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PRESENCE OF CANDIDA SPECIES IN THE ORAL MICROBIOME AND THEIR INFLUENCE ON THE EXTRACTION SOCKET HEALING

ПРИСУСТВО НА ВИДОТ КАНДИДА ВО ОРАЛНИОТ МИКРОБИОМ И НИВНОТО ВЛИЈАНИЕ ВРЗ ЗАЗДРАВУВАЊЕТО НА ЕКСТРАКЦИОНИТЕ РАНИ

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Abstract

Introduction: The positive finding of *Candida* in the oral cavity does not represent a pathological finding per se. This fungus has all the characteristics of the opportunistic pathogen, meaning it may cause an infection in the mouth when conditions altering the local oral environment and mucosal resistance arise. Under normal conditions, the balance between microbial colonization and host immune response ensures successful re-epithelialization and tissue regeneration in post-extraction sites. **Aim:** The aim of this review is to provide comprehensive comparison of the contemporary studies on candida colonization, oral microbiomedysbiosis and wound healing impairment. **Materials and methods:** To provide a comprehensive review of the *Candida* overgrowth, oral microbiome and wound healing, we have conducted an extensive literature search in multiple databases including PubMed, Google Scholar and Web of Science. **Results:** *Candida* adheres to epithelial and dental surfaces through adhesins and forms complex biofilms composed of yeast and hyphal morphotypes embedded in an extracellular matrix, facilitating persistent infection.Interactions of *Candida* with oral bacteria can promote biofilm formation. Biofilm contribute to increased virulence and resistance to antimicrobial agents. Clinical and in vivo studies have confirmed that fungal colonization of extraction sockets correlates with prolonged healing time, delayed epithelial coverage, and an increased risk of secondary infection such as alveolar osteitis, or chronic non-healing ulcers in severe cases. **Conclusion:** Effective management of post-extraction wounds in the presence of *Candida* requires maintaining optimal oral hygiene, controlling predisposing factors, promoting a balanced oral microbiome and supporting local immune responses,which are essential for favorable wound healing outcomes. **Key woards:** candida species, oral microbiome, wound healing, socket healing.

Апстракт

Вовед: Позитивниот наод на *Candida* во усната шуплина не претставува патолошки наод сам по себе. Оваа габа ги има сите карактеристики на опортунистички патоген, што значи дека може да предизвика инфекција во устата кога ќе се појават услови што ги менуваат локалната орална средина и мукозната отпорност. Во нормални услови, рамнотежата помеѓу микробната колонизација и имунолошкиот одговор на домаќинот обезбедува успешна реепителизација и регенерација на ткивата на местата по екстракција. **Целта** на овој ревијален труд е да се обезбеди сеопфатна споредба на современите студии за колонизацијата со *Candida* species, дисбиозата на оралниот микробиом и за нарушувањето на физиолошкото заздравување на постекстракционите рани.
Методи на пребарување: За да се обезбеди сеопфатен преглед на прекумерниот раст на *Candida*, оралниот микробиом и на заздравувањето на раните, спроведовме обемно пребарување на литературата во повеќе бази на податоци, вклучувајќи ги PubMed, Google Scholar и Web of Science при што се вклучени околу педесетина трудови. **Резултати:** *Candida* се атхерира на епителните и на денталните површини преку адхезини и формира сложен биофилм составен од квасни и од хифални морфотипови вградени во екстрацелуларен матрикс. Ваков комплексен состав на биофилмот овозможува услови за перзистентна инфекција. Интеракцијата на *Candida* со бактерии од оралниот микробиом придонесува за зголемена вирулентност и за отпорност на антимикробни агенси. Клиничките и invivo студиите потврдуваат дека габичната колонизација на екстракционите рани е во корелација со продолженото време на заздравување, одложената епителна пролиферација и со зголемениот ризик од секундарна инфекција, како што е алвеоларен остеитис или хронични рани без тенденција за

заздравување. **Заклучок:** Ефикасното управување со постекстракционите рани во присуство на *Candida*, подразбира одржување на оптимална орална хигиена, контрола на предиспонирачките фактори, промовирање на избалансиран орален микробиом и поддршка на локалните имунолошки одговори, за да се добие оптимален ефект во заздравувањето на раните. **Клучни зборови:** *candida* вид, орален микробиом, заздравување на екстракциона рана, заздравување на алвеола.

