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PROTEZNI STOMATITIS – ETIOPATOGENEZA I TERAPIJSKI PRISTUP

DENTURE STOMATITIS: ETHIOPATHOGENESIS AND THERAPEUTIC APPROACH

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Sažetak

Uvod: Protezni stomatitis je najčešća zapaljenska reakcija koja se javlja kod osoba koje nose zubne proteze, sa najčešćom lokalizacijom na palatinalnoj sluzokoži. Etiopatogeneza zapaljenja je multifaktorijalna i kompleksna. Infekcija gljivicama iz roda *Candida*, prevashodno *Candida albicans*, loša oralna higijena i dugotrajno nošenje proteze su najznačajniji etiološki faktori. Razvoju zapaljenske reakcije mogu doprineti i neki opšti činioci kao što je pušenje, upotreba lekova i sistemske bolesti, poput dijabetesa melitusa. Kako je zapaljenje najčešće bez subjektivnih simptoma, a ima veliku prevalenciju među nosiocima zubnih proteza, poželjno je pacijentima zakazivati redovne preglede kako bi se rano postavila dijagnoza i sprovela adekvatna terapija.

Zaključak. U radu je dat prikaz etiopatogeneze proteznog stomatitisa i najčešće terapijske procedure koje se sprovode pri njegovom lečenju.

Cljučne reči: protezni stomatitis, *Candida albicans*, oralna higijena, zubne proteze

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Abstract

Introduction: Denture stomatitis is the most common inflammatory reaction that occurs in people who wear dentures, localized mostly in the palatal mucosa. Etiopathogenesis of inflammation is multifactorial and complex. Infection by yeast of the genus *Candida*, mainly *Candida albicans*, poor oral hygiene and long-term wearing of dentures are the most important etiological factors. Factors that may contribute to the development of inflammatory reactions are some general factors, such as smoking, use of different drugs, and systemic diseases such as diabetes mellitus. As the inflammation usually goes without any symptoms and has high prevalence among denture wearers, it is desirable for patients to schedule regular examinations to obtain diagnosis early and to receive adequate therapy.

Conclusion. The manuscript presents the etiopathogenesis of denture stomatitis and usual therapeutic procedures that are carried out during treatment.

Key words: denture stomatitis, *Candida albicans*, oral hygiene, dental prostheses

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Uvod

Protezni stomatitis predstavlja zapalje-nsku reakciju koja se sreće kod zdravih nosioca mobilnih zubnih proteza¹. Najčešće se javlja na palatinalnoj i na sluzokoži alveolarnog grebena, koja ostvaruje direktan kontakt sa bazom zubne proteze^{2,3}. Prevalencija se kreće u rasponu od 15% do 75%, dok je incidencija značajno veća kod starijih osoba ženskog pola⁴. Etiologija ovog zapaljenja je multifaktorijalna, a potencijalni uzročnici su: infekcija gljivicama iz roda *Candida*, bakterijske infekcije, loša oralna, loša higijena zubnih proteza, hronična iritacija sluzokože zbog slabe retencije proteze, neprekidno nošenje proteze, alergijske reakcije na materijale koji se koriste za izradu zubnih proteza, imunološki faktori, korišćenje lekova i neka sistemska oboljenja^{1,5}. Još uvek se gljivice iz roda *Candida*, prvenstveno *Candida albicans*, najčešće dovode u vezu sa nastankom ovog zapaljenja¹. Brojne studije pokazuju da dve trećine pacijenata koji nose zubnu protezu pate od ovog oblika zapaljenja⁶⁻⁹. Bez obzira na njegovu učestalost, protezni stomatitis je u najvećem broju slučajeva asimptomatski; mali broj pacijenata oseća bol, peckanje i žarenje, a same promene se primarno dijagnostikuju prilikom pregleda, kada se može primetiti eritem ili edem sluzokože koja je u kontaktu sa protezom¹⁰. Postoji više klasifikacija proteznog stomatitisa, ali je najrelevantnija klasifikacija koju je predložio Newton 1962. godine bazirana isključivo na kliničkim kriterijumima. Prema ovoj klasifikaciji razlikuju se tri oblika proteznog stomatitisa: 1. lokalizovano zapaljenje ili tačkasta hiperemija sluzokože (obično uzrokovana traumom) (slika 1); 2. eritematozni ili generalizovani oblik, koji obuhvata celu ili deo sluzokože koja je pokrivena protezom (slika 2); 3. granularni oblik (inflamatorna papilarna hiperplazija), koji obuhvata središnji deo tvrdog nepca i alveolarni greben (slika 3)¹¹.

