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Research Paper

The Role of Fungi in Periodontitis

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ABSTRACT: *The fungus or mycotic diseases are generally chronic and usually caused by the vegetable parasites known as fungi. Reproduction of fungi in human tissues is brought about by budding, septation or endosporulations. Fungal infections are naturally opportunistic and along with various systemic and local factors, predisposing the infections occur in retarded immunity conditions. The infections can be prevented by improving the host immunity. This review discusses the role of fungi on periodontal infection.*
KEYWORDS: *Fungi in periodontitis - Oral microbiome - Pathogenesis - Antifungal agent - Mucormycosis with COVID-19*

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I. INTRODUCTION

Fungi are eukaryotic, spore bearing, unicellular or multicellular organism which can reproduce sexually or asexually. It is around 5-30 µm long and 1-5 µm wide with its cell wall made of cellulose and glucans, nevertheless lack locomotory organelles. Fungi may be saprophytic (feed dead and decayed matter) or parasitic (feed living organisms). Fungal cells are surrounded by branched filamentous structures called Hyphae, through which it absorbs nutrients from the surrounding environment. Periodontitis is defined as an inflammatory disease involving the supportive dental tissues, resulting in destruction of collagen fibres of the periodontal ligament, leading to irreversible bone resorption. Periodontal diseases are nothing but the interaction of micro-organisms and the host immune system in the periodontal environment (KORNMAN ET AL -1997). The sequential development of the disease is due to some local factors like poor oral hygiene, dental caries, improper dentures, which results in plaque accumulation and some systemic factors like host metabolism, immunosuppressive drugs, malnutrition, AIDS, diabetes etc[1].

Human oral microbiome comprises of approximately 500-600 bacterial species and 90-100 fungal species. Periodontitis is associated with enormous number of microorganisms like gram positive & gram-negative bacteria, facultative anaerobic organisms, yeast and viruses. For suppression of such suspected periodontal microorganisms, antibiotic can be used. But long-term or widespread usage of such antibiotics results in superinfections by fungi (HELOVUO-1986 & RAMS ET AL -1990). Among all the fungal yeast, candida species is more widespread in the oral cavity, which is an obvious commensal of oral cavity. C. albicans plays a predominant role among other candidal species in periodontal disease. In oral cavity, they commonly reside or colonize tongue, palate, buccal mucosa and also subgingival plaque of adults with severe periodontitis. Apart from C. albicans , other candidal species like C. glabrata, C. tropicalis, C. krusei, C. dubliniensis also seen due to broad spectrum antibiotic usage and these are called as Non- Candida Albicans Candida(NCAC), which is most prevalent in immunocompromised individuals and recntly identified in healthy individuals[2].

Certain studies have reported significant role of yeast in periodontal pockets in the pathogenesis of marginal periodontitis (SLOTS ET AL-1988, FIEHN& WESTERGARD-1990). Fungal yeast adheres and penetrate the mucosal epithelium and results in periodontal inflammation (epstein et al- 1984). Nevertheless, the relationship between fungi and periodontal disease is being inappropriate. The most common antifungal agents

used in oral cavity are nystatin and flucanazole. Eventhough, C. albicans which are present in subgingival sites shows resistance to those antifungal therapy. So, in future, new antifungal agents should be used for effective action against fungal isolates.

The prime etiological factor for oral diseases is the lack of oral hygiene which results in accumulation of bacterial and fungal colonies, over the hard and soft tissues of the oral cavity. Many studies reported that these fungal colonies reside mainly in buccal mucosa, periodontal pocket and palate, which inturn results in periodontitis. This review article focuses mainly on the prediction of relationship between fungi and periodontal diseases.

II. CLASSIFICATION OF FUNGI:

1) **MORPHOLOGICAL CLASSIFICATION** (Based on cell structure)

a) YEAST:

These are small, oval, individual cell forms that can propagate or reproduce through budding

b) FILAMENTOUS FUNGI (Molds/ Hyphae):

These are tubular and filamentous forms which may be septate or non-septate and can release conidia in air

c) DIMORPHIC FUNGI:

It can exist in both yeast or mold form and differs depending upon certain factors like temperature.

d) MYCELIUM:

These are intertwined, spore bearing hyphal structures

2) **SYSTEMIC CLASSIFICATION**:(Based on spore formation)

a) ZYGOMYCETES:

These are wide range fungus lacking septae and can release asexual spores called sporangiospores from a sac- like structure called sporangium.

b) ASCOMYCETES:

These are tapered range fungus with septae and can produce sexual spores called ascospores from a structure called ascus. This class includes both yeast and filamentous forms.

c) BASIDIOMYCETES:

These are septated fungi, which comprise of club- shaped structure called basidium, which give rise to basidiospores.

d) DEUTEROMYCETES (fungi imperfectii):

They named as 'fungi imperfectii' because they are free from sexual spores. It includes both yeast and mold form.

