IBEROAMERICAN JOURNAL OF MEDICINE
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Review

Candida species oral detection and infection in patients with diabetes mellitus: a meta-analysis

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ARTICLE INFO

Article history:
Received 28 December 2020
Received in revised form 27 January 2021
Accepted 30 January 2021

Keywords:
Blood glucose
Oral candidiasis
Diabetes mellitus
Risk factors

ABSTRACT

Introduction: Diabetes mellitus is a chronic metabolic disorder that induces elevated plasma glucose levels. Diabetic patients are more susceptible to infections, especially fungal infections. There is a direct relationship between increased blood glucose levels and the number of *Candida* hyphae in the oral mucosa. This study aimed to evaluate oral candidiasis and the different *Candida* species found in patients with and without diabetes mellitus.
Methods: A search for studies on oral candidiasis and diabetes mellitus was carried out in the following databases: PubMed (MEDLINE, Cochrane Library), Web of Science (WoS) and Google Scholar. For dichotomous outcomes, the estimates of effects of an intervention were expressed as odds ratios (OR) using the Mantel-Haenszel (M-H) method with 95% confidence intervals.
Results: 25 studies were included in this meta-analysis. Diabetes Mellitus patients tripled the probability of being infected by *Candida* species (OR:3.16, p<0.001). Likewise, *Candida* species infections were more likely in patients with poor glycemic control (OR:2.94, p<0.001) and with dentures (OR:2.22, p<0.001). In contrast, neither gender nor diabetes mellitus type of diabetes conditioned fungal infections (p>0.05). The most prevalent *Candida* species in both diabetics and controls were *C. albicans* and *C. tropicalis*. Diabetics had significantly fewer C. non-albicans species oral infections than non-diabetics (p=0.04).
Conclusions: Diabetics are more prone to oral candidiasis, especially *C. albicans* infections.

HOW TO CITE THIS ARTICLE: Rodríguez-Archilla A, Piedra-Rosales C. *Candida* species oral detection and infection in patients with diabetes mellitus: a meta-analysis. Iberoam J Med. 2021;3(2):115-121. doi: 10.5281/zenodo.4495286.

1. INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder caused by dysfunction of the β-cells of the pancreatic islets that induces elevated plasma glucose levels. This disease affects more than 425 million people around the world without predilection for either sex. Two types of diabetes mellitus have been described: type 1 and 2. Type 2 DM is the most common, accounting for 90% of cases and is mainly caused by a lifestyle with high-calorie diets, low physical activity, or smoking [1]. Diabetic patients are more susceptible to infections, especially fungal infections. Oral manifestations in diabetics include a higher

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ISSN: 2695-5075 /
http://doi.org/10.5281/zenodo.4495286

prevalence and severity of both dental caries and periodontal disease, salivary flow dysfunction, impaired healing, and opportunistic infections. Patients with diabetes mellitus are more prone to fungal infections, probably due to immune disturbance and salivary composition changes. Considering fungal infections, diabetics show a higher prevalence of oral lesions associated with *Candida* infection, especially denture stomatitis, pseudomembranous candidiasis, median rhomboid glossitis and angular cheilitis. Moreover, diabetics usually have systemic medications that favor the reduction of salivary flow, facilitating the proliferation of microorganisms in oral biofilms. Approximately 30% of diabetics have an oral yeast infection at some point in their life [2]. The main microorganism of oral candidiasis is *Candida albicans*, a polymorphic fungus with the ability to grow in the form of hyphae that colonize and invade the tissues. There is a direct relationship between the increase in blood glucose levels and the number of *Candida* hyphae in the oral mucosa [3]. This study aimed to evaluate oral candidiasis and the different *Candida* species found in patients with and without diabetes mellitus.

2. METHODS

A search for studies on oral candidiasis and diabetes mellitus was conducted in the following databases: PubMed (MEDLINE, Cochrane Library), Web of Science (WoS) and Google Scholar. Search strategies were developed for each database with a combination of Medical Subjects Headings (MeSH) terms and free text terms. The search terms were: "candidiasis, oral" [MeSH Terms] AND "diabetes mellitus" [MeSH Terms]; "oral candid*" AND "diabet *"; allintitle: "oral" ("candidiasis" OR "candida") ("diabetes" OR "diabetic"). After this initial search, 481 articles (145 in PubMed, 241 in WoS and 95 in Google Scholar) were found between 1967 and 2020; 173 of them duplicates, leaving 308 articles for elegibility. Two researchers (ARA and CPR) examined the titles and abstracts of the articles independently, and later, both selected the papers that were included in this meta-analysis. The inclusion criterion was subjects of any age with a diagnosis of either type 1 or type 2 diabetes mellitus. The exclusion criteria were: a) articles without full-text availability (n = 174), b) articles with a score below 6 stars from a maximum of 9 on the Newcastle–Ottawa methodological quality assessment scale [4] (n = 52), and