Introduction

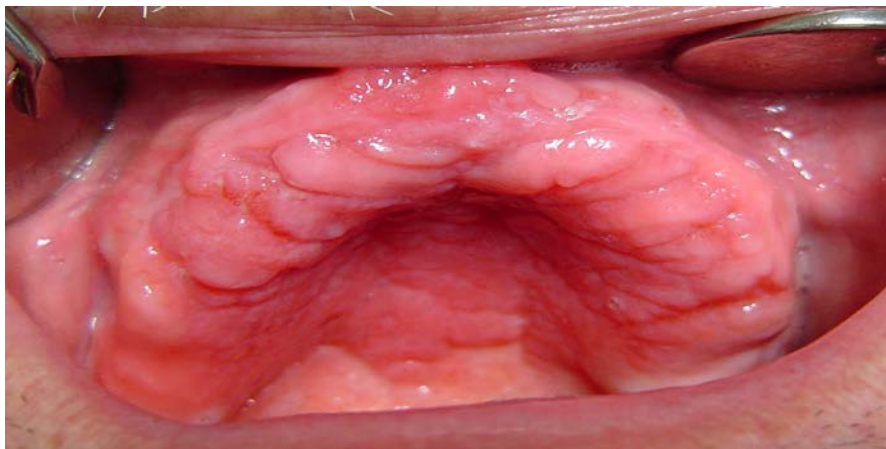
Denture stomatitis is an inflammatory reaction that occurs in healthy patients wearing dentures¹. It is most common in the palatal mucosa and the alveolar ridge, which makes direct contact with the base of dental prostheses^{2,3}. Research shows that the prevalence of denture stomatitis ranges from 15% to 75%, while the incidence is significantly higher in women and in the elderly⁴. The etiology of this inflammation is multifactorial, and the potential causes include: *Candida* yeast infections, bacterial infections, poor oral hygiene and denture hygiene, chronic irritation due to poor denture retention, constant wearing of dentures, allergic reaction to materials used for making dentures, immunological factors, the use of different drugs and some systemic diseases^{1,5}. Still, *Candida* yeast infections, especially *Candida albicans*, are the most frequently associated with the development of this inflammation¹. Numerous studies have shown that two-thirds of patients who wear dentures suffer from this type of inflammation⁶⁻⁹. Despite its prevalence, denture stomatitis in most cases is asymptomatic; a small number of patients feel pain, tingling and numbness, and the changes are primarily diagnosed during the examination, when erythema or edema can be observed, affecting the areas of the mucosa which is in contact with the prosthesis¹⁰. There are several classifications of denture stomatitis, but the most relevant classification was proposed by Newton in 1962, being based only on clinical criteria. According to this classification, there are three types of denture stomatitis 1. Localized inflammation of the mucosa or pinpoint hyperemia which is usually caused by trauma (Figure 1); 2. Erythematous or generalized type, involving a part or the entire denture-covered mucosa (Figure 2); 3. Granular type (inflammatory papillary hyperplasia), involving the central part of the hard palate and the alveolar ridge (Figure 3)¹¹.



Slika 1. Tačkasta hiperemija sluzokože uzrokovana traumom pri nošenju gornje totalne proteze
Figure 1. Localized pinpoint hyperemia of the mucosa, which is caused by denture trauma.



Slika 2. Eritematozni (generalizovani oblik) proteznog stomatitisa
Figure 2. Erythematous (generalized type) denture stomatitis.



Slika 3. Granularni oblik (inflamatorna papilarna hiperplazija) proteznog stomatitisa
Figure 3. Granular type (inflammatory papillary hyperplasia) of denture stomatitis.

Etiopatogenetski aspekti

Protezni stomatitis je u većini slučajeva posledica hronične infekcije ili mehaničke iritacije i traume. Danas se smatra da je etiologija multifaktorijalna, što znači da će se zapaljenski proces češće razviti pri sinergističkom delovanju većeg broja faktora nego pri delovanju jednog. Loša oralna higijena, patogena infekcija gljivicom iz roda *Candida* i dugotrajno nošenje proteze su dominantni udruženi etiološki faktori koji dovode do razvoja zapaljenja¹².

