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Review article

THE ROLE OF CANDIDA ALBICANS ON THE DEVELOPMENT OF STOMATITIS IN PATIENTS WEARING DENTURES

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Abstract: Denture stomatitis is the most common inflammatory reaction that occurs in people who wear dentures. It is believed that in 60-65% of cases the cause of this inflammation is infections by yeasts from the genus *Candida* (*C.*), primarily *Candida albicans* infection. *C. albicans* is a part of the normal microflora of the respiratory and digestive tract. This yeast has the ability to adhere to the oral mucosa and to the base of the denture, as well as to form a biofilm. Its virulence is especially supported by the state of weakened resistance of the organism, when *C. albicans* expresses its pathological effect. This paper presents the pathogenesis of *C. albicans*-associated denture stomatitis, as well as the most common diagnostic and therapeutic procedures used to diagnose and successful therapy.

Key words: dentures, stomatitis, *Candida albicans*, biofilm, oral hygiene.

INTRODUCTION

Denture stomatitis is a very common inflammatory reaction occurring in the carriers of the dentures and involves the mucous membrane underneath the base of the denture (1, 2). The etiology of this process is multifactorial, but in 89% of cases, the occurrence of denture stomatitis is associated with infection of yeast of the genus *Candida* (*C.*) (3). *Candida* species are microorganisms that form part of the normal microflora of the oral cavity. However, if the condition of the normal flora is disturbed or the general resistance of the organism is reduced, *Candida* species cause inflammation on the surface of mucosa, which is most often ma-

nifest in the form of denture stomatitis in the denture carriers. For the first time *Candida* species were described by Cahn in 1936 as possible causes of this inflammatory process (4). *Candida albicans* is thought to be most responsible for the development of inflammation, although there are studies proving the participation of other yeasts of this strain in the development of oral candidiasis and, therefore, denture stomatitis. Among them there are *C. dubliniensis*, *C. parapsilosis*, *C. krusei*, *C. tropicalis* and *C. glabrata* (5, 6). Their primary localization is on the dorsal side of the tongue and on the oral mucosa, while the biofilm covering the surface of the teeth colonizes secondary (7). Increased use of antifungal drugs in the treatment of candidiasis has lead to that non-albicans *Candida* species can also contribute to the development of this infection (8).

Therapy of denture stomatitis involves the maintenance of adequate oral hygiene, removal of dentures during the night, the use of various disinfectants such as sodium hypochlorite and chlorhexidine, as well as the use of local and systemic antifungal drugs (1, 9). In addition to antifungal agents, in the treatment of *Candida*-associated denture stomatitis, extracts of various plants that have antifungal, anti-inflammatory and antioxidant effect are increasingly applied.

PATHOGENESIS OF DENTURE STOMATITIS ASSOCIATED WITH CANDIDA ALBICANS

C. albicans is a part of the normal microflora of the respiratory and digestive tract. However, in certain

situations, especially in the case of immunodeficiency, it can exhibit pathological effects and cause candidiasis. Factors that contribute to its pathological effect are the ability of this yeast to adhere to mucosal cells, to convert from single cell to filamentous form, to secrete enzymes such as aspartyl proteinase and phospholipase, as well as to build biofilm (10).

The role of *C. albicans* in the development of denture stomatitis is associated with the fact that this yeast has the ability to colonize the oral mucosa and the surface of the dentures and build aggregates with oral bacteria (11). What also increases the incidence of denture stomatitis associated with *Candida* is the fact that the presence of denture reduces the flow of saliva and oxygen to the tissues below the denture base, which increases the local acidity and anaerobic conditions and thus contributing to the growth of yeasts (12).

On the other hand, *C. albicans* has the affinity to adhere to the acrylic from which denture is made, and the acrylic resin possesses certain characteristics, such as hydrophobicity, which accelerates adhesion as a major step associated with the formation of biofilm (12, 13).

Formation of *C. albicans* biofilm goes through three phases. In the first phase, which lasts 1-11 hours, the *C. albicans* cells adhere to the rough surface of the denture, due to the action of hydrophobic and electrostatic forces between the cells and the surface of the denture. In a second phase that lasts 12-30 hours, the biofilm consists of a non-cellular layer or a so-called extracellular polymer substance that covers microcolonies of yeasts, while the third phase is the maturation phase of biofilm occurring within the 38-72 hours (9, 14).

Factors that favoring the adherence and formation of biofilm are the roughness of the inner surface of the dentures, the influence of salivary pellicle, as well as hydrophobic and electrostatic interactions (9).