Introduction

Oral microbiome is vibrant ecosystemand microbial consortium of over 700 known bacterial species[1]. The oral microbiome acts as a protective barrier, preventing the colonization of harmful pathogens and potential infections in the oral cavity[2].

The oral microbiome is composed of **Gram-positive cocci** *Abiotrophia, Peptostreptococcus, Streptococcus,* and *Stomatococcus* assume pivotal roles (*Streptococcus sanguinis* and *salivarius*), **Gram-positive rods** *Actinomyces, Bifidobacterium, Corynebacterium, Eubacterium, Lactobacillus, Propionibacterium, Pseudoramibacter,* and *Rothia,* **Gram-negative cocci** *Moraxella, Neisseria,* and *Veillonella* and **Gram-negative** rods, *Campylobacter, Capnocytophaga, Desulfobacter, Desulfovibrio, Eikenella, Fusobacterium, Hemophilus, Leptotrichia, Prevotella, Selemonas, Simonsiella, Treponema,* and *Wolinella*[3,4,5].

Fungi are less than 0.1% of the total oral microbial population[6]. *Candida* species is most observed fungus. Additionally, fungi species are identified in oral microbiome as *Cladosporium, Saccharomycetales, Aspergillus and Cryptococcus*[7].

Viruses (Herpesviridae, Papillomaviridae, Anelloviridae, Redondoviridae) can be present either as free phage particles (virions) or as prophages integrated within bacterial lysogens[8].

Physical interactions between fungi and bacteria in the oral cavity influence the oral microbiota diversity. *Candida* and other oral fungi act as bridging organisms facilitating bacterial adhesion to epithelial cells surfaces. Additionally, these interactions contribute to bacterial resistance against antimicrobial agents[9].

There are a numerous factors influencing the oral microbiome composition and leading to disturbance: diet, alcohol consumption, lifestyle choices, smoking, poor oral hygiene practices, medical conditions and medications.

The oral microbiome inhealthy conditions thrives in a favorable commensal association with its environment. Disruptions in the oral microbiota balance (dysbiosis) are under the influence of harmful factors. In the state of dysbiosis, opportunistic microorganisms within the oral microbiome undergo a transformation into harmful pathogensand a decline in beneficial microorganisms[10].

Significant progress has been made in understanding the impact of the oral microbiome in the development of oral and systemic diseases by innovative genomic technologies such as next-generation sequencing (16S rRNA sequencing, metagenomics, shotgun metagenomics, quantitative real-Time PCR) and advanced bioinformatic tools[8].

Latest research also indicates potential links between oral microbiome dysbiosis and systemic health conditions including metabolic endocrine diseases such as diabetes, obesity, gastrointestinal disorders-inflammatory bowel disease, cardiovascular disease, adverse pregnancy outcomes, Alzheimer'sand Parkinson's disease, autism spectrum disorders, systemic lupus erythematosus, rheumatoid arthritis, and even cancer[8].

A high increase of fungal infections has been reported over the last decades. The most common infections arecaused by *Candida species* (candidiasis). *Candida albicans* is the most common one, but *Candida krusei, Candida stellatoidea, Candida tropicalis, Candida glabrata, Candida guilliermondii* and *Candida dubliniensis* are other species that can also be present in oral candidiasis lesions[11].

The positive finding of *Candida* in the oral cavity does not represent a pathological finding per se. This fungus has all the characteristics of an opportunistic pathogen, meaning it may cause an infection in the mouth when conditions that alter the local oral environment and mucosal resistance arise (changes in the host's immune system, smoking, hyposalivation, inadequate oral hygiene, various types of dentures, antibiotics administration, diabetes, or advanced age[12].

Materials used for prosthetic rehabilitation can directly affect the presence of *Candidain* an oral environment due to their properties (surface structure, degree of porosity, roughness, hydrophobicity, surface-free energy, all of which affects the adhesion of microorganisms andplaque formation)[13].

The ability of *Candida* species to colonize host tissuesis influenced by diverse virulence factors, including biofilms development. *Candida albicans* biofilms have been associated withpersistent high virulence factors and drug resistance. In biofilms, *Candidais* very important factor involved in the adherence of bacteria to soft tissues and further in the deep invasion, invading the connective tissue in association with anaerobic microorganisms (*Porphyromonas gingivalis*, *Prevotella intermedia*, and *Aggregatibacter actinomycetemcomitans*)[14].