Samo prisustvo proteze u usnoj duplji može delovati kao katalizator koji doprinosi pojavi proteznog stomatitisa. Njeno prisustvo menja lokalnu mikrosredinu tako što smanjuje nivo pH, protok pljuvačke i mehaničko samočišćenje, delujući kao rezervoar za razvoj mikroorganizama³. *Candida albicans* je mikroorganizam koji je najčešće izolovan iz sluzokože nepca (89%) i/ili sa gornje proteze (78,5%) kod pacijenata sa proteznim stomatitisom¹³. Uloga *C. albicans* u razvoju zapaljenja povezana je sa činjenicom da ova gljivica ima sposobnost da kolonizuje oralnu sluzokožu i površinu proteze i da gradi agregate sa oralnim bakterijama¹⁴. *C. albicans* je normalni stanovnik usne duplje, a u slučaju imunodeficijencije može postati patogena kada dovodi do razvoja kandidijaze. Protezni stomatitis može biti udružen sa angularnim heilitisom, atrofičnim glositisom, akutnom pseudomembranoznom kandidijazom i hroničnom hiperplastičnom kandidijazom¹⁵. Pored *C. albicans*, izolovane su i druge vrste roda *Candida* koje učestvuju u nastanku proteznog stomatitisa: *C. glabrata*, *C. tropicalis*, *C. krusei*, *C. kefir* i *C. dubliniensis*¹⁶. Ipak, njihova uloga u razvoju ovog zapaljenskog procesa je mnogo manja. Kod pacijenata sa proteznim stomatitisom izolovane su i određene bakterijske vrste poput *stafilokoka*, *sreptokoka*, *fuzobakterija* i *bakteroidesa*³.

Među faktorima koji utiču na adherenciju *Candide* i formiranje biofilma na površini akrilata, ističu se hrapavost površine proteze, hidrofobne i elektrostatske interakcije¹⁷. Hrapava površina akrilata, koji se najčešće koristi kao materijal za izradu proteza, promoviše povećano zadržavanje mikroorganizama i štiti ih od sila koje teže da ih uklone, pri čemu mikroorganizmi ostaju zarobljeni nepravilnom površinom proteze, čak i nakon njenog čišćenja. Poliranje proteza čini njihovu površinu glatkom i smanjuje inicijalnu adheziju i akumulaciju mikroorganizama¹⁸.

Etiopathogenic aspects

Denture stomatitis is in most cases a consequence of chronic infection or mechanical irritation and trauma. It is considered that the etiology of denture stomatitis is multifactorial, and it is more likely to develop due to synergy with other factors than during the action of just one of them. Poor oral hygiene, pathogenic infection caused by *Candida* and constant wearing of dentures are dominant synergistic etiological factors that lead to inflammation¹².

The presence of dentures in the mouth can act as a catalyst that contributes to denture stomatitis. Its presence change the local microenvironment by reducing the pH level, the flow of saliva and a mechanical self-cleaning, by acting, in this way, as a reservoir for the growth of microorganisms³. *Candida albicans* is a microorganism which is most frequently isolated from the palatal mucosa (89%) and/or the upper prosthesis (78.5%) in patients suffering from denture stomatitis¹³. The role of *C. albicans* in the development of inflammation is associated with the fact that this yeast has the ability to adhere and colonize the oral mucosa and the surface of the prosthesis and the ability to build aggregates with oral bacteria¹⁴. *C. albicans* is a normal inhabitant of the oral cavity, and in the case of immune deficiency can become a pathogen when it leads to the development of candidiasis. Denture stomatitis may be associated with angular heilitis, atrophic glossitis, acute pseudomembranous candidiasis and chronic hyperplastic candidiasis¹⁵. In addition to *C. albicans*, other species of the genus *Candida* were isolated, participating in the development of denture stomatitis: *C. glabrata*, *C. tropicalis*, *C. krusei*, *C. kefir*, *C. dubliniensis*¹⁶. However, their role in the development of this inflammatory process is much smaller. In patients with denture stomatitis, certain bacterial species such as *Staphylococcus*, *Streptococcus*, *Fusobacterium* and *Bacteroides* were isolated³.

Among the factors which influence the adherence of *Candida* and the formation of biofilm on the surface of acrylate, there are roughness of the inner surface of the prosthesis, hydrophobic and electrostatic interactions¹⁷. The rough surface of the acrylate, which is most commonly used as a material for making dentures, promote increased retention of microorganisms and protect them from the forces that seek to remove them, in which microorganisms are

Ovo je pokazano u studiji Sesma i saradnika¹⁹. Starost proteze je takođe bitan faktor, jer kod dugo nošenih proteza teže se održava higijena i prisutna je sklonost ka poroznosti baze proteze, što favorizuje nastanak infekcije²⁰.