The rough surface of the acrylate promotes increased retention of microorganisms and protects them from the forces that tend to remove, leaving the microorganisms trapped by the irregular surface of the prosthesis, even after cleansing (15). Also, the traumatic factors such as mechanical trauma caused by loose prosthesis can increase the risk of tissue penetration and colonization of *Candida* species (16). The age of the prosthesis is also an important factor, because it is more difficult to maintain hygiene if prosthesis are worn for a long time and there is a tendency towards porosity of denture base, which favors the occurrence of infection (17).

As for the effect of saliva on *C. albicans* adhesion on the prosthesis surface, this effect is still controversial (7, 16, 18). Saliva plays an important role in mechanical cleansing and contains certain innate immune molecules such as lysosomes, lactoferrin, calprotectin,

and IgA immunoglobulin, which reduce adhesion of *C. albicans* for oral surfaces (2, 19). Increased saliva flow allows the elimination of carbohydrates that are metabolized by bacteria that produce acidic products, and also the buffer saliva system neutralizes these acidic products, as well as the acids introduced through food and drink (20).

On the other hand, saliva proteins such as mucin and statherin act as adhesion receptors for mannoproteins present in *Candida* species (12). Reduction or complete absence of saliva in individuals with xerostomia causes a disbalance in the normal microbiological composition, favoring the proliferation of *Staphylococcus aureus* which inhibits the adaptation of the commensal (21).

A particularly important factor that promotes the adhesion and proliferation of *C. albicans* for oral mucosa and therefore the base plate of the dentures is a low pH in the oral cavity. It is believed that pH 3 is critical, because it provides enzymatic activity of proteinases and phospholipases, which are the main factors of *Candida* virulence, due to their cytotoxic and cytolytic effects (12, 16). It is also observed that the pH value of oral mucosa in the elderly and edentulous patients are significantly lower than in younger and in patients with teeth, because the function of the salivary glands is reduced in the elderly, and this is in favor of the development of denture stomatitis in these patients because they are the most frequent carriers of dental prostheses (22, 23).

Hydrophobicity and electrostatic interactions influence the development of denture stomatitis caused by *C. albicans* by the fact that hydrophobic surfaces reduce cell adhesion, while yeasts whose surface has a positive charge are more adherent unlike the repulsive forces which exist between the negatively charged yeast and polymer surfaces (16).

In addition to numerous local factors responsible for the adhesion and colonization of *C. albicans* for oral mucosa and the base of the denture, there are also certain systemic factors that can accelerate the development of this infection. Particularly important is the state of immunodeficiency, in which *Candida* becomes more virulent and leads to the formation of oral candidiasis, including one or more places in the oral cavity (7). The most significant immunodeficiency are HIV infection, hereditary deficiency of myeloperoxidase and some syndromes, such as DiGeorge's syndrome (12).

Some of systemic factors that can increase a risk of denture stomatitis are diabetes mellitus, long-term use of antibiotics and corticosteroids, as well as kidney diseases (16, 24).

Particularly diabetes mellitus is associated with the onset of oral candidiasis, and consequently in pati-

ents who wear dental prostheses is associated with denture stomatitis (25).

Some studies find that it is not important only the presence of disease how much is important to control glycemic in diabetes, because poorly controlled glycemic will reduce salivary flow and pH in the oral cavity, increasing salivary glucose levels (24). Moreover, besides the presence of a high concentration of salivary glucose combined, low salivary secretion may enhance growth of yeasts and their adherence in epithelial oral cells (26).

Different kidney diseases requiring repeated and prolonged antibiotic therapy and sulphonamide therapy indirectly lead to the occurrence of oral candidiasis and denture stomatitis because these drugs change normal microflora and promote the growth of yeasts (16).

DIAGNOSIS AND TREATMENT OF DENTURE STOMATITIS ASSOCIATED WITH CANDIDA ALBICANS

Denture stomatitis is usually the asymptomatic inflammatory process and in this case it is usually revealed on routine dental examinations in the form of erythema or edema of the mucosa that is in contact with the prosthesis. Symptoms that the patients may complain are halitosis, slight bleeding, and swelling in inflamed area, or burning sensation, xerostomia or any alterations of taste (27). Denture stomatitis can be also associated with some other oral diseases such as medial rhomboid glossitis, atrophic glossitis and angular cheilitis, and these states have been recognized as *Candida*-associated lesions (28).

In general, to establish the diagnosis of oral candidiasis, there are several methods that can be used, such as taking a swab, target tissue biopsy (eg. palate), examining a saliva sample, so which method will be used depends on the nature of the lesion being examined (12). Seeding of samples on the nutrients the presence of yeasts is demonstrated. By increasing the colonies of yeasts on different nutrient media, a diagnosis of the species within the genus *Candida* (*C.*) can be given, however, the detection of hifa (an important factor for invasiveness, adhesion and virulence) by microscopy is for now a "golden" standard for the exact diagnosis of *Candida*-associated denture stomatitis (29).