III. PREDISPOSING FACTORS FOR FUNGAL INFECTIONS:

Some common predisposing factors include;

1. Genetic susceptibility
2. Compromised immune status
3. Mucosal injury
4. Improper hygiene maintenance
5. Patients under steroid therapy
6. Patients under cytotoxic drug therapy or under chemotherapy
7. Patients affected by viral infections like CMV
8. Patients with uncontrolled comorbidities
9. Patients with debilitating diseases like AIDS
10. Posttransplant patients
11. Preterm babies in Neonatal Intensive Care Unit [4]

IV. TISSUE RESPONSE IN FUNGAL INFECTIONS:

Fungal infections commonly affect the skin and subcutaneous tissue and even some vital organs and causes various tissue reactions. Some among them are acute or chronic reaction, severe allergic effects, granulomatous lesions, necrosis and even vascular lesions.

Antigen presenting cells helps in activation of lymphocytes, particularly T- cells by secretion of IL-12, also lymphocytes help in transformation of macrophages into epitheloid cells through Interferon- γ, which results in granuloma formation. Vascular invasions in fungal infection are rare and leads to inflammation and infarction of tissues, in turn results in tissue necrosis. Some virulent enzymes and adhesive molecules being secreted by fungi can also results in tissue invasion[3].

V. DISEASE ENTITIES

Fungal infections evolve because of some irregularities in immune response and also by imbalance in host resistance, which leads to colonisation of fungal organisms. Fungal infections may be superficial or deep depending upon the dissemination of pathogens. Some common fungal infections include Candidiasis, Aspergillosis, Cryptococcosis, Mucormycosis, Blastomycosis and Histoplasmosis. Candidiasis is the most common systemic as well as oral fungal infection. It occurs in 3 forms namely pseudomembranous, erythematous and hyperplastic. Of which pseudomembranous is the most common type. Candidiasis is known for its classical whitish pattern, which is scrapable on oral sites.

Aspergillosis is the second common fungal infection which appears as an opportunistic infection in immunocompromised individuals. It comprise of 3 forms- invasive (aggressive and lethal), non- invasive and destructive non- invasive. In head and neck region, it affects oral cavity, paranasal sinuses, larynx, ears, and eyes. Cryptococcosis is another one fungal infection which initially affects lungs and later aggects meninges. It is also frequently seen in immunocompetent patients lke AIDS.

Mucormycosis/ Zygormyosis is one more fungal infection principally affects immunocompromised patients and also affects patients with blood dyscrasias, uncontrolled diabetes and stem cell transplantation. At cellular level, imbalance in phagocytosis cause increased blood pathogenic levels and in-turn causes ischemia, infarction and necrosis of tissues. Oral mucormycosis commonly affects nasal and paranasal areas and results in palatal ulceration and perforation[5]. Histoplasmosis and blastomycosis are dimorphic fungal infections which commonly affects lungs. Some other fungal infections like Rhinosporidiosis, Coccidioidomycosis, Paracoccidioidomycosis, Penicilliosis, Geotrichosis, Sporotrichosis, Chromoblastomycosis were reported as rare.

VI. FUNGI IN ORAL MICROBIOME:

Fungal organisms present in both healthy and diseased individuals. They are commonly present in subgingival biofilms of the oral cavity and is more prevalent in HIV- seropositive patients, Cancer, Diabetes patients and also in patients with chronic periodontitis[6]. A study done by Siqueria and Rocas found the relationship between candidal species and bacteria around the root surface of patients with periodontitis. They also observed that those fungi colonize the dentinal tubules and results in endodontic infections. Fungus like C. albicans are interlinked with bacterial species such as Streptococcus and Fusobacterium which are frequently associated with periodontal infections[7].

Several features of candidal biofilms are associated with bacterial biofilms which plays as significant role in periodontal and oral infections. Dental prosthesis is one of the major sites for bacterial and fungal colonisation[8]. Some oral infections like Candida associated Denture stomatitis and Angular stomatitis are caused by Candida and they are also interconnected with some bacterial species such as S. aureus, E. coli and Klebsiella etc, of which, C. glabrata is very commonly found in denture wearing and angular stomatitis patients. Candida cause dental implant failure in association with some bacterial microbiota[9].