Uticaoj pljuvačke na adheziju *C.albicans* za površinu proteze još uvek je kontraverzan. Neke studije ukazuju da pljuvačka smanjuje adheziju gljivice. Sa druge strane, pljuvačka sadrži zaštitne molekule kao što su lizozim, laktoferin, kalprotektin i imunoglobulin IgA, koji smanjuju adheziju *C.albicans* za oralne površine³. Smanjenje ili kompletno odsustvo pljuvačke kod osoba sa kserostomijom izaziva disbalans u normalnom mikrobiološkom sastavu, favorizujući proliferaciju bakterije *Staphylococcus aureus* koja inhibira adaptaciju komensala²¹.

U prostoru između gingivalne površine baze gornje totalne proteze i sluzokože nepca usled dobrog zaptivanja smanjuje se pljuvačni protok i dinamika promene pH pljuvačke, što dovodi do stvaranja kisele sredine i povoljnih uslova za nastanak infekcije. U donjoj vilici ventilni učinak zubne proteze je slabiji tako da se menja i pH i protok pljuvačke, zbog čega je u donjoj vilici ređa pojava proteznog stomatitisa.

Sa druge strane, hidrofobnost površine proteze utiče na adheziju *C.albicans* tako što hidrofobne površine smanjuju ćelijsku adheziju²². Što se tiče elektrostatske interakcije, gljivice čija površina ima pozitivno naelektrisanje su mnogo adhezivnije za razliku od odbojnih sila koje postoje između negativno naelektrisanih gljivica i polimerne površine²³.

Veruje se da je jedan od etioloških faktora za nastanak proteznog stomatitisa trauma, koja može nastati usled loše retencije i stabilizacije proteze u ustima. U istraživanju koje su sproveli Zissis i sar. pokazano je da su trauma, izazvana lošom retencijom proteze i dugotrajno nošenje proteze bili značajni faktori koji su uticali na razvoj zapaljenja²⁴. U studiji Emami i sar. testirana je i prihvaćena hipoteza da povećan okluzalni ptitisak može izazvati traumu sluzokože, što rezultuje zapaljenskom reakcijom koja dalje može stvoriti takvu sredinu koja favorizuje razvoj mikroorganizama odgovornih za nastanak proteznog stomatitisa²⁵.

U rizične faktore za razvoj proteznog stomatitisa ubraja se i loša oralna higijena. Brojne studije potvrdile su jasnu vezu između loše oralne higijene i povećanog rizika za nastanak i prevalenciju zapaljenskog procesa²⁶⁻³¹.

trapped by irregular surface of the prosthesis, even after its cleaning. Polishing of prosthesis makes their surfaces smooth and reduce the initial attachment and accumulation of microorganisms¹⁸. This has been shown in the paper of Sesma et al¹⁹. In addition, an important factor is the age of prosthesis, because it is more difficult to maintain hygiene if prosthesis are worn for a long time and there is a tendency towards to porosity of the denture base, which favors the occurrence of infection²⁰.

The role of the saliva in the colonization of *C. albicans* to the surface of the prosthesis is still controversial. Some studies suggest that it reduces the adhesion of *C. albicans*. On the other hand, saliva possesses defensive molecules as lysozyme, lactoferrine, calpro-tectin, IgA that decrease the adhesion of *Candida* to the oral surfaces³. The decrease or the complete absence of saliva in individuals with xerostomia induces the change and the imbalance of the normal microbial communities favoring the proliferation of bacteria as *Staphylococcus aureus* that inhibits the normal adaptation of the commensals²¹.

In the space between the gingival surface of the base of the upper denture and palatal mucosa due to good retention, salivary flow is reduced, as well as the dynamics of change in pH of saliva, that leads to the formation of acidic environment and favorable conditions for the occurrence of infections. In the lower jaw dentures, valve effect is weaker so that it changes the pH and flow of saliva, and the development of denture stomatitis in the lower jaw is an uncommon phenomenon.

On the other hand, the hydrophobicity of the prosthesis surface affects the adherence of *C. albicans*, in the way that hydrophobic surfaces decrease the adherence of the cell²². As for the electrostatic interaction, yeasts, which surface has a positive charge, are more adherent unlike the repulsive forces which exist between the negatively charged yeast and polymer surfaces²³.

