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Review Article

Candida in health and disease -A review

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Abstract: Candida is a relatively common inhabitant of the oral cavity, skin, gastrointestinal tract and vagina of clinically normal individuals. So the mere presence of the fungus is not just sufficient to produce the disease. There must be actual penetration of the tissues, although such invasion is usually superficial and occurs only under certain circumstances. Oral health is of the individual is dependent on the integrity of the mucosa, which normally prevents the penetration of microorganisms as well as macromolecules that might be antigenic. Innate, humoral and cell-mediated immunity (CMI) are all involved in protection against C. albicans infections. This review article aims at the role of Candida in both health and disease conditions, which involves the immunity and the host defence mechanisms against Candida species, especially the Candida albicans.
Keywords: Candida albicans, cell-mediated immunity, oral cavity.

INTRODUCTION

The mouth contains a plethora of organisms. The oral cavity harbours hundreds of different microbial species. This complex microflora show great quantitative and qualitative variation at different locations within the oral cavity. The saliva contain pigmented and non pigmented micrococci, some of which are aerobic, gram positive aerobic spore bearing bacilli, coliformis, proteus, Lactobacilli [1].

Anaerobic micrococci, microaerophilic and anaerobic streptococci, vibrios, fusiform bacilli, corynebacterium species, actinomyces, mycoplasma, nisseria, bacteriodes are all found in varying extent [1]. Among fungi, it is Candida which is present in the normal flora, skin, gastrointestinal tract and vagina of clinically normal persons. Thus it appears that the mere presence of the fungus is not sufficient to produce the disease. There must be actual penetration of the tissues, although such invasion is usually superficial and occurs only under certain circumstances [2].

The disease caused by it is said to be the most opportunistic infection of the world[2]. In oral cavity and skin of healthy individuals, among 8 species of the candida, it is Candida albicans which is present, where as in GIT it is C. krusei and in vagina it is C. glabrata predominantly present[3].

ORAL CAVITY

The mean carriage rates of Candida albicans for normal persons and patients are 18% and 41%, respectively. Carriage of yeast is also influenced by age; the highest incidence is approximately 50% in infants from 1st week to 18months of age, followed by adults with a mean carriage age rate of 20%. The neonates and children have the lowest carriage rates at 16% and 9% respectively[4]. Healthy subjects who are Candida carriers have approximately 300 to 500 colony- forming units per millimeter of saliva[4,5]. The number of colony-forming units has a diurnal variation, with higher counts, in the early morning and late afternoons[7]. Organisms are more prevalent on the tongue, followed by the palate and buccal mucosa[6]. Tissue bearing surfaces of removable dental appliances exhibit a much higher concentration of organism than those of known occluded mucosa[8].

IN HEALTHY PEOPLE

Commensal existence of oral candida is seen both in healthy non-dentulous and dentulous population, as growth on surfaces is a natural part of the Candida lifestyle.

The well-known factors involved in the adhesion of Candida to the mucosa and to the acrylic

resin base, the factors are (1) cell wall component of the Candida[3] (2) Saliva (3) Dentures (surface free energy, surface roughness, hydrophobicity of the cell surface, denture liners),[9] Candida species shift, bacteria and Candida interactions[10].

Cell wall component of the Candida:

Cell walls of Candida albicans, the best-studied species, include mannan, glucan, mannoproteins, chitin and proteins[3].

Proteins of the cell wall have not been chemically characterized but are important in adherence to buccal epithelial cells, and most likely in adherence to endothelial cells, monocytes, subendothelial matrix, and plastic as well. All the adherence properties of the Candida are most marked with C. albicans, rather than other species, and with pseudohyphae, rather than blastospores. Growth conditions, including source of carbon, also influence adherence in some systems[3].

SALIVA

The role of human saliva in the Candida adhesion process is still controversial. Saliva shows a physical cleaning effect and innate defence molecules, including lysozyme, histatin, lactoferrin, calprotectin and IgA interact with Candida species, thereby decreasing adherence to and colonization of oral surfaces. Other components in whole saliva, including mucins, stathein and proline-rich-proteins have been reported to adsorb to C. albicans thereby facilitating adherence to saliva-coated acrylic resins[10].

