more research work is warranted in this context.

CONCLUSION

C. albicans is one of the commensals of the oral cavity which tends to increase in number under favorable circumstances. The increase in oral candidal colonization may be due to local or systemic factors. Mechanical alterations like presence

of a denture or orthodontic appliance also favor candidal proliferation in the oral cavity. Local factors such as mucosal barrier and salivary constituents play an important role too. While certain enzymes present in saliva may inhibit the growth of *Candida*, conditions like xerostomia accelerate its growth. Similarly, an intact mucosa would be inhibitory for the growth of *Candida* whereas any atrophy/discontinuity would favor its growth. Other contributing factors can be the use of obturators, prophylactic antibiotics given before surgical repair of the cleft and inability to maintain a good oral hygiene.

CLP are one of the most commonly seen forms of congenital craniofacial defects with a high prevalence rate in the Indian subcontinent. They lead to mechanical alteration of the oral cavity making it more prone to plaque accumulation which is favorable for the growth of microorganisms in the oral cavity.

However, very few studies exclusively on CLP patients and oral *Candida* colonization have been done worldwide and only one study has been done in India. Therefore, further research and studies in finding correlation of candidal colonization with CLP patient's is warranted.

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Conflicts of interest

There are no conflicts of interest.

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