Review Article

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HOST FACTORS AND ORAL CANDIDIASIS: A REVIEW

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ABSTRACT:

Various host factors has been implicated in the pathogenesis of oral candidiasis. *Candida albicans* is a dimorphic fungus that causes severe opportunistic infections in humans. Species of the genus Candida comprise part of the oral commensal microflora of healthy individuals,with Candida albicans being the most common pathogen of the genus. This article focuses on various local, systemic and miscellaneous factors affecting oral candidiasis.

Keywords: Oral candidiasis, Host Factors

INTRODUCTION:

The epithet "disease of the diseased" is given to the candida infections because it occurs when host defenses are inadequate. Thus the host factors are of utmost significance for development of disease state since candida species turn pathogens only when host system becomes functionally inadequate[1]. (Figure 1)

Local host factors for Oral Candidiasis

Mucosal barrier

The mucosal epithelium is the primary cell layer that initially encounters the majority of micro-organisms. During the period of colonization of C. albicans, extensive fungal growth is limited through the release of antimicrobial peptides from epithelial cells, or due to the existence of other bacteria of the microbial flora. However, during oral infection with *Candida*, many pro-inflammatory cytokines (IL-1α, IL-1β, IL-6, IL-8, TNF, GM-CSF, and others) are secreted by oral epithelial cells, which maintain a central role in the protection against fungal organisms. These cytokines regulate leukocyte trafficking and/or activate a strong antifungal response by these cells.[2,3] In addition, oral epithelial cells are capable of inducing antimicrobial peptides, such as defensins,cathelicidins, and histatins which control *C. albicans* growth and infection.[4] Among these peptides, human β-defensin-2 (hBD-2), hBD-3 ,LL-37 and histatin-5 exhibit potent anti-candidal properties.[5,6,7] The oral epithelium can induce an immune inflammatory response to activate myeloid cells in the submucosal layers to clear the invading pathogens . Weindl et al

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had reported the divison of experimental oral infection into 3 stages: an attachment phase of C.albicans, an invasion phase and tissue destruction.[21] Recognition of *C. albicans* by the mucosal host defense system is mediated by Pattern-recognition receptors (PRRs). PRRs includes Toll-like receptor (TLR), C-type lectin-receptor (CLR), Nacht like receptor (NLR) families and RLRs (RIG- like receptors).[8,9] C.albicans causes suppression of TLR 4 and does not stimulate cytokine production. A new PRR, Dectin-1, has been attributed to phagocytosis whereas TLR2 (Phospholipomann) has been known to induce cytokine production. Several extracellular and transmembrane CLRs—including the mannose receptor (MR), Dectin-2, dendritic cell-specific intercellular adhesion molecule 3-grabbing nonintegrin (DC-SIGN), galectin -3, macrophage-inducible C-type lectin (Mincle)—are involved in antifungal immunity, although their roles have not been completely understood.[10] Importantly, these receptors mediate fungal binding, uptake, and killing and also contribute to the initiation and/or modulation of the immune response to these organisms.

Saliva

The constant flushing action of saliva essentially removes the unattached or loosely attached candida from the oral cavity. Furthermore, the secretory IgA component of saliva is thought to inhibit candidal adhesion to host surfaces. In addition saliva contains antifungal factors such as lysozyme, lactoferrin, lactoperoxidase and histidine rich polypeptides, all of which keeps control of candidal colonization. Specifically, the host salivary antimicrobial peptide histatin-5 (Hst-5) has been proposed to play a protective role in the oral cavity against C. albicans.[25]The important role saliva plays as a front line defense mechanism is exemplified in clinical situations where the quantity and quality of saliva is affected. Tanida et al. in 2003 conclusively suggested that OC is associated with salivary gland hypofunction and that decrease of salivary antibacterial proteins induce candida overgrowth [11]. They also concluded that salivary levels of hbd-1 and hbd-2 are lower in patients with OC as compared to healthy patients.