Studies have shown that where patients with low or impaired salivary flow presented with higher Candida species counts when compared with saliva from patients with normal salivary flow. Collectively this confirms the regulating role of saliva in inhibiting Candida species adherence[10].

The nature of the substratum may influence the formation and the composition of the salivary pellicle, which layer may then become more relevant than the surface properties of the dental material itself. It has been shown that saliva immersion decreases the surface roughness and surface free energy of acrylic resins. This might explain the general decrease of Candida species in those studies where specimens are coated with saliva[10].

RELATIONSHIP TO ORAL HYGIENE

Candida species have frequently been isolated from the oral cavities of a variety of patients, such as elderly people, denture users, immunocompromised and health patients. Yeasts may be associated with immune response and local factors such as poor oral hygiene[11].

Denture wearing patients have colonization in the oral cavity by Candida species and other microorganism. Reports and studies have shown that tongue cleaning has reduced the degree of coating, does not significantly reduce the Candida species. Menon and Coykendall [12] and Quirynen et al. [13] who reported small changes in bacterial load after tongue scraping[14].

There is difficulty in reducing the bacterial load on the tongue is not suprising, considering the surface characteristics of the tongue dorsum. Quirynen et al. [14] related that the tongue has innumerable depression on the surface which are considered ideal niches for bacterial adhesion and growth, sheltered from cleaning actions. Another theory is that patients may re-contaminate the oral cavity by the use of infected cleaners. Another hypothetical theory state that bad maintenance of the denture causing candidal colonization. These factors may justify the low reduction of saliva and tongue coat Candida species after tongue cleaning[11].

Studies have demonstrated a higher frequency of denture stomatitis in patients not cleaning their denture properly[15]. In their study Kulak et al[16] found a statistically significant relationship between denture stomatitis, yeasts presence and denture cleanliness[15].

Jeganathan et al. [16] studied Asian edentulous population and observed a significant relationship between denture cleanliness and the presence of denture stomatitis.

Sadomari et al [17] investigated 643 denture wearers and found out that soaking dentures in denture cleanser reduced the degree of denture stomatitis and dental plaque.

Thus denture stomatitis is more frequent in patients with poor denture hygiene. Therefore, the patients should be instructed carefully on denture hygiene and denture cleaning habits [18]. Health programs should be developed to instruct the patients about oral hygiene, good, conservation of dentures and tongue cleaning to prevent re-infection [11].

RELATIONSHIP TO DENTULOUS AND EDENTULOUS STATE

Wearing removable dental prosthesis causes an alteration in the oral micro flora[19]. For certain individuals; this new environment is responsible for the development of a particular condition: dental prosthetic stomatitis or denture associated stomatitis[20].

Despite therapeutic progress, opportunistic oral fungal infectious diseases have increased in prevalence, especially in denture wearers. The combination of entrapment of yeast cells in irregularities in denture-base and denture-relining materials, poor oral hygiene and several systemic

factors is the most probable cause for the onset of the infectious diseases. Hence colonization and growth on prostheses by Candida species are of clinical importance[21].

Commensal existence of oral Candida species varies from 20% to 50% in a healthy dentulous population. As growth on surfaces is a natural part of the Candida lifestyle, one can expect that Candida colonizes denture. Candida adheres directly or via a layer of denture plaque to denture base (polymethylmethacrylate- PMMA). Without this adherence, micro-organisms would be removed from the oral cavity when saliva or food is being swallowed[21].

In edentulous patients denture stomatitis is commonly associated, presenting diffuse or punctuated erythematous areas, besides other unspecific aspects mainly observed on the palate. Soft tissue alterations are sometimes associated with angular cheilitis, glossitis, and burning sensation, although a great number of patients do not refer any symptom[22].

Budtz - Jorgensen, compared C. albicans samples from patients with and without prosthetic stomatitis, suggested that the pathogenecity of the yeasts could be related to the enzymatic activity, even when an association between the proteolytic activity in vitro and the severity of the lesions has not been observed. Proteinase production can interfere in the pathogenic potentiality of bacterial components of plaque through cleavage of salivary antibacterial immunoglobulins [22].