Although the culture-based identification is the gold standard for the diagnosis of fungal infection, detection and identification of fungal DNA by PCR is one of the most powerful and popular tools for the early detection and identification of pathogenic fungi, including *Candida* species (30). The PCR is the most sensitive of the existing rapid methods to detect microbial

pathogens in clinical specimens. The PCR include several critical steps such as, DNA extraction, PCR amplification and the detection of amplicons (31). On the other hand, conventional PCR has a big impact with very good results in fungal identification, but researchers have difficulties due to the post-PCR steps for amplicon evaluation such as agarose gel electrophoresis (32). Due to it is suggested to use real-time PCR or real-time quantitative PCR (qPCR) assays, because of these methodes allows the researchers to actually view the increase in the amount of DNA as it is amplified and post-PCR manipulation of the amplicon is not required (32, 33).

Although *Candida*-associated denture stomatitis is often asymptomatic, this inflammatory process should be treated properly, because it can act as a reservoir for the development of severe inflammation which consequently leads to bone resorption (12). Therapy approach is complex due to multifactorial etiology, but some basic postulates in the therapy of these changes involve the use of local and systemic antifungal drugs, the use of disinfectants, the maintenance of adequate oral hygiene and hygiene of the prosthesis (7, 9, 16).

The use of antifungal drugs depends on the oral symptoms and the history of the patient's disease. In the case of an uncomplicated inflammatory process, the use of local antifungal drugs, available in the form of gel, lozenge, cream and oral suspensions is recommended (2).

The most commonly drugs used locally are nystatin and amphotericin b, while fluconazole oral suspension is proving to be a very effective drug in the treatment of oral candidiasis. Another topic drugs widely used are miconazole and clotrimazole (34). Mostly all drugs lead to the cessation of symptoms after administration of 12 to 14 days.

Nystatin is the most commonly used drug in oral candidiasis therapy, which is administered four times a day for two weeks in the form of oral pastille and suspension. The oral rinse contains sucrose, so it is useful in edentulous patients and those with oral dryness such as patients receiving radiotherapy and those with HIV infection (26). In some studies, nystatin has been shown to be ineffective for *Candida* lesions in cancer patients (35). In addition, nystatin, myconazole cream (2%) and clotrimazole cream (1%) are also used in the treatment of denture stomatitis associated with angular cheilitis (23). Fluconazole oral suspension is administered in a dosage of 10 mg/ml aqueous suspension by administering 5 ml daily for 7 or 14 days (34).

There have been several studies comparing topical and systemic drugs. Isham N et al. compared the use of ketoconazole tablets (200 mg daily) with topical ketoconazole (2% twice daily) and miconazole muco-

adhesive tablets in the treatment of denture stomatitis (36). Due to the adverse effects of ketoconazole like nausea, vomiting and gastrointestinal problems it has been suggested the use of other drugs when treating candidiasis associated with wearing of dentures (37, 38). Thus the use of miconazole mucoadhesive tablet was established as the drug of first line of defense for this type of candidiasis (34).

The use of systemic antifungal drugs is recommended for severe forms of *Candida*-associated denture stomatitis, when local therapy has not been effective, as well as in immunodeficiency patients. Among systemic antifungal drugs, fluconazole is particularly useful due to low toxicity and good tolerability. The appropriate dose is between 50-100 mg daily (26, 34). On the other hand itraconazole is applied in case of resistance to fluconazole. Ketoconazole is also effective as fluconazole, but its use is not recommended in the elderly due to interactions with macrolide antibiotics and antihistamines, and because of adverse effects such as hepatotoxicity (26). Amphotericin B has previously been administered intravenously in the treatment of *Candida*-associated denture stomatitis, but today its application was reduced due to nephrotoxicity (39).

Antifungal drugs of new generations used in the treatment of oral candidiasis and severe forms of denture stomatitis associated with *Candida* are posaconazole, ravuconazole and echinocandin such as caspofungin, micafungin and anidulafungin. They represent less toxic alternatives than amphotericin B (26).

The aim of the disinfectants used in denture stomatitis is to reduce the formation of biofilm on the prostheses and inhibit the growth of yeasts (12). Especially applied disinfectants are chlorhexidine gluconate and sodium hypochlorite (16). Chlorhexidine gluconate is effective against numerous bacteria, viruses, bacterial spores and against yeasts (12). It can be applied as a 0.2% solution for rinsing the oral cavity, however, much better results are obtained when it is used in the form of a 2% solution for immersing of the prosthesis. However, it is good to have in mind that chlorhexidine reduces the effectiveness of nystatin when it is administered at the same time, so the advice is to use nystatin at least 30 minutes after rinsing the mouth with chlorhexidine (40). Another very effective disinfectant that reduces the formation of *C. albicans* biofilms is sodium hypochlorite, which is used in the form of a 0.2% solution, and it is also advised to immerse the dentures into this solution. However, the use of sodium hypochlorite must be restricted to a shorter period of time because it has the ability to damage the dentures (12, 16).