It is believed that one of the etiological factors for the development of denture stomatitis is trauma, which may occur due to poor retention and stabilization of the prosthesis. In a study conducted by Zissis et al., it has been shown that the trauma caused by poor denture retention and long-term wear of dentures were significant factors that lead to the development of inflammation²⁴.

Ove studije su utvrdile da među osobama koji nose zubne proteze većinu čine starije osobe koje oralnu higijenu održavaju samo pranjem proteze. Međutim, ovo nije dovoljno za održavanje pravilne higijene proteze kao i za prevenciju akumulacije oralnog biofilma. Poželjno je dodatno koristiti komercijalno dostupne dezinfekcione rastvore ili potapati protezu u razblažen rastvor natrijum hipohlorita. Neadekvatno čišćenje proteza dovodi do brzog razvoja i akumulacije biofilma. Biofilm sadrži bakterije i gljivice koje ostaju na površini proteze i tako mogu kolonizovati oralnu sluzokožu, a sam biofilm i gljivice imaju već pomenutu ulogu u razvoju zapaljenja sluzokože u proteznom stomatitisu^{32,33}. Takođe, nošenje proteze noću u toku spavanja može biti povezano sa lošom oralnom higijenom i sa razvojem proteznog stomatitisa²⁶⁻³¹.

Materijal od kojeg se izrađuje zubna proteza može otpuštati određene hemijske sastojke koji izazivaju alergijsku reakciju u vidu lokalizovanog ili generalizovanog stomatitisa. Ova reakcija se povezuje sa prisustvom rezidualnog monomera iz akrilatnih smola, hidrokinon peroksida, dimetil-p-toluidina ili metakrilata u protezi. Reakcija preosetljivosti se češće javlja ukoliko se za izradu proteze koristi hladni, tj. autopolimerizujući umesto topopolimerizujući akrilat³⁴.

Pored lokalnih etiloških faktora, razvoj proteznog stomatitisa može biti potpomognut nekim opštim faktorima. U ove faktore spadaju dijabetes melitus, pušenje, dugotrajna primena antibiotika i kortikosteroida, radio i hemoterapija, neadekvatna ishrana – nedostatak vitamina B12, folata i gvožđa, psihotropni lekovi³⁵⁻³⁷. Na postojanje sistemskog oboljenja, kao što je dijabetes melitus, može ukazati prisustvo i oralne kandidoze³⁸. Kandidoza kod dijabetičara koji nose zubnu protezu povezuje se sa lošim održavanjem oralne higijene i dugotrajnim nošenjem proteze. Takođe, smatra se da je rast gljivica olakšan zbog povećanih vrednosti šećera u tkivnim tečnostima. Povećana glikosilacija utiče na pojačanu adheziju gljivica za epitelne ćelije, pa se prisustvo gljivica povezuje sa kvantitativnim (kserostomija) i kvalitativnim poremećajem pljuvačne sekrecije i oslabljenim ćelijskim imunitetom³⁹. Još jedan faktor koji favorizuje gljivičnu infekciju kod dijabetičarskih bolesnika je poremećena funkcija neutrofilnih leukocita³⁷.

In their study, Emami et al. tested and accepted the hypothesis that increased occlusal pressure can cause trauma of mucosa, resulting in inflammatory reaction which can create an environment that favors the growth of microorganisms responsible for the formation of denture stomatitis²⁵.

The risk factor for the development of denture stomatitis is poor oral hygiene. Numerous studies have confirmed a clear relationship between poor oral hygiene and increased risk for the occurrence and prevalence of inflammatory process²⁶⁻³¹. These studies have found that the majority of people who wear dentures are elderly who maintain the oral hygiene by washing dentures. However, this is not enough to maintain the proper hygiene of dentures nor to prevent the accumulation of the oral biofilm. It is preferable to use additional commercially available disinfecting solutions or immerse the denture in diluted sodium hypochlorite solution. Inadequately cleaning of dentures accelerates the development and accumulation of pathogenic denture biofilm. Biofilm contains bacteria and yeasts that reside on the denture surfaces and can also colonize the oral mucosa. The role of biofilm and yeast biofilm in the development of inflammation have already been mentioned^{32,33}. Also, wearing dentures overnight may be associated with poor oral hygiene and the development of denture stomatitis²⁶⁻³¹.

