

PART III. OTHER
DZIAŁ III. RÓŻNE

OCCURRENCE OF *CANDIDA* SPP. IN HEALTHY ORAL MICROBIOTA

WYSTĘPOWANIE *CANDIDA* SPP. W MIKROBIOCIE JAMY USTNEJ
W WARUNKACH ZDROWIA

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Summary

Background. *Candida* is a strain of fungi that is found on the surface of healthy mucous membranes of the oral cavity. Yet, *Candida* may also be considered opportunistic microorganisms. The pathogenicity of *Candida* spp. depends on strain-specific characteristics including, invasiveness, adhesion, and production of biofilm abilities as well as the production of enzymes allowing the colonization of tissue. The aim of the paper was to evaluate the frequency of *Candida* spp. occurrence in the oral microbiota of healthy adults, and its relation with risk factors and colonization. **Material and methods.** This study consisted of 72 healthy participants (from the Lubelskie Voivodeship between 19 and 73 years of age). Medical history was collected to determine potential relationships to risk factors affecting oral microbiota (past oral cavity infections, chronic diseases, and smoking). The participants who were qualified had no oral cavity infections during the study. The collected clinical samples (oral cavity swabs) were disseminated on the chromogenic base for isolation and differentiation of *Candida* spp. **Results.** The frequency of *Candida* spp. occurrence was at the level of 63.8%. *C. albicans* was the most frequently identified species (56.5%). *C. glabrata* (45.6%) and *C. tropicalis* (23.9%) were identified less often. In 21.7% of swabs, two species of *Candida* were identified and in 2.2% of swabs three species identified. The most common colonization risk factor was associated with smoking (32.6%). **Conclusions.** Yeasts of *Candida* species are part of the healthy microflora of the oral cavity in people of different ages and may occur as single species or coexist with other species. The coexistence of chronic diseases, propensity for oral cavity infections and smoking significantly influence the *Candida* colonization. This may result in future clinical consequences, for example in cases of immunodepression.

Keywords: *Candida*, *Candida albicans*, *Candida tropicalis*, *Candida glabrata*, oral cavity, microbiota

Streszczenie

Wprowadzenie. Grzyby z rodzaju *Candida* mogą w warunkach fizjologicznych występować na powierzchni błony śluzowej jamy ustnej, jednak równocześnie uznawane są za drobnoustroje oportunistyczne. Chorobotwórczość *Candida* spp. zależy od właściwości szczepu, inwazyjności, zdolności do adhezji i tworzenia biofilmu oraz wytwarzania enzymów umożliwiających kolonizację tkanek. Celem pracy była ocena częstości występowania *Candida* spp. w mikrobiocie jamy ustnej u osób dorosłych w warunkach zdrowia oraz określenie związku pomiędzy czynnikami ryzyka a kolonizacją. **Materiał i metody.** Grupę badaną stanowiły 72 zdrowe osoby (mieszkańcy województwa lubelskiego, w wieku od 18 do 73 lat), od których zebrano wywiad odnośnie obecności czynników wpływających na stan mikrobioty jamy ustnej (występowania w przeszłości chorób jamy ustnej, istnienia chorób przewlekłych oraz palenia papierosów). Do udziału w badaniach zakwalifikowano osoby, które w trakcie ich prowadzenia zadeklarowały brak infekcji w obrębie jamy ustnej. Pobrany materiał kliniczny (wymazy z jamy ustnej) posiano na podłoże chromogenne do izolacji i różnicowania *Candida* spp. **Wyniki.** Częstość występowania *Candida* spp. odnotowano na poziomie 63,8%. Najczęściej zidentyfikowano *C. albicans* (56,5%), rzadziej *C. glabrata* (45,6%) i *C. tropicalis* (23,9%). W 21,7% wymazów rozpoznano po dwa gatunki *Candida*, a w 2,2% wymazów trzy. Najczęstszym deklarowanym czynnikiem ryzyka kolonizacji było palenie tytoniu (32,6%). **Wnioski.** Drożdżaki z rodzaju *Candida* są obecne w mikroflorze jamy ustnej w warunkach zdrowia u osób w różnym wieku i mogą występować jako pojedyncze gatunki lub współistnieć obok siebie w różnych konfiguracjach. Współistnienie chorób przewlekłych, skłonności do infekcji w obrębie jamy ustnej oraz palenie papierosów wpływają istotnie na kolonizację jamy ustnej drożdżakami, co może w przyszłości skutkować konsekwencjami klinicznymi w przypadku spadku odporności.

