There is an association between colonization by *Candida spp*. and periodontal disease - results of a systematic review

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• Conflicts of interest: none declared.

ABSTRACT

Objective: to evaluate the level of available scientific evidence that associates *Candida spp*. with periodontitis. **Materials and Methods:** to do this, an electronic search was conducted in the main electronic databases (PubMed, Scopus, Web of Science, Gray Literature) without restriction on the language or date of publication on case-control studies, systematic reviews and meta-analyses that evaluated the association between the presence of Candida spp. in patients with periodontitis and healthy patients. The risk of bias in the studies was assessed using the Newcastle-Ottawa criterion for case-control studies, and the data related to the statistical parameters of interest (e.g., odds ratio, confidence interval and p-value) were extracted from the studies. **Results:** initially, 1553 articles were identified, but only 04 met the inclusion criteria and were included for analysis. Only one study had a high risk of bias. Among the selected studies, two demonstrated that patients with periodontitis have a higher concentration of Candida sp. in subgingival sites when compared to healthy patients. **Conclusion:** based on the results, it was possible to establish an association between the presence of Candida spp. in subgingival sites with periodontitis. However, the number of studies on the subject is still small. Further case-control studies are recommended so that a better consensus can be defined.

Keywords: *Candida spp*.; Periodontal disease; Periodontitis.

Introduction

Although present in healthy individuals, *Candida spp*. (e.g.: C. albicans, C. parapsilosis, C. tropicalis, C. krusei, C. dubliniensis) is recognized as opportunistic pathogens in immunologically compromised humans.[1] In the oral mucosa, these microorganisms mainly colonize the palatal, jugal and alveolar mucosa, as well as the dorsal surface of the tongue.[2]

Over the years, the presence of *Candida spp*. in subgingival sites, including elevated counts in patients diagnosed with periodontitis — a more destructive form of periodontal disease —, which seems to suggest a possible association of these microorganisms with the etiology of this disease.[3-5]

In fact, research has shown that this species has relevant virulence factors that allow them to colonize these sites and are also capable of causing damage to the insertion periodontium. Among these factors, the ability to adhere to the epithelial cells of the gingiva and invade the underlying connective tissue can be highlighted, which are consequent to the production of enzymes that cause the rupture of cell membranes.[6,7] In the periodontal pockets, Candida spp. is still able to coagulate with bacteria, through commensal relations.[8,9] Still, in this same place, researches have suggested the potential *Candida spp*. of has to interfere with immune responses by inhibiting the polymorphonuclear leukocyte function and producing proteases capable of degrading immunoglobulins.[10]

In this way, understanding the role of *Candida spp*. in the etiology of periodontitis is essential, since this disease is considered a public health problem due to its high prevalence and the costs involved in its treatment.[11]

Currently, in relation to *Candida spp*., there are a number of studies that demonstrate presence in sites of patients affected by a periodontal disease.[12-15] However, the absence of control groups in these studies, composed of individuals without the disease, hinders or even prevents the association between the presence of these microorganisms and the etiology of periodontitis.

Thus, the objective of this study is to investigate the current literature on the association between the presence of Candida spp. at subgingival sites with the occurrence of periodontitis in humans.

Material and Methods

This systematic review was performed according to PRISMA standards[16] — Preferred Reporting Items for Systematic Reviews and Meta-Analysis — and was recorded in the PROSPERO (CRD) electronic database.

PECO Question

Based on the components that define the PECO question [i.e.: (P) patients with periodontitis; (E) presence of Candida spp. in subgingival sites; (C) patients without periodontitis; (O) association between the presence of *Candida spp*. and clinical diagnosis of periodontitis], the following clinical question was formulated: is there an association between

the presence of *Candida spp.* in subgingival sites and peri-odontitis?

Research Strategy and Study Selection

An extensive electronic search was performed in the PubMed, Web of Science and Scopus databases using MeSH terms, their synonyms and free terms combined with the Boolean operators "OR" and "AND". The search strategy used is expressed in (Table 1). No restriction was made regarding the language or date of publication of the articles. However, only studies published until August 1, 2018 were considered.

following were assessed: relation between the presence of *Candida spp.* and the severity of the disease (i.e. chronic or aggressive) and the relation between the different species of the genus Candida (i.e. C. albicans, C. parapsilosis, C. krusei, C. tropicalis, C. glabrata) and the occurrence of peri-odontitis.

Duplicates (identical studies available in different electronic databases) and the following types of study were excluded: narrative literature reviews, editorials, clinical cases, uncontrolled cross-sectional studies, clinical case reports, and book chapters.