The process of oral wound healing following tooth extraction represents a highly coordinated cascade of cel-

lular and molecular events involving hemostasis, inflammation, proliferation, and remodeling phases. The post-extraction socket provides a transient yet complex microenvironment, characterized by changes in pH, oxygen tension, nutrient availability, and microbial composition. Under normal conditions, the balance between microbial colonization and host immune response ensures successful re-epithelialization and tissue regeneration. However, microbial dysbiosis-particularly the overgrowth of opportunistic fungi such as *Candida* species-can significantly impair the healing trajectory and lead to pathological outcomes. The colonization of extraction sockets by *Candida* species disrupts the balance of the oral microbiome and leads to prolonged mucosal erythema, delayed epithelial closure, and increased susceptibility to alveolitis[15].

Aim

The aim of this review is to provide a comprehensive comparison of the contemporary studies on *Candida* colonization, oral microbiome dysbiosis and wound healing impairment.

Search methods

To provide a comprehensive review of the *Candida* overgrowth, oral microbiome and wound healing, we have conducted an extensive literature search. We used the following keywords: candida, oral microbiome, wound healing, oral care. Our search spanned multiple databases including PubMed, Google Scholar and Web of Science.

Inclusion criteria: This review paper included case-control studies, cross-sectional studies, retrospective and prospective cohort studies, and randomized controlled trials that examined the composition of and factors that influence oral microorganisms, connections between oral candida and wound healing. Exclusion criteria: non-peer-reviewed articles and articles not available in English.

Results and discussion

The simplest oral surgery intervention-ooth extraction - initiates changes in the oral cavity environment and increases the risk of fungal growth. The wound area after extraction becomes susceptible to infection with *Candida* species. The contamination of the socket by microorganisms results in delayed wound healing. *Candida* species play an important role as an opportunistic component in wounds. Decreased immunity directly affects the prevention ofmucosal infections by *Candida* species which is primarily mediated by the innate immune response function.

Experimental and clinical studies have demonstrated that *Candida*-associated post-extraction sites exhibit increased proinflammatory cytokine levels (such as IL-1β, TNF-α, and IL-6), elevated oxidative stress markers, and delayed epithelial closure compared to non-infected wounds[16].

Clinical and in vivo studies have confirmed that fungal colonization of extraction sockets correlates with prolonged healing time, delayed epithelial coverage and increased risk of secondary infection such as alveolar osteitis or chronic non-healing ulcers in severe cases[17].

Candida adheres to epithelial and dental surfaces through adhesins and forms complex biofilms composed of yeast and hyphal morphotypes embedded in an extracellular matrix, facilitating persistent infection. Additionally, *Candida albicans* biofilms formed on the wound surface exhibit enhanced resistance to antifungal agents and immune clearance. The fungal biofilm architecture composed of dense yeast and hyphal networks within an extracellular polysaccharide matrix acts as a physical and chemical barrier, facilitating chronic infection and delayed tissue repair[18,19].

Candida species exhibit morphological plasticity, transitioning between yeast, pseudohyphal, and hyphal forms, which enhances its tissue invasiveness and persistence. The hyphal phase is associated with the secretion of virulence factors, including aspartyl proteases (SAPs), phospholipases, and hemolysins, which contribute to epithelial degradation, disruption of the extracellular matrix, and modulation of the inflammatory response. These pathogenic mechanisms can prolong the inflammatory phase, delay epithelial proliferation and migration, and impair angiogenesis and collagen deposition within the granulation tissue[20,21].

Unlike *C. albicans*, most non-*albicans Candida* (NAC) species (*C. glabrata, C. tropicalis, C. krusei, C. parapsilosis*) are incapable of forming true hyphae. They compensate through strong adhesion ability, biofilm formation, and intrinsic resistance to commonly used antifungal agents, such as azoles[22]. *C. glabrata*, for example, adheres to host tissues via cell wall adhesins and survives in the host cells macrophages, evading immune detection[23].

