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%
owing to factors such as age, smoking, gender, oral hygiene status, and association of systemic diseases 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/adequate 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]

**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 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.[10]

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

| Factors | Effect on candidal colonization |
|---------|-------------------------------|
| Local factors |                     |
| Mucosal barrier | Inhibits               |
| Healthy oral mucosa (proteins) | Promotes               |
| Atrophy/hyperplasia/dysplasia | Inhibits               |
| 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) | Promotes              |
| 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               |
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.\cite{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.\cite{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.\cite{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.\cite{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.\cite{20}

Saliva

Salivary role in Candidal Colonization is not very clear.\cite{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,\cite{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.\cite{21-24} Xerostomia causes 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.\cite{25}

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.\cite{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.\cite{26} Table 2 summarizes the work of various researchers in establishing a correlation between orofacial clefts and prevalence of Candida species.

Table 2

| Researcher | Study Title | Correlation |
|------------|-------------|-------------|
| Newton | Congenital Craniofacial Anomalies and Oral Candidiasis | Increased prevalence of Candida in cleft patients |

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.\cite{22}

An inflammatory mycotic infection, denture stomatitis presents mainly as oral mucosal inflammation below the tissue surface (intaglio surface) of maxillary dental prosthesis.\cite{23} 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.\cite{24-26} Earlier, studies reported that about 54%–74% of denture stomatitis cases were due to C. albicans\cite{35,37-39} but now there are reports of cases demonstrating non-albicans species in denture stomatitis.

Newton in 1962.\cite{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-Pieniżek 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 | Number of denture wearers | DS | Individuals with DS | Prevalence of DS |
|-----------------------------|---------------------------|---------------------------|---------------------------|----|---------------------|------------------|
| Garcia-Pola Vallejo et al [32] | Spain, 2002              | 102                       | 31                        | 19.6% |
| Kulak-Ozkan et al [33]      | Turkey, 2002              | 70                        | 44%                       |
| Khasawneh and Al-Wahadni [34] | Jordan, 2002             | 321                       | 29%                       | 94  | 45 males           | 22.2% males |
| Espinoza et al [35]         | Chile, 2003               | 574                       | 395 females               | 179 males           | 41.5% females |
| Peltola et al [36]          | Finland, 2004             | 106                       | 25 males                  | 153 females          | 25.1% males |
| Marchini et al [37]         | Brazil, 2004              | 236                       | 100                       | 42.4% |
| Mumcu et al [38]            | Turkey, 2005              | 178                       | 14 males                  | 18.5% |
| Triantos [39]               | Greece, 2005              | 222                       | 33                        | 14.9% |
| Baena-Monroy et al [40]     | Mexico, 2005              | 105                       | 50                        | 47.6% |
| Marchini et al [41]         | Brazil, 2006              | 201                       | 21 males                  | 48.8% males |
| Dikbas I. et al [42]        | Turkey, 2006              | 234                       | 29 females                | 46.8% females |
| Emami et al [43]            | Montreal, 2007            | 40                        | 31                        | 77.5% |
| Al-Dwairi [44]              | Jordan, 2007              | 300                       | 157                       | 52%  |
| Thiele et al [45]           | Brazil, 2008              | 59                        | 26                        | 44.1% |
| Freitas et al [46]          | Brazil, 2008              | 146                       | 26                        | 58.2% |
| Coco et al [47]             | Scotland, 2008            | 37                        | 26                        | 70.3% |

Contd...
hygiene. These factors contribute towards increased oral candidal colonization in patients undergoing fixed orthodontic therapy. 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 denture prosthesis, FOA, etc., can further exacerbate the situation. Therefore, the need for preventive measures against Candida colonization is very crucial for the patients with orthodontic appliances and denture wearers.
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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