Dietary carbohydrates

Candidal adherence to either epithelial or denture acrylic surfaces is markedly enhanced in the presence of dietary carbohydrates, including glucose and sucrose.[12,13] This enhanced adhesion is thought to be due to, a sticky extracellular fibrillar layer analogous to bacterial fimbriae whose importance in adhesion is widely recognized [13].

Trauma

The integrity of oral mucosa may also be breached by a variety of factors, the most important of which appears to be the presence of prosthesis such as denture. It is likely that continuous maceration of the oral mucosa consequent on a well fitting maxillary denture may result in microscopic breaches of the epithelium.

Systemic factors which predispose to oral candidosis

Infancy

The usual delay before the onset of thrush in neonates is about 4 days .Contributing factors are immature immune defenses, antibiotic therapy, congenital defects (thymic aplasia), maternal cross infection and cross infection from nursery staff.[12]

Old age

The disease and therapeutic procedures (antibiotic and corticosteroid therapy) associated with old age may lead to oral candidosis.[14] The presence of prosthesis is another key factor, which promotes oral yeast colonization and subsequent morbidity. It is also known that oral colonization of candida is minimal in individuals who are totally edentulous prior to insertion of dentures, but that carriage rate tends to increase shortly after prosthesis is worn.[15]

Altered hormonal state

Conditions such as hypothyroidism, hypoparathyroidism and adrenal insufficiency can lead to oral, vaginal, cutaneous and systemic candidosis.[16]

Diabetes and oral candidiasis

Guggenheimer et al in 2000 concluded, candida pseudohyphae and oral soft tissue manifestations of candidosis were more prevalent in subjects with insulin dependent diabetes mellitus than in control subjects without diabetes. The presence of candida was significantly associated with cigarette smoking, use of dentures and poor glycemic control.[17]

Vitkow. Weitgasser, Hannig, Fuchs and Krautgartener in 2003 found a strong relationship between burning mouth sensations and glycaemic disorders. They introduced a term “candida-induced stomatopyrosis”. The perception of burning sensation was hypothesized to occur via stimulation of the capsaicin (vanniloid) receptor by candida metabolites. The candida-induced stomatopyrosis should be regarded as a single symptom indicating type 2 diabetes mellitus in non-inhalers of the concerned population.[18]

HIV and Oral candidiasis

OC and the amount of oral yeast present have been postulated to be predictive of HIV disease progression and viral load. The predominant host factor associated with susceptibility to OC is reduced CD4 cells (< 200 cells/mm^3) in HIV-infected persons as they progress to AIDS. The host pathogenicity factors associated with OC in the HIV-positive patient include reduction in CD4 cells and overgrowth of *Candida*, reduced migration of CD8 cells, Th2-type cytokines in saliva, reduced antifungal activity by oral epithelial cells, reduced histatin-5, increased SAP5 and SAP9, and potentially, *Candida* specific biofilm formation.[19] A greater prevalence of candida dubliensens as compared to candida albicans is found in patients with HIV.

Altered nutritional states

Samarnayake and MacFarlane found a significant number of folate deficient individuals suffering from chronic atrophic candidosis when compared with appropriate control group. Nevertheless, restoration of serum folate to normal levels in these individuals had no effect on the recurrence of this disease, thus demonstrating that folate deficiency in itself may not be a factor in chronic atrophic candidosis. An isolated case of malnourished patient with chronic atrophic candidosis whose oral condition responded to vitamin B-complex and vitamin C supplements has been described.[13]

Iatrogenic factors

Antibiotic therapy

The broad-spectrum antibiotics lead to candidal overgrowth than narrow spectrum antibiotics. The most common broad-spectrum drug associated with oral candidosis is tetracycline.[20] The mechanism by which antibiotics enhance candidal growth is by reducing the commensal bacterial population; as a consequence that yeasts would multiply in an environment free from antagonistic flora and hence replete with nutrients.[13]