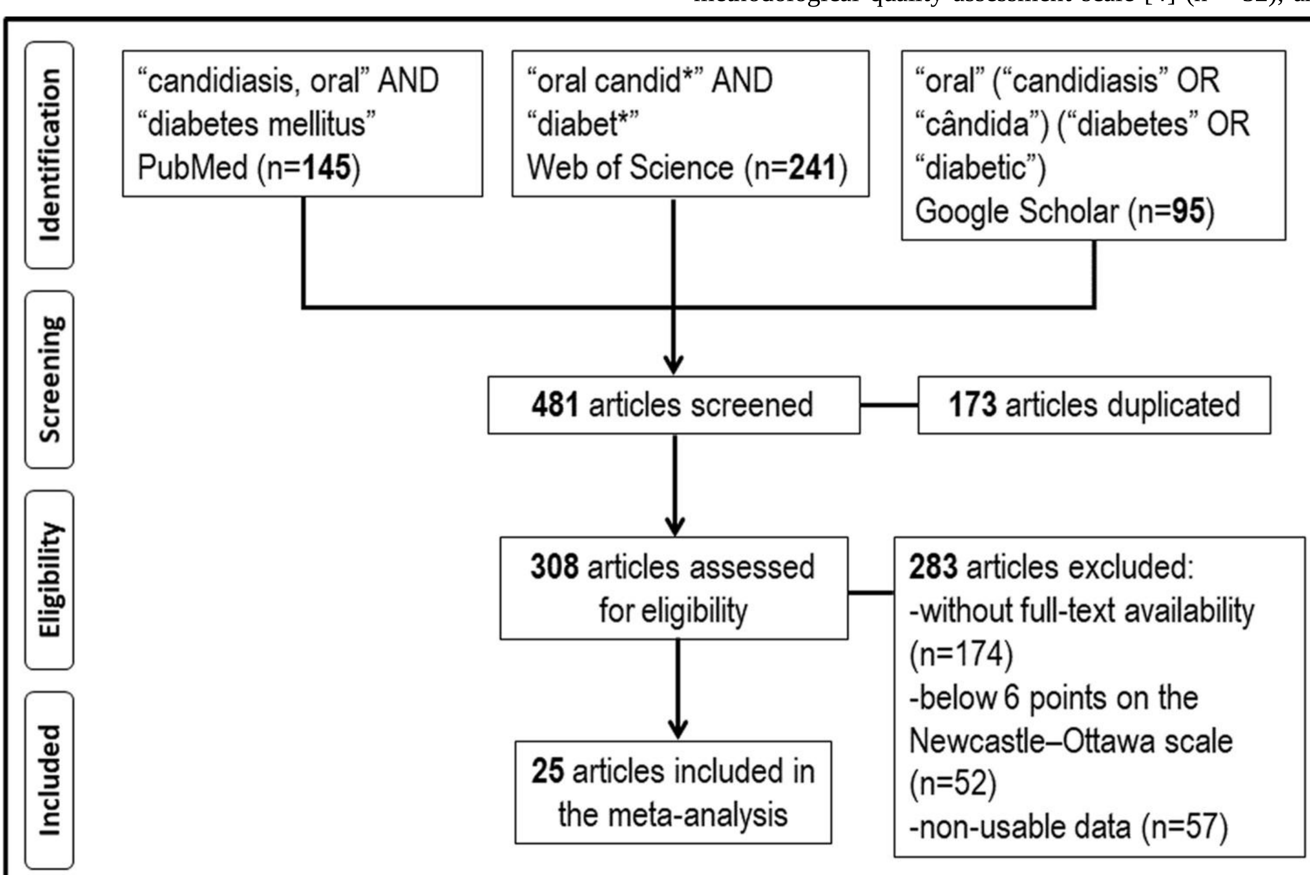

Figure 1: *Study flow diagram.*

c) studies with non-usable data (n = 57). Finally, twenty-five studies were included in this meta-analysis (Figure 1).