Kreher et al reported that isolation of yeasts is positive in edentulous patients without denture stomatitis (DS). C. albicans, C.krusei, C.glabrata and C.tropicalis are identified in association with C.glabrata, which are results similar to those of Budtz-Jorgensen, although C. tropicalis and C. guilliermondii are not observed, in their study suggesting that a variability of species can occur also in totally edentulous patients without DS[22].

In relation to the enzymatic activity of C. albicans, the high level of protienase production suggests that this enzyme can play a role in the establishment and maintenance of DS. Thus C. albicans are the most frequent yeasts along with other species seen in complete denture wearers presenting DS, compared with patients without DS [22].

Host Defence Mechanism against Candida albicans

Oral health is dependent on the integrity of the mucosa, which normally prevents the penetration of microorganisms as well as macromolecules that might be antigenic[23].

Innate, humoral and cell-mediated immunity (CMI) are all involved in protection against C. albicans infections. Although each may contribute to some entent at any tissue site, innate immunity by polymorphonuclear leukocytes (PMNL) and macrophages dominates protection against candidaemia, whereas CMI by T-cells and cytokines predominantly protect the mucosal tissues from infection[23].

The mucosa is protected by two independent immune systems, the systemic immune system and secretory immune system. The oral cavity is part of the secretory or mucosal immune system that can be stimulated locally or systemically[23].

Candidiasis is of particular interest because potentially both the secretory and systemic immune systems may be involved in the maintenence of oral health[23].

SECRETORY IMMUNE SYSTEM

It is a system of local immunity that protects mucosal surfaces and that can be stimulated independently of systemic immunity. The system comprises the secretions bathing the mucous membranes of the body and their associated glands[23].

The epithelium of the oral cavity contains all the required cellular elements to mount and to maintain effective immune responses. Antigen presentation can occur through Langerhans cells in the epithelium, or if antigens penetrate to the connective tissue, cells of macrophage lineage can be found in abundance. CD1 positive cells can be found within the basal layers and up to the stratum spinosum. Intraepithelial lymphocytes can be found in the normal oral mucosa, usually close to the basal cells. Both CD4 and CD8 positive cells are present in approximately equal numbers. It thus appears quite possible that antigen presentation to lymphocytes can take place within the epithelium[23].

In saliva the antibodies can be induced by local immunization, that is, directly into or near the glands, or alternatively by stimulation of gut –association lymphoid tissue either by ingestion or deposition of antigen in the small bowel. This leads to the release of IgA precursor cells from the Peyers patches that selectively migrate to (or are selectively retained in) mucosal tissues that have passed through mesenteric lymph nodes and the thoracic duct. Subsequently local immunization leads to the proliferation of these cells, recruitment of others, and an enhanced local SIgA response. It is possible therefore that antibodies to Candida found in the saliva may actually have been stimulated in some other mucosal site[23-24].

Salivary gland lymphoid tissue, particularly that surrounding minor salivary glands (duct-associated lymphoid tissue) is thought to play a role in local

production of secretory antibody [23,24]. Minor salivary glands contribute only about 10% of the total volume of saliva, but as the secretory IgA contents is much greater than found in the main salivary glands [25,26] the contribution to the total salivary IgA could be as great as 25%. It is possible that direct access of bacterial and fungal antigens in the oral cavity to lymphoid aggregates can occur through the short ducts of the minor salivary glands. Thus, it may be important to analyze responses of minor as well as major salivary glands when assessing immune responses in the oral cavity. It should also be noted that in addition to saliva from major and minor salivary glands, fluids from serum can be present in the oral cavity in sufficient concentration to seriously entertain the possibility that some of it may be functional. It has been calculated that between 1 and 2ml of serum comes into the oral cavity per day via crevicular fluid (in dentate persons) or inflammation. Thus, if the total volume of saliva produced per day is between 750 and 1000 ml and if serum IgG is active at a concentration of 1:500, it could act throughout the oral cavity[23, 27].