Słowa kluczowe: *Candida*, *Candida albicans*, *Candida tropicalis*, *Candida glabrata*, jama ustna, mikrobiom

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Introduction

In a healthy physiological state, the mucous membrane of the oral cavity creates a suitable environment for the colonization of many microorganisms, including *Candida* spp. yeasts. The ability to colonize tissue and the nature of infections caused by yeasts depends on the strain-specific features including invasiveness, adhesion and biofilm creation abilities, enzymatic activity and the immune status of the host [1-6]. *Candida albicans* is the main pathogenic species and the most frequent cause of candidiasis in humans. It was shown that this species caused proportionally more exogenous and endogenous infections (50-70%) and is the most frequent microorganism isolated from other yeast-like fungi in oral cavity candidiasis [2, 7]. *Candida glabrata* is the second most frequently obtained isolate from the mucous membrane of the oral cavity. It can occur independently or coexist with *C. albicans*. *Candida parapsilosis* and *C. tropicalis* are different species of yeast. They can also be isolated and proliferate in particular in cancer patients with generalized infection [8, 9]. *C. krusei*, *C. guilliermondi*, *C. famata*, *C. pseudotropicalis*, and *C. dubliniensis* are less common species but can also cause human infections [1, 2]. *Candida albicans*, as an opportunistic microorganism, may be a cause of superficial as well as systemic candidiasis, especially in patients with immunological disorders [3]. Steroid treatment, invasive medical procedures, skin injuries resulting from burns, diabetes, low birth weight and infection e.g. HIV are factors influencing the development of candidiasis [10, 11]. Local factors facilitating infections within the oral cavity include the usage of acrylic dentures, radiotherapy and anticancer medication and the resulting alteration of the oral cavity epithelium, salivary secretion disorders as well as its quantitative and qualitative alterations, bad oral hygiene, smoking, and alcohol consumption [12].

The first phase of tissue colonization and invasion of microorganisms is the phenomenon of adhesion [8]. *Candida* yeasts show the ability to adhere to various types of epithelial and endothelial cells, blood platelets, lymphocytes, leukocytes as well as biopolymers. *C. albicans*, in particular, adheres to the protein receptors of the salivary proteins, extracellular matrix and serum proteins [13]. The main adhesive proteins of *Candida* spp. are mannoproteins as well as Als (agglutinin-like sequence) Hwp (hyphal wall protein), Eap (enhanced adherence to polystyrene) [8, 12, 14]. Mannoproteins constitute around 15.2-22.9% of dry weight of cell wall of yeasts [10]. Enzymatic activity is the virulent trait that allows survival in the organism of the host. The ability of *Candida* spp. to produce enzymes facilitates invasion into the tissues [4] and secreted aspartic protease causes the degradation of the epithelium constituents, keratin, and collagen. This results in the destruction of proteins participating in the immunological response [8, 15]. This leads to epithelial damage in the invaded area and allows the pathogen to penetrate. *Candida* spp. produces acidic proteases that protect it from phagocytosis by the host's inflammatory cells which are significant in the first phase of the infection [8, 15].

The aim of the paper was to evaluate the frequency of *Candida* spp. occurrence in the microbiota of the oral cavity in healthy adults as well as establish the relationship between risk factors and colonization.