2.1. STATISTICAL ANALYSIS

Data were processed with the RevMan 5.4 meta-analysis software (The Cochrane Collaboration, Oxford, UK). For dichotomous outcomes, the odds ratio (OR) with the Mantel-Haenszel Chi-square formula (M-H) and 95% confidence interval (95% CI) was used. Heterogeneity was determined according to the P values and the Higgins statistic (I^2%). In cases of high heterogeneity ($I^2 > 50\%$), the random-effects model was applied. Pearson Chi-square test with Fisher's exact test was also used when required. Tables and a forest plot graph were used to present the results. The minimum level of significance was set at $p < 0.05$.

3. RESULTS

Only articles with low to moderate risk of bias (≥6 stars from a maximum of 9 stars) according to the Newcastle-Ottawa (NOS) quality scale [4], were considered in this study.

Table 1 presents the twenty-five studies [5-29] that reported oral *Candida* species detection in patients with and without diabetes mellitus, considering the different *Candida* detection methods used. Oral *Candida* species were detected in 1453 (47.3%) of 3073 diabetics (range: 16.4% [28] – 83.7% [16]) and 488 (25.0%) of 1953 non-diabetics (range: 4.0% [23] – 81.4% [25]).

Twenty-two studies [5-11, 13, 15-25, 27-29] assessed the oral detection of *Candida* species in patients with and without diabetes mellitus (Figure 2). Diabetic patients were 3.16 times more likely to have *Candida* species in their oral microbiota, finding highly significant statistical differences (OR = 3.16; 95% CI: 2.21 to 4.52; p < 0.001).

The main risk factors related to oral *Candida* infection in patients with diabetes mellitus are shown in Table 2. Eight studies [10, 12, 14, 15, 19, 23, 25, 26] examined the possible influence of gender on the probability of *Candida* oral infection. Gender did not affect to fungal infection

Table 1. Characteristic of the patients and effects of diphenhydramine ointment

Ref.	Year	Country	Medium	Diabetics			Non-Diabetics			NOS
				n	N	(%)	n	N	(%)	
Al-Attas [5]	2010	Saudi Arabia	SDA	50	150	(33.3)	7	50	(14.0)	7
Ayinampudi [6]	2018	India	CAC	9	14	(64.3)	17	31	(54.8)	6
Babatzia [7]	2020	Greece	PCR	22	74	(29.7)	13	70	(18.6)	8
Balan [8]	2015	India	SDA	39	60	(65.0)	4	30	(13.3)	7
Bartholomew [9]	1987	USA	SDA	45	60	(75.0)	20	57	(35.1)	8
Belazi [10]	2005	Greece	SDA, CAC	82	128	(64.1)	34	84	(40.5)	8
Bissong [11]	2015	Cameroon	SDA	32	149	(21.5)	5	102	(4.9)	8
Farooq [12]	2018	India	SDA	91	305	(29.8)				6
Guggenheimer [13]	2000	USA	PAS	93	405	(23.0)	15	268	(5.6)	8
Hill [14]	1989	Canada	SDA	25	51	(49.0)				6
Jafari [15]	2003	Iran	SDA	24	40	(60.0)	9	40	(22.5)	6
Javed [16]	2014	Pakistan	SDA, PCR	67	80	(83.7)	36	70	(51.4)	8
Jhugroo [17]	2019	Saudi Arabia	SDA, CAC	141	250	(56.4)	91	250	(36.4)	8
Kadir [18]	2002	Turkey	SDA	22	55	(40.0)	14	45	(31.1)	7
Kumar [19]	2005	India	SDA	78	103	(75.7)	27	100	(27.0)	8
Kumar [20]	2014	India	SDA	46	60	(76.7)	16	30	(53.3)	7
Matic-Petrovic [21]	2019	Serbia	SDA	25	68	(36.7)	15	78	(19.2)	8
Mohammadi [22]	2016	Iran	SDA, PCR	32	58	(55.2)	17	48	(35.4)	7
Obradovic [23]	2011	Serbia	SDA	59	100	(59.0)	2	50	(4.0)	7
Rajakumari [24]	2016	India	SDA	64	200	(32.0)	17	200	(8.5)	8
Sampath [25]	2019	Sri Lanka	SDA, PCR	204	250	(81.6)	66	81	(81.4)	8
Sampath [26]	2017	Sri Lanka	SDA, PCR	72	100	(72.0)				6
Shenoy [27]	2014	India	SDA, CAC	19	60	(31.7)	2	30	(6.7)	7
Trentin [28]	2017	Brazil	SDA	19	116	(16.4)	8	134	(5.9)	7
Zomorodian [29]	2016	Iran	CAC, PCR	93	137	(67.9)	53	105	(50.5)	8
TOTAL				**1453**	**3073**	**(47.3)**	**488**	**1953**	**(25.0)**	