Secretory IgA and cellular immunity might play a role in protection of oral mucosal surfaces against candidal infections. Candida organisms are present as commensals in the mouths of 40% of healthy subjects, it can be assumed that in the immunocompetent dentate adult, local defense mechanisms are sufficient to prevent infection by Candida, which is of low innate pathogenicity. The skin and mucous membranes of human beings not only present formidable barriers to most pathogenic microorganisms but are protected by various antimicrobial factors in their secretions. The species C. albicans is not considered to be a normal member of the commensal flora of the skin but can be present on mucous membranes [23, 28]. Non-immune host factors such as the continuous shedding of surface epithelial cells may play a role in limiting surface adherence and infection as well as nonspecific antibacterial factors in saliva such as lactoferrin, a chelating agent that competes with oral microorganism for free iron radicals that are apparently essential for bacterial and fungal multiplication[23].

As well as containing specific antibodies, saliva has a nonspecific role in oral mucosal health by its buffering and washing effects. Salivary flow dislodges yeasts and bacteria from mucosal surfaces and brings the nonspecific antimicrobial factors including lysozyme, lactoperoxidase, histatins, calprotectin and lactoferrin into contact with the microbes. Calprotectin is normally produced in granulocytes, monocytes, macrophages, and mucosal squamous epithelium[23, 29].

MECHANISM OF ACTION OF SALIVARY IgA:

The main actions of secretory antibodies in relation to mucosal microbes are inhibition of adherence, enzymes and growth. In secretions these have to be independent of cells and complement components. The only functional studies with respect to salivary IgA and Candida are those relating to adherence. Candidal species are able to adhere to human oral and vaginal epithelial cells and adherence to oral epithelial cells, is enhanced by whole saliva in comparison with saline[23, 30] Salivary IgA (SIgA) antibodies to whole cells of Candida do seem, however, to be able to inhibit the adherence of candidal cells to oral mucosa. As salivary antibodies are raised in those patients with oral candidal infections, they are not effective in vivo in limiting infection. However, it is possible that in common with most infections there is a critical concentration of fungi above which salivary antibodies are ineffective. A further factor in the balance between carriage and infection may be the production of specific factors from the fungi. Strains of C. albicans and C. glabrata isolated from the oral cavity have been shown to produce IgA proteinases that were able to degrade IgA1, IgA2, and SIgA, probably by cleaving inter- α-chain disulphide bridges[23, 31]. It is possible that strains producing such proteinases may be more pathogenic on mucosal surfaces than those that do not[23].

SYSTEMIC IMMUNE RESPONSE

Serum antibodies against whole cells or Candida antigens are present in the sera of most persons[23,32]. This probably reflects the fact that not only is Candida present as a commensal in the mouths and other mucosal surfaces, particularly the vagina, of a large number of persons, but also that antigens from Candida are able to stimulate a systemic serum antibody response[23].

A wide variety of tests have been used to study serum antibodies, and in early days these did not identify specific isotypes of antibody, such as the agglutination and precipitation tests. These tests nevertheless established a quantitative relationship between the levels of serum antibodies in patients with candidiasis in comparison with controls and thus are potentially useful in diagnosis[23].

Antibody responses are directed against a variety of Candida a ntigens, ranging in size from 18 to 100 kDa. Of particular interest is an antigen of molecular weight 47 kDa because antibodies against this antigen seem to be predictive of recovery from systemic Candida albicans infection[23].

MECHANISMS OF ACTION OF SERUM ANTIBODIES

Serum antibodies usually exert biological activity in combination with complement and PMNL. It is probable that antibody and complement acting alone, that is, without cells, cannot kill Candida. Serum antibody to Candida can act as opsonins for PMNL and for macrophages and by complement fixation generate

chemotactic factors, particularly C3a and C5a, which attracts these cells to the site of infection. There appears to be receptors for complement components on both the host PMNL and macrophages and on the Candida cells. The former assists in immune adherence, but the role of the latter is as yet unclear[23].

INNATE IMMUNE RESPONSE

PMNL are considered to be the predominant host defence mechanism against Candida in the systemic circulation. This is evidenced by the high incidence of invasive and systemic candidiasis in neutropenic patients and those with qualitative neutrophil disorders[24].

CONCLUSION

The most important method of preventing oral candidiasis is by strengthening the immune system. Other preventive measures include use of antifungals, smoking cessation, good oral hygiene, avoidance of unnecessary antibiotics, alcohol, sugars and steroids, ill-fitting dentures should be corrected.

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