The material of which denture is made can release certain chemical substances that cause an allergic reaction in the form of localized or generalized stomatitis. This reaction may be related to the presence of residual monomers from the acrylic resins, the presence of hydroquinone peroxide, dimethyl-p-toluidine or methacrylate in the prosthesis. Hypersensitivity reactions more commonly occur with cold or autopolymerized resins than with heat-cured denture-base materials³⁴.

In addition to local etiological factors, the development of denture stomatitis can be aided by some general factors. These factors include diabetes mellitus, smoking, long-term use of antibiotics and corticosteroids, radio - and chemotherapy, inadequate nutrition - lack of vitamin B12, folate and iron, psychotropic drugs³⁵⁻³⁷. The presence of oral candidiasis may be a sign of systemic diseases, such as diabetes mellitus³⁸. Candidiasis in diabetic patients who wear dentures

Terapija proteznog stomatitisa

S obzirom da na razvoj proteznog stomatitisa utiče veliki broj faktora, terapija ovog zapaljenja je kompleksna. Osnova uspeha svakog terapijskog postupka je dobra oralna higijena i higijena zubnih proteza. Ujedno, dobra oralna higijena se ubraja i u osnovne preventivne mere koje smanjuju mogućnost nastanka zapaljenskog procesa.

Jako je važno isključiti sve lokalne faktore koji favorizuju rast gljivica, kao što su pušenje i nošenje proteza tokom noći. Zubne proteze treba skidati tokom spavanja, a sa druge strane, dok su u ustima, bitno je da su dobro retinirane i stabilne kako ne bi izazvale traumu na oralnoj sluzokoži³. Ukoliko proteze nisu dobro retinirane, u terapijske svrhe može se vršiti podlaganje proteze tkivnim kondicionerima sa antifungalnim agensima ili, ako je potrebno, mogu se izraditi nove proteze^{40,41}. Tkivni kondicioneri sa antifungalnim agensima, kao što je nistatin, ostvaruju inhibitorni efekat na rast *C.albicans*, *C.krusei* i *C.tropicalis*⁴¹. U nekim studijama je potvrđeno da se prevalencija proteznog stomatitisa može redukovati ukoliko se u donjoj vilici proteze stabilizuju primenom implanata, jer se na ovaj način sprečava trauma oralne sluzokože kod bezubih pacijenata²⁵.

Što se tiče higijene proteza, ona podrazumeva njihovo pranje uz upotrebu četkice i paste, kao i potapanje proteze tokom noći u rastvor antiseptika. Među antisepticima najčešće se koriste razblaženi rastvor natrijum hipohlorita (0,1%), u koji se proteza potopi u trajanju od 15-30 minuta, kao i rastvor hlorheksidin glukonata⁴². Rastvor hlorheksidina u koncentraciji od 0,2% može se koristiti za ispiranje usne duplje tri puta dnevno, što značajno smanjuje akumulirani biofilm, ali ne utiče značajno na redukovanje količine *C.albicans*³⁴. Jedan od načina dezinfekcije proteze, koji se u nekim studijama pokazao efikasnim, jeste izlaganje proteze mikrotalasnim zracima⁴³.

Kada se kao uzročnik proteznog stomatitisa izoluju gljivice iz roda *Candida*, potrebno je sprovesti terapiju antimikoticima. Ova terapija podrazumeva lokalnu ili sistemsku primenu antimikotičnih lekova. Njihov mehanizam delovanja podrazumeva inhibiciju enzima i puteva bitnih za sintezu ćelijske membrane, menjanje propustljivosti ćelijske membrane i metabolizma RNK i DNK, ili unutarćelijsku akumulaciju peroksida koji toksično deluje na gljivice.

is associated with poor oral hygiene and long wearing of dentures. Also, it is considered that the growth of yeast is promoted by elevated tissue fluid glucose levels. Moreover, besides the presence of a high concentration of salivary glucose, low salivary secretion may enhance the growth of yeasts and their adherence in epithelial oral cells³⁹. Another factor that favors yeast infection in diabetic patients is impaired function of neutrophils, particularly in the presence of glucose³⁷.

The therapy of denture stomatitis

Due to the etiology of the development of denture stomatitis, which is multifactorial, the therapy of inflammation is complex. The basis of success of any therapeutic procedure is good oral hygiene and hygiene of dentures. At the same time, this is the one of the basic and preventive measures that decreases the possibility of inflammatory processes.