Ref: References; NOS: Newcastle-Ottawa quality scale; n/N: number of Candida positive cases/total number of cases; (%): Percentage of positive cases; USA: United States of America; SDA: Sabouraud's dextrose agar; CAC: CHROMagar Candida; PAS: Periodic Acid-Schiff stain; PCR: Polymerase chain reaction.

Table 2. Risk factors related to oral *Candida* infection in patients with diabetes mellitus (DM)						
Risk factor	**Ref.**	**Outcome**	**OR**	**[95% CI]**	**I^2**	**p-value**
Gender	[10, 12, 14, 15, 19, 23, 25, 26]	Female	1.40	[0.95 to 2.08]	52%	0.09
DM type	[5, 19, 27, 29]	Type 1 DM	1.55	[0.74 to 3.24]	62%	0.24
Glycemic control	[7, 8, 14, 19, 20]	Poor	2.94	[1.73 to 5.01]	30%	< 0.001*
Denture wearer	[10, 14, 25, 26]	Yes	2. 22	[1.48 to 3.33]	47%	< 0.001*

*Ref: References; OR: Odds Ratio; [95%CI]: 95% confidence interval; I^2: Higgins statistic for heterogeneity (percentage); *statistically significant.*

with no statistically significant association (OR = 1.40; 95% CI: 0.95 to 2.08; p = 0.09). In the case of the diabetes mellitus type, four studies [5, 19, 27, 29] evaluated this parameter, noticing a higher prevalence of oral candidiasis in type 1 diabetes patients, although without reaching statistical significance (OR = 1.55; 95% CI: 0.74 a 3.24; p = 0.24).

Respect to glycemic control, five studies [7, 8, 14, 19, 20] pointed out that poor glycemic control increased 2.94 times the risk of oral *Candida* species infection, with highly significant statistical differences (OR = 2.94; 95% CI: 1.73 to 5.01; p < 0.001).

Other four studies [10, 14, 25, 26] also corroborated denture wearers were more than twice as likely to be infected with *Candida* species. In the statistical analysis, a highly significant association was found (OR = 2.22; 95% CI: 1.48 to 3.33; p < 0.001).

Table 3. Distribution of the different oral microbiota Candida species between diabetics and non-diabetics		
Candida species	**Diabetics n (%)**	**Non-diabetics n (%)**
C. albicans	441 (78.1)	183 (71.2)
C. tropicalis	53 (9.4)	33 (12.8)
C. parapsilosis	24 (4.2)	14 (5.5)
C. glabrata	23 (4.1)	10 (3.9)
C. krusei	21 (3.7)	12 (4.7)
C. kefyr	3 (0.5)	5 (1.9)
TOTAL p = 0.17[a]	**565 (100)**	**257 (100)**
Candida species	**Diabetics n (%)**	**Non-diabetics n (%)**
C. albicans	441 (78.1)	183 (71.2)
C. non-albicans species	124 (21.9)	74 (28.8)
TOTAL p = 0.04[a]*	**565 (100)**	**257 (100)**

*References: [5, 10, 16, 17, 21, 23, 25, 29]; [a]Pearson chi-square test; *statistically significant.*

Table 3 displays the distribution of the different *Candida* species found in oral microbiota between diabetic and non-diabetic subjects. The most prevalent species was *C. albicans* in both diabetics (78.0%) and non-diabetics (71.2%), followed by *C. tropicalis* (9.4% in diabetics and 12.8% in non-diabetics) and, the least prevalent, *C. kefyr* (0.5 % in diabetics and 1.9% in non-diabetics). When the different *Candida* species are classified in two groups (*C. albicans* species and *C. non-albicans* species), non-albicans species were more frequent in non-diabetics (28.8%) than in diabetics (21.9%), with statistically significant differences (p = 0.04).