Table 1. Search strategy performed in electronic databases

Database	Search Strategy
PubMed	**#1** (((((((((Gingivitis[MeSH Terms]) OR Periodontitis[MeSH Terms]) OR Chronic periodontitis[MeSH Terms]) OR Agressive periodontitis[MeSH Terms]) OR Periodontal diseases[MeSH Terms]) OR Gingivitis[Title/Abstract]) OR Periodontitis[Title/Abstract]) OR Chronic periodontitis[Title/Abstract]) OR Agressive periodontitis[Title/Abstract]) OR Periodontal diseases[Title/Abstract] **#2** (((((((((Candida[MeSH Terms]) OR Candida albicans[MeSH Terms]) OR Candida glabrata[MeSH Terms]) OR Candida tropicalis[MeSH Terms]) OR Candida parapsilosis[MeSH Terms]) OR Candida[Title/Abstract]) OR Candida albicans[Title/Abstract]) OR Candida glabrata[Title/Abstract]) OR Candida tropicalis[Title/Abstract]) OR Candida krusei[Title/Abstract]) OR Candida dubliniensis[Title/Abstract] **#3** (((((((((Nystatin[MeSH Terms]) OR Mycostatin[MeSH Terms]) OR Antifungal agents[MeSH Terms]) OR Therapeutic fungicides[MeSH Terms]) OR Antifungal antibiotics[MeSH Terms]) OR Nystatin[Title/Abstract]) OR Mycostatin[Title/Abstract]) OR Antifungal agents[Title/Abstract]) OR Therapeutic fungicides[Title/Abstract]) OR Antifungal antibiotics[Title/Abstract] **#1 AND #2**
Scopus	**#1** (TITLE-ABS-KEY (gingivitis) OR TITLE-ABS-KEY (periodontitis) OR TITLE-ABS-KEY (chronic AND periodontitis) OR TITLE-ABS-KEY (agressive AND periodontitis) OR TITLE-ABS-KEY (periodontal AND diseases)) **#2** (TITLE-ABS-KEY (candida) OR TITLE-ABS-KEY (candida AND albicans) OR TITLE-ABS-KEY (candida AND glabrata) OR TITLE-ABS-KEY (candida AND tropicalis) OR TITLE-ABS-KEY (candida AND parapsilosis) OR TITLE-ABS-KEY (candida AND krusei) OR TITLE-ABS-KEY (candida AND dubliniensis)) **#1 AND #2**
Web Of Science	**#1** (Gingivitis) OR TOPIC: (Periodontitis) OR TOPIC: (Chronic periodontitis) OR TOPIC: (Agressive periodontitis) OR TOPIC: (Periodontal diseases) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Stipulated time = All years **#2** (Candida) OR TOPIC: (Candida albicans) OR TOPIC: (Candida glabrata) OR TOPIC: (Candida tropicalis) OR TOPIC: (Candida parapsilosis) OR TOPIC: (Candida krusei) OR TOPIC: (Candida dubliniensis) Indixes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Stipulated time=All years **#1 AND #2**

Definition of Inclusion Criteria for the Studies

Control-case studies, systematic reviews and meta-analyses on the subject were included. The inclusion criteria were defined based on the question to be answered in this review. Thus, (P) included patients with clinical and radiographic diagnosis of periodontitis, who might or might not show associated systemic problems. Subsequently, (E) included the presence of *Candida spp.* in periodontal sites, detected by laboratory tests, and (C) included patients with or without systemic problems without clinical diagnosis of periodontitis. The primary outcome (O) included the association between the presence of *Candida spp.* in subgingival sites and the diagnosis of periodontitis. As secondary outcomes, the

Study Selection

The titles and abstracts of the articles were independently assessed by two reviewers (BMS and BLS), who excluded those who did not meet the inclusion criteria. If the title and/or abstract did not provide the information to determine whether or not the study should be included, the articles were evaluated in their entirety to see if they met the inclusion criteria. Studies that appeared in more than one database were considered only once. The cases of disagreement were solved by creating a consensus between the two examiners. After the selection of the articles based on the reading of the titles and abstracts, they were read in full in order to verify if they fulfilled the eligibility criteria.

Qualitative Risk Assessment of Bias

The quality of the studies was assessed independently based on the Newcastle-Ottawa (NOS) rating scale for cohort and case-control study designs.[17] The scale contemplates nine items, so that each item is assigned a single star — except for the item "comparability", which can be contemplated with two stars. In this way, the maximum score that a study can achieve is nine stars, which defines high methodological quality and, therefore, low risk of bias.