It is important to exclude all local factors that favor the growth of yeast, such as smoking and wearing dentures overnight. Dentures, during sleep, should be removed; on the other hand, it is essential that they are well retained and stable to avoid trauma of the oral mucosa³. If prostheses are not well-retained, therapy can be performed by relining dentures with conditioners with antifungal agents, or, if it is necessary, a new prostheses can be created^{40,41}. Tissue conditioners with antifungal agents, such as Nystatin, have an inhibitory effect on the growth of *C. albicans*, *C.tropicalis* and *C.krusei*⁴¹. In some studies, it was confirmed that the prevalence of denture stomatitis can be reduced if the mandibular denture is stabilized by using implants, because in this way it prevents trauma of oral mucosa in edentulous patients²⁵.

Hygiene of dentures includes their washing, using brushes and paste, as well as the immersing of dentures overnight in an antiseptic solution. Among the most commonly used antiseptics are diluted sodium hypochlorite solution (0.1%), in which the prosthesis is submerged for a period of 15-30 minutes, and a solution of chlorhexidine gluconate⁴². A solution of chlorhexidine at a concentration of 0.2% can be used for rinsing the oral cavity three times a day, which significantly reduces the accumulated biofilm, but it does not significantly affect the reduction of the number of *C. Albicans*³⁴. The exposure of prosthesis to microwave radiation is another way for the disinfection of dentures, which has proved effective in some studies⁴³.

Efekat antimikotičnih lekova zavisi od koncentracije leka i osetljivosti različitih sojeva⁸. Tretman obično započinje lokalnom primenom ovih preparata, dostupnih u obliku gela, pastila, krema i oralnih suspenzija³. Najviše primenjivane su suspenzije na bazi nistatina, amfotericina B, flukonazola i mikonazola. Sa druge strane, klotrimazol se primenjuje u obliku kreme ili rastvora, s tim da krema ima i antistafilokoknu aktivnost. Uglavnom, svi lekovi dovode do prestanka simptoma nakon primene od 12 do 14 dana. Klotrimazol (1% krem) se primenjuje samo lokalno, jer sistemski aplikovan pokazuje toksični efekat na nervni sistem i gastrointestinalni trakt. Ekonazol postoji samo u obliku za lokalnu primenu, a mikonazol se u obliku 2-4% kreme primenjuje lokalno⁴⁴⁻⁴⁶. Sistemski antimikotični lekovi se primenjuju kod pacijenata sa posebnim potrebama i kod imunokompromitovanih pacijenata, kao i kod pacijenata kod kojih lokalna terapija nije dala rezultate³. Flukonazol je slabo toksičan i široko se primenjuje u obliku kapsula (50-100 mg); itraconazol se primenjuje u obliku kapsula u dozi od 100 mg, a ketokonazol u dozi od 200-400 mg, jedanput dnevno u toku 14 dana⁴⁷. Ketokonazol je hepatotoksičan i može izazvati srčane aritmije ukoliko se primenjuje u kombinaciji sa makrolidnim antibioticima ili sa antihistaminicima. Amfotericin B se ranije intravenozno primenjivao u tretmanu kandidom izazvanog proteznog stomatitisa, ali je danas njegova primena redukovana zbog nefrotoksičnosti⁴⁸. Amfotericin B za lokalnu primenu u obliku 3% losiona primenjuje se dva puta dnevno, ali ima neprijatan ukus, pa može izazvati gastrointestinalne smetnje poput mučnine, povraćanja i dijareje³⁴.

Sve više se u terapiji proteznog stomatitisa izazvanog *C.albicans* primenjuju alternativna sredstva koja zamenjuju hemijske preparate i imaju manje neželjenih efekata. To su prirodni preparati na bazi biljaka koji ispoljavaju antibakterijsku i antifungalnu aktivnost, a takođe imaju i antiinflamatorni i antioksidativni efekat⁴⁹. Najčešće se primenjuju etarska ulja i ekstrati biljaka kao što je timijan, čajno drvo, bergamot, limun i grejpfrut. Hammer i sar. su testirali 20 etarskih ulja i pokazali da ulje timijana ima najnižu inhibitornu koncentraciju za *C.albicans* i *E.coli*⁵⁰. U studiji u kojoj je ispitivan efekat etarskih ulja na gljive roda *Candida*, utvrđeno je da ulje timijana ima najveći inhibitorni efekat.