4. DISCUSSION

Data from twenty-five studies on oral candidiasis and *Candida* species detection in diabetics have been included in the present meta-analysis.

In this study, diabetic patients were 3.16 times more likely to have *Candida* species in their oral microbiota than non-diabetics, with a highly significant statistical relationship (p < 0.001). Of the 22 studies that studied this variable, 20 of them [5-10, 13, 15-25, 27, 29] found a higher prevalence of *Candida* species detection in diabetics compared to the two studies [11, 28] that found oral *Candida* species more frequently in non-diabetics, although without statistical significance. *Candida* species have a predilection for colonizing the oral cavity, particularly in patients with diabetes mellitus, with percentages ranging between 60% and 80% of diabetics. Oral mucosa in diabetics provides a less hostile ecosystem for oral colonization by *Candida* species. This fact could be related to factors such as hyposialia, the use of dentures, the degree of glycemic control and the intake of drugs. In diabetics with poor metabolic control, an oral environment rich in sugars permits high levels of glucose in saliva and can contribute to the persistence of aciduric yeasts in the oral cavity. Moreover, carbohydrates in the diet may be a contributing factor, promoting adhesion, biofilm formation, and yeast colonization in the oral environment [25]. Some studies [11] report a lower frequency of oral candidiasis in diabetics because they do not establish well-defined diagnostic criteria and the diagnosis is not made by calibrated examiners or specialists. The diagnosis made by a calibrated examiner guarantees a correct evaluation of oral candidiasis, increasing the reliability of the clinical

Study or Subgroup	Diabetics Events	Diabetics Total	Non-diabetics Events	Non-diabetics Total	Weight	Odds Ratio M-H, Random, 95% CI
Al-Attas 2010 [5]	50	150	7	50	4.6%	3.07 [1.29, 7.32]
Ayinampudi 2018 [6]	9	14	17	31	3.4%	1.48 [0.40, 5.45]
Babatzia 2020 [7]	22	74	13	70	4.9%	1.86 [0.85, 4.05]
Balan 2015 [8]	39	60	4	30	3.7%	12.07 [3.71, 39.24]
Bartholomew 1987 [9]	45	60	20	57	4.8%	5.55 [2.50, 12.33]
Belazi 2005 [10]	82	128	34	84	5.5%	2.62 [1.49, 4.62]
Bissong 2015 [11]	32	149	30	102	5.4%	0.66 [0.37, 1.17]
Guggenheimer 2000 [13]	115	382	16	243	5.5%	6.11 [3.52, 10.61]
Jafari 2013 [15]	24	40	9	40	4.3%	5.17 [1.95, 13.70]
Javed 2014 [16]	80	80	46	70	1.3%	84.83 [5.04, 1427.60]
Jhugroo 2019 [17]	141	250	91	250	5.9%	2.26 [1.58, 3.24]
Kadir 2002 [18]	22	55	14	45	4.7%	1.48 [0.64, 3.39]
Kumar 2005 [19]	78	103	27	100	5.3%	8.44 [4.49, 15.85]
Kumar 2014 [20]	46	60	16	30	4.4%	2.88 [1.13, 7.32]
Matic-Petrovic 2019 [21]	24	68	11	78	4.8%	3.32 [1.48, 7.46]
Mohammadi 2016 [22]	32	58	17	48	4.8%	2.24 [1.02, 4.93]
Obradovic 2011 [23]	59	100	2	50	3.1%	34.54 [7.94, 150.14]
Rajakumari 2016 [24]	64	200	17	200	5.4%	5.07 [2.84, 9.04]
Sampath 2019 [25]	229	250	66	81	5.0%	2.48 [1.21, 5.08]
Shenoy 2014 [27]	19	60	2	30	2.9%	6.49 [1.40, 30.09]
Trentin 2017 [28]	8	116	19	134	4.6%	0.45 [0.19, 1.07]
Zomorodian 2016 [29]	93	137	53	105	5.6%	2.07 [1.23, 3.50]
Total (95% CI)		**2594**		**1928**	**100.0%**	**3.16 [2.21, 4.52]**
Total events	1313		531			

Heterogeneity: Tau² = 0.53; Chi² = 101.68, df = 21 (P < 0.00001); I² = 79%
Test for overall effect: Z = 6.31 (P < 0.00001)