Saliva plays an important role in oral health and hygiene maintenance by means of cleansing, lubricating and buffering actions. Salivary proteins like lactoferrin and lysozyme promotes defence and antifungal regulating effects on candidal organisms. Other minor proteins like histatins, lactoperoxidase and estaterins exerts cytotoxic effect on fungi and bacterial organisms[10].

VII. FUNGI IN SUBGINGIVAL MICROBIOME:

There is an availability of scanty information in concern of fungal involvement in periodontal diseases. Derangements in the periodontium occurs due to imbalance between immune response and host tissues. Periodontal inflammation may be related with fever and sepsis because ulcerated pocket epithelium act as a gateway for entry of micro-organisms and dissemination of such organisms in bloodstream. Breakdown of immunoglobulins causes periodontal breakdown due to release of toxins and antigens released by the subgingival microbiota[11]. This in-turn results in colonisation of different microorganisms such as candida in subgingival microbiome. A study done by Slots et al- 1988, Dahlen and Wilstrom- 1995 found that C.albicans in periodontal pockets may presents from 7.1- 19.6% patients with chronic periodontitis.

Jarvensivu et al done a study to determine the extent of C-albicans in periodontal tissues of chronic periodontitis patients. He found the presence of hyphae into the periodontal tissues through immunohistochemistry[12]. Presence of fungi in the subgingival tissues not only causes periodontal diseases, but also results in Candidiasis, particularly in immunocompromises patients. Candida is also associated with periodontal pathogens such as A.A. comitans, P.gingivalis , T.forsythia etc.. to cause periodontal destruction[13]. Candidal species can be isolated from different manifestations of periodontal pathogenesis like in chronic periodontitis, in aggressive periodontitis, diabetes, periodontal pockets of smokers, in peri-implantitis etc.

Urzua et al found that colonis of C.albicans and C. dublinienis may present in periodontal pockets particularly in patients with chronic periodontits[14]. In a study, it was found that in diabetic patients, 57% C.albicans, 75% C.dubliniensis, 16% C. tropicalis and 5% C. glabrata seems to be present in the periodontal pockets of the

patients. AIDS is one of the most common opportunistic infection caused by fungi, One study observed that 42.3%, HIV - positive children and 7.1% in control individuals were present with candida spp. in their subgingival sites[15].

VIII. NON-YEAST FUNGI IN ORAL CAVITY

Non -yeast fungus is extremely rare in periodontal tissues and oral cavity. Fungal infection like Histoplasmoses (Histoplasma capsulatum), Blastomycosis (blastomyces dermatitides), Coccidioidomycosis (coccidioides immitis),
Paracoccidioidomycosis (paracoccidioides brasifiences) which are having their initial habitat in oral cavity. Sporotrichosis (sporothrix-schenckii) rarely present and can be extracted from the oral cavity. Aspergillus can be isolated from mouth of the immunocompromised patients. Other fungal species like Geotrichum candidum, Rhizomucor, Rhizopus and Absidia can also rarely isolated from oral cavity, particularly from diabetes patients[16].

Mucormycosis is one of the aggressive, invasive, potentially devasting opportunistic fungal infection which belong to the class- Zygomycetes and family- Mucoraceae. Common causes for mucormycosis are severe hematological disorders, uncontrolled diabetes mellitus, renal insufficiency, organ transplants, malnutrition etc.,mainly due to neutrophilic defects. Mucormycosis of oral cavity occurs due to the extension of rhinocerebral type and also by local invasion of mucormycosis in periodontal tissues.
Periodontal Mucormycosis is an extremely rare condition. In 25 years of literature, only 6 cases have been reported in periodontal mucormycosis[17].

IX. ROLE OF VIRULENCE FACTORS IN PATHOGENESIS OF FUNGI

Candida exhibits various virulence factors to cause infections. Some of them are,

1. Biofilm formation
2. Adhesion and invasion
3. Secretion of hydrolases
4. Dimorphism
5. Thigmotropism
6. Coaggregation with other microorganisms
7. Presence of hemolysin
8. Phenotypic switching

BIOFILM FORMATION:

Biofilm is formed in the form of biotic (mucosa) or abiotic (dentures) surfaces.
Sequence of biofilm formation:

Adherence of yeast cells to substrate

↓

Proliferation of yeast cells

↓

Formation of hyphal cells

↓

Accumulation of extracellular matrix

↓

Dispersion of yeast from biofilm matrix

Antimicrobial drug resistance is seen with fully matured biofilms[18].