Material and methods

The study group consisted of 72 participants (59 women and 13 men), inhabitants of Lubelskie Voivodeship, Poland, in ages between 18 and 73 (average age amounted at 30, SD 14.2). Medical history concerning occurrence of oral diseases in the past, stabilized chronic diseases and smoking (classic cigarettes and electronic cigarettes) was collected from all participants. People qualified for the research declared no yeast infections in the oral cavity during the study. Swabs collected in the laboratory conditions from the interior cheek and palate surface constituted the clinical material. Swabs were collected once. The collected material was disseminated in the chromogenic microbiological bases for isolation and differentiation of species of *Candida* yeast (BIOMAXIMA; differentiation of *C. albicans*, *C. tropicalis*, *C. krusei*, *C. glabrata*). The cultures have been incubated in aerobic conditions in the temperature of $37^{\circ}\text{C} \pm 1^{\circ}\text{C}$ for 48 hours. The results and reading of the breeding were interpreted according to the base producer's guidelines: green colonies – *C. albicans*, blue colonies – *C. tropicalis*, pink-purple, shiny colonies – *C. glabrata* and matte, flossy, pink colonies – *C. krusei*. The consent for the study was obtained from the Bioethics Committee at Pope John Paul II State School of Higher Education in Białą Podlaska, Poland (no 9/2018). The collected data were statistically analyzed utilizing the Statistica v.10 software (Pearson's chi-square test, U Mann-Whitney's). The significance level in all analyzed cases was assumed at $p < 0.05$.

Results

The analysis of the mycological research

Out of 72 study participants, 46 patients (63.8%) tested positive for the colonization of *Candida* spp. yeast. The occurrence of only one species was reported in 76.1% of the positive samples (35 swabs): *C. albicans* (n=17; 36.9%), *C. glabrata* (n=13; 28.3%), *C. tropicalis* (n=5; 10.9%). The growth of *C. krusei* was not observed.

The growth of two species of *Candida* spp. was reported in 10 positive cultures (21.7%) *C. albicans* and *C. glabrata* – 10.9% (5 swabs), *C. albicans* and *C. tropicalis* – 6.5% (3 swabs), *C. glabrata* and *C. tropicalis* – 4.3% (2 swabs).

The growth of three *Candida* spp. species (*C. albicans*, *C. glabrata*, *C. tropicalis*) was observed in material from 1 patient.

C. albicans was reported in a total of 26 swabs (56.5%), *C. glabrata* in 21 swabs (46.6%) and *C. tropicalis* in 11 swabs (23.9%)

There was no significant dependence between the occurrence of certain *Candida* species and gender or age of the studied group. Details of the mycological results are presented in Table 1 and Table 2.

Table 1. The results of breeding toward *Candida* spp. in swabs from oral cavities of healthy people

The results of breeding	Swabs	<i>C. albicans</i>	<i>C. glabrata</i>	<i>C. tropicalis</i>	Swabs
	N(%)				N(%)
Positive	46(64)	+	-	-	17(36.9)
		-	+	-	13(28.3)
		-	-	+	5(10.9)
		+	+	-	5(10.9)
		+	-	+	3(6.5)
		-	+	+	2(4.3)
		+	+	+	1(2.2)
Negative	26(36)	-			

Table 2. *Candida* spp. species noted in cultures from oral cavity – classification according to the age of study participants

Age	Studied group N(%)	<i>C. albicans</i>	<i>C. tropicalis</i>	<i>C. glabrata</i>
18-30	27(58.7%)	9	x	-
		4	-	x
		8	-	-
		2	x	x
		4	x	-
31-40	8(17.4%)	3	x	-
		3	-	x
		1	x	
		1	-	x
41-50	4(8.7%)	1	x	-
		1	-	x
		1	-	x
		1	x	-
>50	7(15.2%)	4	x	-
		1		x
		1	-	x
		1	x	x
Total	46	26(36.1%)	11(15.3%)	21(29.2%)

The analysis of the physical examination

Participants were also asked about past oral cavity ailments such as dental caries, gum diseases, mucosal inflammation, and others. Sixteen people (16/72, 22%) reported the occurrence of one or multiple of the above-mentioned ailments (Table 3). Out of them, in eleven people (11/16, 69%) the growth of different yeast species was observed. *C. albicans* was reported most often ($p=0.01$). Seven out of eleven people (63.6%) informed about caries lesions in teeth. *C. albicans* were present in the cultures of four of them. In two cases *C. albicans* and *C. tropicalis* coexisted while in one case the coexistence of *C. albicans*, *C. glabrata*, and *C. tropicalis* was reported. The detained data was presented in Table 3.