When genus of *Candida* is isolated as a cause of denture stomatitis, it is necessary to prescribe the antifungal therapy. This therapy includes the local or systemic administration of antifungal drugs. Their mechanism of action include the inhibition of various enzymes and pathways that are essential for the synthesis of cell membranes, alteration of the yeast cell membrane permeability, RNA and DNA metabolism change and intracellular accumulation of peroxide which has a toxic effect on yeasts. The effect of antifungal drugs depends of their concentration and the sensitivity of the various strains⁸. Treatment usually begins with local administration of these drugs, that are available in the form of gels, pastilas, creams and oral suspensions³. Suspensions are mostly based on nystatin, amphotericin B, fluconazole and miconazole.

On the other hand, clotrimazole is applied in the form of a cream or a solution, and the cream has an antistaphylococcal activity. Basically, all drugs lead to cessation of symptoms after the application of 12 to 14 days. Clotrimazole (1% cream) is applied only locally because it shows a toxic effect on the nervous system and the gastrointestinal tract. Econazole exists only in the form for atypical use; Miconazole is in the form of 2-4% cream and it is applied topically⁴⁴⁻⁴⁶. Systemic antifungal drugs are administered to patients with special needs and in immunocompromised patients, and in patients in whom topical treatment has not yielded results. Fluconazole³, which is widely applied in the form of capsules (50-100 mg), is sparingly toxic and cost-effective; Itraconazole is also applied in the form of capsules at a dose of 100 mg, and ketoconazole is used in a dosage of 200-400 mg, once a day for 14 days⁴⁷. Ketoconazole is hepatotoxic, and can cause cardiac arrhythmia when it is administered in combination with antihistamines or a macrolide antibiotic. Amphotericin B was previously intravenously used in the treatment of *Candida*-induced denture stomatitis. However, its administration has been reduced because of its nephrotoxic effect⁴⁸. Amphotericin B for topical application in the form of a 3% lotion is applied twice a day, but it has an unpleasant taste and may cause gastrointestinal disturbances such as nausea, vomiting and diarrhea³⁴.

In the therapy of denture stomatitis caused by *C. albicans*, alternative agents

Pokazano je da terpinen-4-ol (glavna komponenta ulja čajnog drveta) ima fungistatsko i fungicidno dejstvo na izolovane sojeve *C.albicans*, posebno na one sojeve koji su rezistentni na flukonazol⁵¹.

Kao poslednji vid terapije proteznog stomatitisa, a koji je obično namenjen težim slučajevima proteznog stomatitisa, kao što je papilarna hiperplazija nepca, može se sprovesti kriohirurški tretman, elektrohirurgija, tretman laserom ili ekscizija promena²⁰.

Zaključak

Imajući u vidu da je protezni stomatitis najčešća zapaljenska reakcija koja se javlja kod nosioca zubnih proteza i da je u većini slučajeva asimptomatski, poželjno je da se kod ovih pacijenata zakazuju redovne stomatološke kontrole u cilju rane dijagnostike i lečenja promena. Izbor terapije zavisi od uzroka promena. Kod većine pacijenata uklanjanje mehaničkih i traumatskih faktora, kao i dobra oralna i higijena zubnih proteza, daje zadovoljavajuće rezultate.

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which replace chemical preparations and have less side effects are increasingly applied. These are natural products based on herbs that exhibit antibacterial and antifungal activity, but also have antiinflammatory and antioxidant effects⁴⁹. Most commonly applied are essential oils and extracts of plants such as thyme, tea tree, bergamot, lemon and grapefruit. Hammer et al. tested twenty essential oils and showed that thyme oil has the lowest inhibitory concentration for *C. albicans* and *E. coli*⁵⁰. In a study that examined the effects of essential oils on the yeasts of the genus *Candida*, it was found that thyme oil has the highest inhibitory effect. It has been shown that the terpinene-4-ol (major component of tea tree oil) has fungistatic and fungicidal action on the isolated *C. albicans* strains, particularly those strains which are resistant to fluconazole⁵¹.

The last form of therapy of denture stomatitis, which is usually designed for severe cases of denture stomatitis, such as papillary hyperplasia of the palate, may include criosurgical treatment, electrosurgery, laser treatment or excision of lesions²⁰.

Conclusion

Having in mind that the denture stomatitis is the most common inflammatory reaction that occurs in the carriers of dentures, being mostly asymptomatic, it is desirable that these patients schedule regular dental checks for early diagnostics of changes and their treatment. The choice of treatment depends on the cause of a change. In most patients, the removal of mechanical and traumatic factors, as well as good oral hygiene and hygiene of dentures, yields satisfactory results.

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