Corticosteroid therapy

Corticosteroids promote the oral carriage of candida.[20]The propensity to develop candidiasis is greater if the patient harbors candida intraorally prior to inhaler therapy, that the lesion is generally localized in areas where the aerosol is deposited, and the degree of candidiasis is probably related to dosage and frequency of therapy.[21] The incidence of oral candidiasis secondary to topical oral use of steroids might be expected to be greater than that associated with inhaled steroids, due to greater time of contact in the oral cavity.[20]

The putative mechanism by which inhaled, topically applied or systemic steroids predispose to oral candidiasis has not been fully clarified as yet. There is little doubt that generalized immunosuppressive and anti-inflammatory effects of steroids may play a major role in pathogenesis (Budtz-Jorgensen, 1975). Patients treated with corticosteroids have a high level of salivary glucose and this may also promote the growth, proliferation and adhesion of candida. The effect of steroids on the local production of secretory IgA and other aspects of immune mechanisms is not well understood.[20]

Radiation Therapy

Leung et al in 2000 found that irradiation induced xerostomia seems to favor intraoral colonization of C.albicans which appeared to undergo temporal modifications in clonal profiles both phenotypically and genotypically following hygiene and preventive oral care which include topical antifungal therapy, if indicated. They postulated that observed ability of candida species to undergo genetic and phenotypic adaptation could strategically enhance its survival in the human oral cavity particularly when salivary defenses are impaired.[22]

Spencer et al in 2004 concluded that C.glabrata is an emerging cause of oropharyngeal candidosis in patients receiving radiation for head and neck cancer. Even though appearing clinically identical to those caused by C.albicans, infections with C.glabrata alone and mixed with C.albicans will often require high doses of fluconazole for clinical cure. Previous fluconazole use may be a risk factor for emergence of C.glabrata as an oral pathogen, but not with all patients.[23]

Cigarette smoking and oral candidosis

It has been suggested that cigarette smoking might lead to localised epithelial alteration, which allows colonisation by candida.[24] Smoking may produce a degree of xerostomia that, combined with a reduction in salivary IgA and reduced leukocyte function in smokers, could facilitate inavaion by candida species.[25] C.albicans can also catalyse the formation of carcinogenic nitrosamine N-nitrosobenzylmethylamine in vitro.[20]

Miscellaneous host factors

Materials with the roughest surface usually exhibit higher adherence, because such surfaces provide an increased chance of microbial retention and protection from shear forces.[26] Aging of acrylic and liner surfaces results in increased roughness, and therefore increased attachment.[27] Not only dentures can act as reservoirs of candida species, other inanimate objects that are transiently or permanently present in oral and laryngeal region may act as a nidus for candidal colonization. Thus silicone voice prosthesis and pacifiers or dummies have been shown to promote laryngeal or oral candidal carriage and consequent infection.[20] Candida species have also been reported to adhere in other medical devices like blood and urinary catheters and heart valves.[28] The adhesion to polymer material used in medical devices has been considered due to a specific adhesive known as CaEap 1.

Marchant et al in 200 found that proportions of C.albicans were significantly greater in the carious dentine than in the plaque samples.[29] Roskweicz in 2006 also showed a greater number of C.albicans carriage in schoolchildren with carious teeth.[30] Epstein, Hancock and Nantel in 2003 found a significant relationship among allogenic and autologous hemopoetic cell transplantation, length of hospital stay, and colonization by candida species.[31] Systemic infection by candida was associated with increase in duration and severity of neutropenia, broad-spectrum antibiotic and steroid use, and the number of body sites colonized.[31] Shin et al in 2003 concluded that oral candida carriage was not significantly related to blood group and secretor status of ABH and Lewis blood group antigens in healthy individuals.[32] Hence unequivocal conclusions on blood group secretor status and its relationship to oral candidiasis cannot be reached unless further research is carried out. Tongue piercing has also recently been shown as a risk factor for colonization of C. albicans.[33]

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