Table 3. The occurrence of *Candida* spp. species depending on the declared oral cavity diseases

Oral cavity diseases	Number of people (N)		<i>C. albicans</i>	<i>C. tropicalis</i>	<i>C. glabrata</i>
Dental caries	8	4	x	-	-
		1	-	x	-
		1	-	-	x
		1	x	-	x
		1	x	x	x
Gum diseases	3	1	x	x	-
		2	x	-	x
Dental caries/ gum diseases	5		-	-	-
Total	16		9(56.2%)	3(18.7%)	5(31.2%)

Self-reports by the participants revealed 59 participants (81.9%) did not have any stabilized chronic diseases, 4 participants (5.6%) declared cardiovascular diseases, 3 participants (4.1%) atopic skin diseases and 10 people (13.9%) indicated other diseases (endocrinologic, autoimmune, Lyme borreliosis, asthma). The growth of *C. albicans* was reported more often in the smears of people who declared chronic diseases ($p=0.02$).

Nineteen participants were smokers (19/72, 26.4%). Of these 14 smoked standard cigarettes (19.4%), 3 used electronic cigarettes (4.2%) and 2 (2.8%) used both interchangeably. No growth of *Candida* spp. in smears from oral cavities was observed in 4 out of 19 smokers (4/19, 21%) and in 15 participants (15/19, 79%) growth of *Candida* spp. yeasts was observed. Eleven participants (11/15, 73%) had growth of single species *C. albicans*, *C. tropicalis*, *C. glabrata*. In three of these (3/15, 20%) there was simultaneous growth of two *Candida* spp. species and in one person (1/15, 7%) who smokes more than 20 cigarettes a day, the growth of three species - *C. albicans*, *C. tropicalis*, *C. glabrata* was observed (Table 4). The growth of *C. tropicalis* was more often noticed in samples gathered from smokers ($p=0.02$).

Table 4. The occurrence of *Candida* spp. species in people smoking regular cigarettes and electronic cigarettes

Smoking	Number of cigarettes	Number of people (N)	<i>C. albicans</i>	<i>C. tropicalis</i>	<i>C. glabrata</i>
Regular cigarettes	up to 10	4	x	-	-
		2	-	x	-
		1	-	-	x
		1	x	-	x
	11-20	1	-	x	-
	>20	1	-	x	x
		1	x	x	x

Electronic cigarettes	1	x	-	-
	1	x	x	-
Regular cigarettes and electronic cigarettes interchangeably	1	x	-	-
	1	-	-	x
Total	15	9(60%)	6(40%)	5(33%)

Discussion

It is currently assumed that, in healthy people, oral cavity microbiota may include *Candida* spp. When exposed to certain predisposing factors this may constitute a danger as *Candida* spp. participates in the formation of local and generalized mycoses [2, 16, 17]. *Candida* spp, especially *C. albicans* as a commensal species may be included in the population colonizing the oral cavity of healthy adults [18]. Initial contact and colonization usually occur in infancy. This study shows that the obtained strains can exist in the microflora for many years. Mild commensal colonization may change pathogenic nature in case of developing immunological disorders or injuries to the mucous membrane. An individual's sensitivity to *Candida* spp. infections increases with the accessibility of modern treatment methods including antibiotic therapy and solid organs transplantation [19]. The introduction of chemotherapy and radiotherapy to treatment processes may weaken immunological barriers predisposing to fungal infections [20, 21]. *Candida* species are also one of the causes of invasive bloodstream infections [19]. Research carried out by Delaney et al. showed that *Candida* species present in the oral cavity and constituting the mycobiome influence the bacterial microbiota and the planning of therapeutic interventions should take into consideration the ability of *Candida* to create biofilms [22].