Data Extraction and Synthesis

The following data were extracted from each study: authors (year of publication); number of participants (n) in the case and control groups; mean age and sex of participants;

periodontal examination protocol; method of detecting the presence of *Candida spp.*; measures of association between presence of *Candida spp.* and periodontal disease.

Results

The flowchart (Figure 1) illustrates the number of studies identified in each database and the process of selecting them. Initially, 1553 studies were found. This number was reduced to 978 after the duplicates were removed. From the preliminary reading of the titles and abstracts, 41 articles were selected and submitted to the analysis, however, only 04 met the eligibility criteria.[18-21] The bibliographic references of these articles were analyzed, however, no additional study was identified. Thus, the final sample consisted of 04 studies.
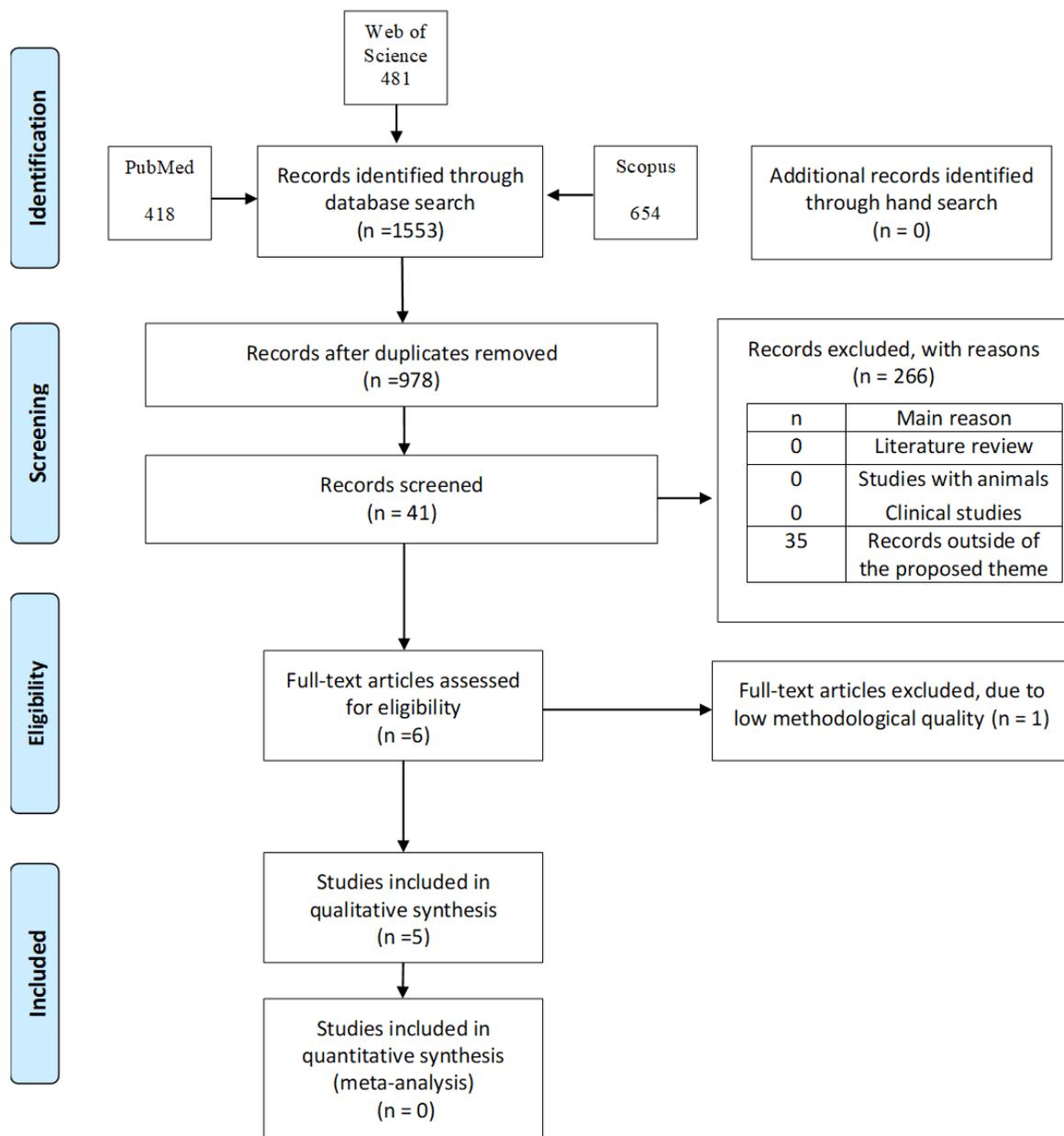

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: Prisma 2009 Flow Diagram. (From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *Preferred Reporting Items for Systematic Reviews and Meta-Analyses*: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097. For more information, visit www.prisma-statement.org)

According to the criteria proposed by the Newcastle-Ottawa qualification scale for case-control studies, most of the studies were considered of high methodological quality (Table 2). Only the study conducted by Koga Ito et al.[19] was characterized by a greater risk of bias, since it was not possible to establish the comparison between the case and control groups.