All therapeutic methods in the treatment of denture stomatitis would not produce results without adequate oral hygiene. Maintenance of adequate oral hygiene and

local application of antifungal drugs in most cases are sufficient for the treatment of uncomplicated oral candidiasis. Oral hygiene includes daily cleaning of teeth, tongue and dental prostheses. Dentures should be removed at night or at least six hours during the day (26).

ALTERNATIVE AGENTS IN THE TREATMENT OF DENTURE STOMATITIS ASSOCIATED WITH *CANDIDA ALBICANS*

In addition to the classic therapy of denture stomatitis associated with *C. albicans*, lately it is increasingly resorting to alternative agents that have less side effects and at the same time exhibit antibacterial and anti-inflammatory activity. There are a large number of preparations based on plants and their essential oils that have an anti-inflammatory effect and as natural antiseptics express antifungal and antibacterial activity (9). Natural compounds from essential oils: eugenol, farnesol, geraniol, linalool, menthol, menthone, terpinen-4-ol, α -terpineol and tyrosol, carvacrol, expressed strong antifungal *in vitro* activity (12).

One of the investigated essential oils exhibiting a remarkable antioxidative and antifungal activity is the thyme oil. Thyme oil is very rich in phenols and is classified as antifungicide due to its strong effect on *Candida* species (41).

Some authors, have shown that timolol as a component of thyme oil possessed pretty strong antifungal activity against *C. albicans in vitro*. In view of its broad activity, thyme essential oil may be used as a natural disinfectant for the prevention of denture stomatitis (42). Omran SM et al. in their study have examined the effect of essential oils on *Candida* yeasts, they found that thyme oil had the highest inhibitory effect (43).

The essential oil of tea tree has a significant effect on *C. albicans*. Pachava et al. have shown that tea tree oil incorporation to denture soft liner decreased *C. albicans* growth significantly (44). Similarly, Amornvit et al. combined lemongrass essential oil to tissue conditioner and demonstrated the anti-*Candida* activity (45).

On forty isolates of *C. albicans* from the oral cavity obtained from twenty-five patients using orthodontic appliance, eight essential oils were applied, the largest antifungal effect was shown by the essential oil of cinnamon, laurel, lemon and mint (46).

It is also considered that garlic in combination with nystatin may be highly effective in the treatment of oral candidiasis, in particular those associated with denture stomatitis (9, 47). Other essential oils that have a positive antifungal effect are the oil of the following plants: *Pelargonium graveolens*, *Satureja hortensis*, *Zataria multiflora*, *Punica granatum*, *Salvia of-*

ficinalis, *Streblus asper*, *Boesenbergia pandurata*, *Phyllanthus emblica*, *Scutellaria baicalensis*, *Azadirachta indica*, *Melaleuca alternifolia* (9, 48).

CONCLUSION

Denture stomatitis is one of the most common inflammatory reactions affecting carriers of dental prostheses, and in most cases it is associated with infection of yeast of the genus *Candida*, primarily with *C. albicans*. Although this is the most common asymptomatic tissue reaction below the prosthesis base, it is important to diagnose the disease as early as possible, otherwise *Candida* would act as a reservoir for more exten-

sive infections that would eventually lead to bone resorption. Treatment of *Candida*-associated denture stomatitis requires the use of antifungal drugs and adequate oral hygiene.

DECLARATION OF INTEREST

The authors declare that there are no conflicts of interests.

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Sažetak

ULOGA CANDIDE ALBICANS U RAZVOJU STOMATITISA KOD PACIJENATA KOJI NOSE ZUBNE PROTEZE

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Protezni stomatitis je najčešća zapaljenska reakcija koja se javlja kod osoba koje nose zubne proteze i obično zahvata palatinalnu sluzokožu. Smatra se da je u 60-65% slučajeva uzrok ovog zapaljenja infekcija gljivicama iz roda *Candida* (*C.*), a prevashodno *Candida albicans*. Ova gljivica ima sposobnost da adherira za oralnu sluzokožu i za bazu protezne ploče, i da for-

mira biofilm. Njena virulencija je naročito potpomognuta stanjima oslabljene otpornosti organizma, kada *C. albicans* ispoljava svoje patološko dejstvo. U ovom radu prikazana je patogeneza proteznog stomatitisa udruženog sa *C. albicans*, kao i najčešće dijagnostičke i terapijske procedure koje se koriste za postavljanje dijagnoze i sprovođenje uspešne terapije.

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