Previous studies on the incidence of yeast occurrence in the oral cavities of healthy individuals have diverse results. For example, fungi are present in 20-60% of the population. In children and adolescents, this ratio is twice as high as in adults [23, 24]. Gajdzik-Plutecka et al. report that in oral cavities of healthy children and adolescents the occurrence of *Candida* spp. is around 45-65% while in adults at 20-50% [25]. Singh et al. reported that *Candida* spp., especially *C. albicans*, may be present in oral cavities in 30-50% of healthy adults [18]. In this study, the presence of these fungi was reported to be 64% of study participants: 58.7% in people ages 18-30, 17.4% in ages 31-40, 8.7% in ages 41-50 and 15.2% in people above 50 years of age. Thus, the result is comparable to the analyses presented by other researchers. Others have shown the presence of *Candida* to be 59.5% and 30.7% of healthy people aged between 20 and 25 years [26]. *C. albicans* is the fungi species most frequently isolated from the oral cavity. *C. glabrata* and *C. tropicalis* appear less often [23]. In this study, the growth of *C. albicans* was found in 56.5% swabs collected from oral cavities of adults. Other species appeared less often. *C. glabrata* was observed in 45.6% of swabs, *C. tropicalis* in 23.9%, and the growth of *C. krusei* was not observed. Single species (*C. albicans* or *C. glabrata* or *C. tropicalis*) appeared in 36.9% of people, 28.3% and 10.9% respectively. Two species of *Candida* spp. in different configurations were observed in 13.9% of study participants while three species in 1.4%.

C. albicans and other species like *C. parapsilosis*, *C. glabrata*, and *C. tropicalis* may cause endogenous and exogenous infections. However, *C. krusei* does not occur in healthy physiological flora and can only cause infect exogenously which frequency increases with the application of intravascular cannulation and parenteral feeding [8].

Dental caries, gum, and periodontal diseases are the factors influencing the microbiota of the oral cavity with *Candida* spp. A significant dependency between the number of teeth with dental caries and the colonization of *Candida* spp. was reported [26, 27]. In this study, in the majority of study participants (69%) who reported the above-mentioned ailments, the presence of *Candida* spp. was observed. Zaremba-Jaworska et al. analyzed patients with prosthetic stomatopathy and reported the occurrence of *C. albicans* in 57.58%, *C. tropicalis* in 18.18% and *C. glabrata* in 14.14% of cases [28]. Another significant factor predisposing to the colonization of the oral cavity by *Candida* spp. is smoking. Smoking influences the composition and amount of saliva which may foster the occurrence of yeast [29]. Krishnan et al. evaluated the occurrence of *Candida* spp. in saliva samples collected from smokers and non-smokers with periodontitis and from the control group (non-smokers without periodontitis). *Candida* spp. was observed in 76.6% of smokers with periodontitis, 73.3% of non-smokers with periodontitis and 36.6% of control group members. Statistical differences were noticed between smokers with periodontitis and the control group. *Candida albicans* was the species most often isolated from smokers' saliva samples (50%), then *C. krusei* (10%) and *C. tropicalis* (10%). To less often observed species belonged *C. glabrata* (3.3%) and *C. parapsilosis* (3.3%) [30]. The analysis showed that the presence of *Candida* spp. (33.6%) was reported in people who declared smoking regular cigarettes or electronic cigarettes. *C. tropicalis* was

observed most often. This observation may be a starting point for further research on the dependency between the presence of individual *Candida* spp. species and the type of smoked cigarettes. According to Wu et al. the substances in cigarettes facilitate the development of many microorganisms including *S. mutans*, *S. gordonii*, *Actinomyces* and *C. albicans*. Moreover, smoking influences the changes in saliva which fosters the creation of an environment favourable for the development of dental caries and potential pathology of the oral cavity [31].

Conclusions

Candida yeasts can show increased presence in the microbiota of the oral cavity in people of any ages. They can occur as individual species (*C. albicans* or *C. tropicalis* or *C. glabrata*) and can coexist with other species. Additionally, chronic diseases, predisposition to oral infections and smoking all significantly influence the composition of microflora and the appearance of fungi (quantitatively and with multitudes of other species). In the future, if the immune system becomes suppressed, this may result in various pathological states which can vary from mild to severe fungal infections, e.g. invasive fungal disease.

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