The data of interest extracted from the selected studies are summarized in Table 3. All the studies were written in English and published over the last two decades, two of them being carried out in Brazil, one in Chile and the other in Norway. The total number of participants varied between studies and only Canabarro et al.[21] mentioned performing sample calculations to define the sample size, although they did not show details of the sample.

Table 2. Criteria assessed according to the Newcastle-Ottawa qualification scale

Author (date)	Selection	Comparability	Outcome
Úrzua et al. (2008)	★★★	★	★★★
Canabarro et al. (2013)	★★★	★	★★★
Koga Ito et al. (2008)	★★	-	★★
Song et al. (2005)	★★★	★	★★★

Table 3. Data extracted from selected studies

Author(s) (year) Country	Studied groups	Characterization of the groups	Periodontal examination	Results
SONG et al. (2005) Norway	• Patients with periodontitis (n=70) • Healthy patients (n=45)	•51.2 ± 12.8 years 35♂ / 35♀ •32.9 ± 14.1 years 19♂ / 26♀	PD	• Heterogeneity of species in the analyzed groups. • Increased genetic diversity in patients with periodontitis • Absence of association between species and oral sites in groups
KOGA-ITO et al. (2008) Brazil	• Patients with chronic periodontitis (n=88) • Healthy patients (n = 68)	• 41.33 ± 5.54 years N.D. • 34.45 ± 7.93 years N.D.	PD	• Biotype 0000 most frequently isolated from patients with periodontitis • Absence of a characteristic model related to the disease
ÚRZUA et al. (2008) Chile	• Patients without periodontitis (n=28) • Patients with aggressive periodontitis (n=20) •Patients with chronic periodontitis (n=26)	• 27.9.2 ± 6.7 years 10♂ / 18♀ • 51.2 ± 12.8 years 35♂ / 35♀ • 51.2 ± 12.8 years 35♂ / 35♀	PI; BI; PD; CI	• Subgingival colonization by Candida spp. was more frequent in patients with chronic periodontitis (69.2%) than in patients without periodontitis (35.7%) (p=0.014) • Patients with chronic periodontitis have a higher density of hyphae at subgingival sites (0-6048 CFU) compared to the other groups (p=0.03) • C. albicans (87.5%); C. dubliniensis (8.4%) and C. glabrata (2.6%) were the most frequently isolated species • There was a strong association between C. albicans, C. glabrata and C. dubliniensis with chronic periodontitis (p <0.001)
CANABARRO et al. (2013) Brazil	• Patients without periodontitis (n=20) •Patients with mild to moderate chronic periodontitis (n=23) • Patients with severe chronic periodontitis (n=17)	•40.59 ± 13.79 years 6♂ / 14♀ • 43.69 ± 9.22 years 7♂ / 16 ♀ • 53.2 ± 11.58 years 9♂ / 8 ♀	PI; BI; PD; CI	• Hyphae were identified in 12 (30%) patients with chronic periodontitis and 3 (15%) patients without the disease • Largest number of species identified in patients with mild chronic periodontitis (C. albicans, C. parapsilosis, C. tropicalis and C. dubliniensis) • Absence of differences between patients with chronic periodontitis and without periodontitis in relation to the presence of hyphae in the subgingival biofilm • Patients with moderate (61.25 CFU/individuals) and mild (51 CFU/individuals) chronic periodontitis showed higher hyphae density compared to patients without periodontitis (1 CFU/individuals) (p = 0.028 and p = 0.013, respectively)

Caption: PD = probing depth; PI = periodontal index; BI = index of gingival bleeding; CI = clinical insertion; ND = not described.

4

In general, the case and control groups were defined based on the clinical diagnosis of periodontitis. In all studies, periodontitis was characterized based on the depth of the periodontal pockets at probing, usually greater than 5.0mm.[18-21] Only in two studies there was greater detailing of other periodontal parameters, such as the visual clinical aspects of the gingiva, biofilm index; index of gingival bleeding and loss of insertion.[20,21]

Both Urzúa *et al.*[20] and Canabarro *et al.*[21] agreed to more frequently detect the presence of Candida spp. at subgingival sites of patients with periodontitis. In these same studies, the authors found that patients with periodontitis showed a greater amount of these microorganisms (expressed in CFU) at subgingival sites.