ADHESION AND INVASION:

i) ADHESION:

Adhesion between candida spp and other microorganisms (biotic/ abiotic surfaces) is done with the help of adhesins. Adhesins are specialised proteins.
Eg: Hyphae associated GPI- linked protein (Hwp 1)[19]

Nikawa.et al found the high adherence rate of c. albicans, c. tropicalis, c. glabrata to gingival epithelial cells and compared with gingival and pulmonary fibroblast cells. Fungal adhesion (candida spp) is further enhanced by factors like large amount of carbohydrate, acidic ph etc.[20]

ii) INVASION:

Endocytosis and active penetration are the two mechanisms occurs in host cell invasion. Endocytosis is mediated by Als3 and Ss91, where active penetration is by some molecular mechanisms[21].

SECETION OF HYDROLYTIC ENZYMES (HYDROLASES):

Hydrolytic enzymes are secreted by the microorganisms, extracellularly. Some of them are phospholipases and proteinases (Secreted Aspartyl Proteinases/ SAP protein). These enzymes facilitate active entry of candida. spp into the cell.

Phospholipases causes cell death by destruction of cell wall phospholipids and facilitate candidal adherence to tissues. SAP bypasses host immune response and causes tissue damage[22].

DIMORPHISM:

Fungi can exist in 2 forms- Yeast and hyphal form and these two forms plays a major role in its pathogenesis. Hyphal form dealt with adhesion and invasion

THIGMOTROPISM (Directional growth of hyphae):

This is one of the property of fungi to sense and respond to changes in surface contours. It helps the pathogenic fungi to locate entry site for producing infection and to initiate invasive growth. It is being balanced by extracellular calcium channels by uptake of calcium.

COAGGREGATION WITH OTHER MICRO ORGANISMS:

It is the interaction between the fungal species with other microorganisms, which is needed for the development of periodontal pathogenesis.

A study done by Thein et al reported that there may a depletion of fungal yest count, when they were cultured with some periodontal pathogens like p gingivalis and p. nigrescens, which is due to the metabolites released by such anaerobic organisms. It may be helpful in the assesment of efficacy of antifungal drugs[23].

HEMOLYSIN:

Hemolysin is another one important virulence factor. Hemolysin secretion is influenced by iron deposition and in raised blood glucose levels (diabetes)[24]

PHENOTYPIC SWITCHING:

Phenoytypic switching in fungi is defined as the spontaneous emergence of the colonies with altered colony morphology at rates higher than the somatic mutation rates (SOLL-1992). It enables the microorganisms to undergo microevolution (SILVERMAN ET AL- 1979 & SLUTSKY ET AL -1985).

It is a reversible process which enables phenotypic heterogeneity. Whole pathogenic flora is influenced by phenoytypic switching whereas, small population of pathogen like fungal hyphae may altered by a process called 'switching'.

X. DIAGNOSIS OF FUNGAL INFECTIONS:

Prior and proper diagnosis is crucial for proper treatment. For that, knowing the virulence of fungal pathogens is very essential. Some common and important diagnostic methods for fungal infections include standard microscopic examination, histopathological examination and culture & antifungal susceptibility.

Staining techniques like periodic acid- schiff (PAS) is used commonly. Other special stain called grocott- gomor methenamine stain is used especially in diagnosis of mucormycosis, histoplasmosis, blastomycosis etc.[25]

Culture media frequently used are Sabouraud dextrose agar (SDA), chloramphenicol, cycloheximide media, blood agar and malt agar which are incubated at 28^0c± 37^0c for 2-3 days(yeast) or 1-2 weeks (dermatophytes).

Now-a-days, molecular diagnostic techniques are gaining popularity. Immune molecular procedures aid proper and rapid diagnosis and overcome the disadvantages of conventional methods. Some methods include enzyme immunoassay, immunohistochemistry, direct fluorescence antibody and PCR are being helpful in spotting of fungal infections. PCR is useful in detection of fungal DNA. A Blend of biomarkers also plays a magnificent role in clinical diagnosis.

XI. ANTIFUNGAL AGENTS IN ORAL AND PERIODONTAL INFECTIONS

Fungal infections can be treated generally in 2 manners- superficial and systemic. Superficial fungal infections can be treated by topical agents depending upon the nature and extent of infection. Systemic fungal infections can be treated by prophylaxis or empirical management. Some commonly used antifungal agents includes Polyenes (Amphotericin- B, Nystatin), Allylamines (Terbinafine), Imidazoles (Ketoconazole, Miconazole), Triazoles (Fluconazole, Itraconazole, Voriconazole, Posaconazole). Topical administration of imidazoles or allylamines for 2-4 weeks generally gives best results for superficial infections. 200-400 mg/day

of itraconazole for 1 week or 250mg/day of terbinafine for 2-4 weeks are also effective regimen for superficial fungal infections.