C. tropicalis has been associated with higher proteolytic and lipolytic enzyme activity compared with *C. albicans*, contributing to extensive epithelial disruption and inflammation[24]. *C. krusei* and *C. tropicalis* are associated with strong biofilm formation and intrinsic resistance to antifungal agents, complicating eradication and contributing to chronic infection[25]. These species can induce a subtle yet sustained inflammatory response that interferes with fibroblast proliferation and angiogenesis during the proliferative healing phase[26].

Co-infection by *C. albicans* and NAC species can lead to synergistic virulence, enhancing biofilm density and resistance profiles. Clinical evidence suggests that mixed

infections, where *C. albicans* coexists with NAC species, may produce synergistic pathogenic effects, resulting in more pronounced inflammation and delayed tissue regeneration[27]. Moreover, the biofilm matrix produced by NAC species can protect *C. albicans* from antifungal agents and host immune responses, thereby sustaining infection within the healing socket[28].

While both *C. albicans* and NAC species delay wound healing, their mechanisms differ. *C. albicans* primarily causes tissue invasion and immune activation through hyphal formation and enzyme secretion, whereas NAC species contribute through persistent colonization, metabolic stress, and drug resistance. The resulting inflammatory microenvironment, characterized by sustained leukocyte infiltration and oxidative stress, disrupts fibroblast proliferation, angiogenesis, and collagen synthesis-key factors in tissue repair. Understanding these species-specific pathogenic mechanisms is therefore essential for targeted therapeutic interventions and the prevention of fungal complications in oral surgery patients[28].

Candida may cause various forms of infections, ranging from superficial to systemic conditions, which in extreme cases may lead to death. The occurrence of infection is influenced by factors altering the local oral environment, host's immune system as well as mucosal resistance. Colonization with *Candida* species and the respective infections are also more frequent among transplant patients compared to non-transplant patients[29]. Furthermore, *Candida* is also closely associated with potentially malignant and malignant oral lesions. Patients who wear dentures are more predisposed to having their mucosa colonized by *Candida* species compared to the denture- free patients[30].

The occurrence of clinical oral signs and symptoms depends on the presence [quantity] of *Candida* species. Local and systemic factors create an imbalance in the natural flora of the mouth, allowing the *Candida* fungus to overgrow and cause an infection. Low *Candida* counts might have no clinical manifestations. Symptoms reported by patients can vary from mild to severe. Symptoms commonly include dry mouth, altered taste, glossalgia and red lesions of oral mucosa and tongue[31].

The symptoms of oral candidiasis may also include white patches on the tongue, inner cheeks, and roof of the mouth, as well as redness and soreness in the affected areas. In severe cases, it can cause difficulty swallowing and a burning sensation in the mouth[32].

Several processes contribute to *Candida albicans* pathogenicity. Initially, it adheres to host surfaces through weak and reversible interactions that are influenced by both hydrophobic and electrostatic forces[33].

Agglutinin-like sequence (Als) genes encode cell-surface proteins in *Candida* fungi and are primarily involved in adhesion to host tissues and biofilms, representing a key factor in fungal virulence and infection. HWP1 (hyphal wall protein) is a surface expressed adhesin in certain *Candida species*, particularly *Candida albicans*, which facilitates adhesion to host cells by acting as a substrate for host transglutaminases, forming covalent cross-links with epithelial cells.

The process of adhesion is facilitated through the presence of specific host tissue receptors. *C. albicans* can adhere to epithelial cells by using various host cell receptors, such as EphA2 (through β-glucan) and E-cadherin. EphA2 is an epithelial cell pattern recognition receptor for fungal β-glucans (PRRs). E-cadherin is a crucial calcium-dependent glycoprotein that forms the main component of epithelial adherens junctions, maintaining tissue integrity by linking epithelial cells together (cellular adhesion and polarity maintenance). E-cadherin is expressed in almost all epithelial cells. Loss of E-cadherin expression is associated with gain of fungal (or tumor) invasiveness[34].

Interaction of *Candida* with oral bacteria can promote biofilm formation. Biofilms contribute to increased virulence and resistance to antimicrobial agents. *Streptococcus gordonii* and *Streptococcus mutans* are common residents that interact with *C. albicans* in the oral cavity, promoting the formation of hyphal structures and biofilms. *C. albicans* can be transformed into an invasive filamentous form after adhering to host surfaces, which significantly improves its ability to penetrate epithelial tissue[35,36].