Among the different species, C. albicans was identified with greater frequency and quantity in subgingival sites in both studies.[20,21] However, only Urzúa *et al.*[20] reported a strong association between chronic periodontitis with the presence of C. albicans, C. glabrata and C. dubliniensis.

Discussion

Considering the number of studies available on the subject, any proposal to associate the presence of Candida spp. in subgingival sites with the etiology of periodontitis is risky. As observed, only 04 studies — 0.41% of the total number of studies found — met the proposed inclusion criteria.

It is important to consider that a series of researches has been demonstrating over the years the presence of Candida spp. in subgingival sites of patients with periodontitis. However, in almost all of these studies, only patients with the disease are evaluated.[12-15] Consequently, the lack of comparison with healthy patients makes it difficult, or even impossible, to attempt to establish an association between these microorganisms and the etiology of periodontitis.

Thus, in this review, only case-control studies were selected, since their design allows establishing association relations between exposure and disease. Initially, based on the inclusion criteria, 05 studies were selected. However, one of the studies was excluded due to the high risk of bias, attributed to the lack of a series of information relevant to its interpretation.

Based on the Newcastle-Ottawa qualification criterion, the remaining 04 studies were at low risk of bias. It is relevant to consider that most of the studies scored once in the "comparison" parameter, considering that only age was contemplated for the purpose of this review, despite the statistical differences detected between the studies.[20,21] Only the study by Koga Ito *et al.*[19] was not punctuated in this parameter due to the lack of relevant information so that it could be interpreted.

Depth to periodontal probing was the clinical parameter used in all selected studies for the division of case and control groups, although there was no consensus on the size of periodontal pockets and the number of sites affected by the disease. However, in only two studies the information on the exams — including other clinical parameters — and the calibration of the examiners were described in detail.[20,21]

The determining factor for treating a disease correctly is to know its cause. Currently, the polymicrobial model is used to explain the etiology of periodontitis. In this context, the bacteria of the so-called red complex are pointed as the main periodontopathogens.[22] However, as pointed out by Canabarro *et al.*,[21] the subgingival environment harbors other non-bacterial species, such as fungi of the genus Candida, whose role in the onset and/or progression of the lesions needs to be better understood.

Both Urzúa *et al.*[20] and Canabarro *et al.*,[21] found more frequent hyphae at subgingival sites of patients with periodontitis compared to healthy patients. Similarly, these authors found a higher density — expressed in CFU/individuals — of these microorganisms in the same sites when patients were diagnosed with the disease.

According to the same studies, C. albicans was the species found in higher frequency and quantity. Other species were found, but always associated with C. albicans (eg C. dubliniensis, C. glabrata, C. parapsilosis and C. tropicalis). Similarly, the two studies agreed to demonstrate that C. albicans was most frequently found in individuals with chronic periodontitis.[20,21]

Among the different species, C. albicans has been most commonly associated with pathological conditions in humans.[23] The results obtained by the selected studies show the presence of these microorganisms inside periodontal pockets, adding important information to scientific literature.

The assumption of this species' participation in the etiology of periodontal diseases — particularly periodontitis — seems to be supported by research that lists relevant virulence factors that would contribute to the invasion and colonization of subgingival sites.[24,25] Among these factors is the production and release of phospholipases and proteases that confer on Candida the ability to adhere to the epithelial cells of the gingiva and to invade the underlying connective tissue deserve attention.[26,27] In addition, the ability of these microorganisms to co-aggregate with bacteria of the subgingival biofilm has been discussed, which represents an additional advantage for the colonization of these sites.[28,29]

It is believed that sites affected by advanced periodontal lesions may favor colonization by *Candida spp.*, since some bacterial species, such as P. gingivalis, when altering the host's response, create favorable conditions for the development of hyphae.[20] The presence of these microorganisms may result in a worse clinical picture in light of the production of enzymes capable of destroying the periodontal tissues of sustentation.[31]

As discussed above, there appears to be an association between Candida spp. and periodontitis, particularly the chronic form of this disease. However, due to the small number of studies on the subject, it is necessary to consider that the evidence is limited and that more research is needed to confirm this assumption.

Conclusion

Based on the results of this systematic review, it should be considered that, although there appears to be an association between the presence of Candida spp. in subgingival sites with periodontitis, the number of case-control studies on the subject is still small. Further case-control studies are recommended so that a better consensus can be defined.

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