Antifungal agents used in dentistry acts by either fungicidal or fungistatic (PFALLER- 2012, KANAFANI& PERFECT- 2008). Commonly used agents in dentistry are fluconazole and/or nystatin and the choice of drug depends upon its efficacy and its resistance. Triazoles like Voriconazole, Posaconazole and Echinocandins like Anidulafungin, Caspofungin and Micafungin are used for prevention and treatment of oral and periodontal infections (MATTIUZZI & GILES- 2005).

Nystatin oral suspension (1,00,000 IU/ml) is the chief agent for oral candidiasis. The additive effect of Clotrimazole (10 mg) and fluconazole (100-200mg) or flucytosine oral suspension (10 mg/ml) gives beneficial effects in oropharyngeal candidiasis[26].

Although C. albicans seems to be resistant for antimicrobial drugs because of its contribution in bacterial biofilm formation. According to NETT ET AL-2011, the biofilm matrix ceases the penetration of drug by creating a barrier. Some studies have found that C. albicans present in outer layer of the bacterial biofilm acts as a barrier against antifungal and antimicrobial agents, thereby preventing the resolution of inflammation. Major antifungal agents like amphotericin- B, fluonazole, ketoconazole and newer azoles like voriconazole and ravuconazole are also unsuccessful against biofilms. Whilst, Echinocandins and lipid formulations of amphotericin- B seems to inhibit metabolic effects in C. parapsilosis biofims[27].

A Study done by FURLETTI ET AL, reported that C. albicans in periodontal pocket shows resistance to amphotericin- B, but sensitive to fluconazole. This resistance is because of the upregulation of efflux genes or inaccessibility of the drug into the periodontal pocket[28]. Fluconazole in low doses can be given as prophylactic agent in immunocompromised patients as a halt in fungal infections.

WALTIMO ET AL observed the susceptibility of C. albicans to antifungal agents in periodontal pockets and found that 100% of fungal isolates were susceptible to 5- flucytosine and amphotericin- B[29].

XII. MYCOSES AND COVID-19:

Corona virus 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome (SARS-COV-2). This virus mainly affects immunocompromised patients, who are having higher chances of getting fungal infections. The pathology behind this infectious disease is the upregulation of inflammatory mediators, decreased T- cell count, deranged immune response etc., which further increase the sensitivity to fungal infections. Common fungal infections seen in patients with COVID-19 are aspergillosis, candidiasis, mucormycosis, and cryptococcosis. If these infections kept untreated, may lead to severe complications and even death. So early diagnosis and prompt treatment will help to prevent severe illness against those infectious diseases. Candidiasis and mucormycosis are common in oral cavity of COVID-19 patients

XIII. CANDIDIASIS IN PATIENTS WITH COVID-19

Causes of fungal infection in COVID-19 patients are usage of broad-spectrum antibiotics, invasive examinations, IV nutrition feeding, patients with neutropenia etc.,[30] The gold standard diagnosis for invasive candidiasis in COVID-19 patients is blood culture. According to Guidelines of Infectious Diseases Society of America-2016, the treatment option for invasive candidiasis includes Echinocandins (caspofungin, micafungin), azoles (fluconazole, voriconazole), and amphotericin-B[31].

XIV. MUCORMYCOSIS IN PATIENTS WITH COVID-19

COVID-19 associated mucormycosis is not so habitual than other fungal infections. Causes of mucormycosis in COVID-19 patients include invasive drug therapy such as high dose steroids, and some immunosuppressive drugs like tocilizumab, prolonged neutropenia, diabetes mellitus, IV infusion of Allo-HSCT (Allogenic Hematopoietic Stem Cells) etc[32]., Treatment recommendations for COVID-19 associated mucormycosis include advanced surgical treatment along with systemic antifungal agents. According to European Confederation of Medical Mycology (ECMM) & Mycoses- 2019, Posaconazole suspension and Amphotericin-B lipid complex are used for first- line monotherpy[32].

XV. CONCLUSION

Fungal organisms like candida are omnipresent, which frequently colonize oral cavity surfaces in both healthy and diseased individuals. Certain noxious factors like biofilm formation might cause the activation of fungal virulence components and leads to periodontal destruction. Another one key factor is the conglomeration of fungal yeast with periodontopathogenic bacteria in subgingival biofilm of periodontal pockets, which also results in periodontal diseases. Its resistance to antifungal and antimicrobial drugs is also a key factor. Even though many literatures have put forth the relationship between fungi and periodontal diseases, its being unclear in revealing of its clinical significance. So, in future further studies will be required for disclosing exact pathogenesis of fungi in periodontal diseases.

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