C. albicans causes host tissue damage by releasing enzymes outside the cell (aspartyl proteinases-SAPs, phospholipases, and lipases). These enzymes degrade host immune factors, such as antibodies and antimicrobial peptides, thereby reducing the effectiveness of host defenses. For tissue invasion, the shift to the hyphal form is crucial[37]. Hyphae can infiltrate and harm the epithelial cells. Thigmotropism (directional growth response to surface contact) is also characteristic of hyphal cells and their ability to successfully explore and infiltrate host tissues[38]. *Candida* can release candidalysin, a hypha-specific toxin that promotes immunological activation and tissue destruction. In addition to this, *Candida* engages in a complementary, passive process called endocytosis[39,40].

Invasive infections from *Candida* only occur in immuno-compromised patients or when barrier leakage is impaired. Yeasts can enter the bloodstream and cause fungaemia and subsequent infections. *Candida* is the most common fungal pathogen that produces fungaemia. Tight adherence to human cells from skin, epithelium or endothelium is the first step in *Candida* infections. The efficacy to bind to those host tissues or catheters/prosthetic devices depends on adhesins located in fungal cell walls and encoded by genes[41].

The first stage of *Candida* infection is colonization due to epithelial adhesion and nutrient acquisition. The second stage includes superficial infection as a result of epithelial penetration and degradation of host proteins. Subsequent third stage of infection is deep-seated infection due to tissue penetration, vascular invasion and immune evasion or escape. The last stage and the most serious one is disseminated infection with endothelial adhesion, infection of other host tissues and activation of blood clotting cascades (coagulation).

Since antifungal resistance is a rising clinical problem worldwide, management strategies should therefore include accurate and precise biochemical identification of the involved *Candida* species. Infections with non-albicans *Candida* species often require alternative antifungal regimens due to intrinsic resistance patterns of some *Candida species*. While *C. albicans* infections typically respond to azoles such as fluconazole, non-albicans *Candida species*, particularly *C. krusei* and *C. glabrata* may require use of echinocandins or amphotericin B[42]. Therefore, antifungal susceptibility testing is necessary if acquired drug resistance is suspected, or when the patient is unexpectedly failing therapy. For each of these scenarios, knowing the in vitro susceptibility pattern would inform the clinician when making therapeutic choices or changes in therapy.

Adjunctive therapies targeting biofilm disruption and modulation of the local inflammatory response may further improve healing outcomes. Additional measures, such as probiotics, antiseptic mouth rinses, and laser phototherapy have also been investigated for their potential to restore microbial balance and enhance mucosal repair[43].

Management of post-extraction wounds complicated by *Candida* infection requires a multifactorial approach. This includes identification and control of predisposing factors (e.g., xerostomia, systemic disease, or prolonged antibiotic use), maintenance of optimal oral hygiene, and administration of antifungal agents, topical (e.g., nystatin, miconazole) or systemic (e.g., fluconazole)[44].

Effective management involves both antifungal therapy and modulation of local environmental factors that favor fungal growth. Topical antifungals such as nystatin and miconazole remain the first-line agents for localized infections, whereas systemic agents like fluconazole or echinocandins are indicated in refractory or disseminated cases. Given the rising antifungal resistance among ***non-albicans Candida* species**, susceptibility testing and identification at the species level are critical for treatment success. Adjunctive approaches, including probiotics, chlorhexidine rinses, and photobiomodulation therapy, have demonstrated potential in enhancing healing by reducing microbial load and modulating local immunity[15].

Conclusion

Both *Candida albicans* and non-*albicans Candida* species can adversely affect oral wound healing following tooth extraction, albeit through distinct pathogenic mechanisms. *C. albicans* primarily induces acute inflammation and epithelial damage through hyphal invasion and enzymatic activity, whereas non-*albicans Candida* species promote chronic inflammation and persistence through biofilm formation and antifungal resistance.

Effective management of post-extraction wounds in the presence of *Candida* requires maintaining optimal oral hygiene, controlling predisposing factors, and, when necessary, using antifungal therapy, such as topical nystatin or systemic fluconazole. Additionally, promoting a balanced oral microbiome and supporting local immune responses are essential for favorable wound healing outcomes. Understanding these species-specific interactions is crucial for accurate diagnosis, targeted antifungal therapy, and optimization of post-extraction healing outcomes.

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