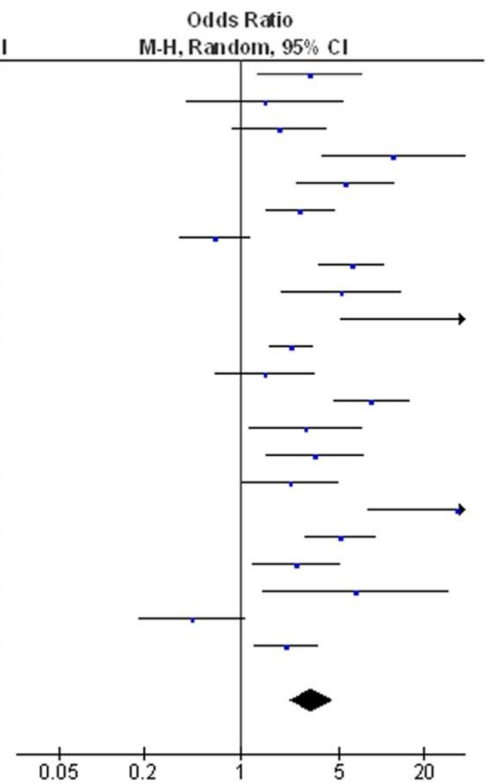

***Figure 2**: Study data and forest plot graph for the Candida species detection in subjects with and without diabetes mellitus.*

data obtained [28].

Gender did not condition the probability of *Candida* species oral infection or detection, with no statistically significant association (p = 0.09). Six studies (4 with statistically non-significant results [12, 14, 19, 23] and 2 with significant results [25, 26] that considered this factor, found a greater predisposition in the female gender. In contrast, two other studies [10, 15] observed a higher susceptibility to *Candida* infection in males. The association between gender and oral *Candida* species colonization is quite poorly defined with conflicting findings. Some studies [25] have observed that, in women with periodontitis, where inflammation of the oral mucosa is favored, there was a greater probability of fungal infection compared to men. In fact, *Candida* species colonization was observed in 88% of women and 73.1% of men. This increased fungi detection in women could be due to the hormonal changes observed in menopause that induces a series of changes in the oral and vaginal mucosa with a higher prone to candidiasis [26].

In the present study, the possible influence of diabetes mellitus (type 1 or type 2) type on the risk of suffering from candidiasis was also analyzed. A higher prevalence of oral candidiasis in patients with type 1 diabetes was found, although statistical significance was not achieved (p = 0.24). Of the four studies that analyzed this parameter, two [5, 19] observed a higher prevalence of type 1 diabetes compared to type 2, but only one [5] had statistical significance. On the other hand, the other two studies [27, 29] did not observe this higher prevalence in type 1 diabetes patients. Although oral candidal colonization appears to be greater in type 1 diabetics than in type 2, it has not been possible to establish a correlation between the rates of *Candida* species carriers, their concentration, the type of diabetes mellitus or antidiabetic drugs used [5]. Another possible explanation for this higher frequency in type 1 diabetics could lie in the resistance to some antifungals observed in these patients, in whom the treatment appears to be less effective [29].

In this study, a poor glycemic control increased 2.94 times the risk of *Candida* species oral infection with a highly significant statistical relationship (p < 0.001). All studies [7, 8, 14, 19, 20] that evaluated this variable were in favor of this inverse relationship between glycemic control and the *Candida* infection risk. Several studies [14,20] have shown that poorly controlled diabetics or those without metabolic control are significantly more susceptible to having oral candidiasis. Salivary glucose forms chemically reversible glycosylation products with proteins in tissues during hyperglycemic episodes and this leads to accumulation of glycosylation products in oral epithelial cells, which in turn may increase the number of receptors available for *Candida*. This finding suggests the fact that uncontrolled or poorly controlled diabetes increases susceptibility to oral opportunistic infections, such as oral candidiasis [20]. Poor glycemic control determines higher mean glycosylated hemoglobin (HbA1c). This hyperglycemia could contribute to the risk of *Candida* oral infection by also increasing salivary glucose levels, and promoting the proliferation of *Candida* in the oral cavity. Furthermore, this conditions a decrease in salivary pH, creating an ideal environment for fungal growth [29].

Denture wearers' diabetics were more than twice as likely to also be *Candida* carriers compared to diabetics no denture wearers, with highly significant statistical differences ($p < 0.001$). The four studies [10, 14, 25, 26] that delved into this parameter confirmed this higher prevalence of *Candida* species in denture wearers. *Candida* species avidly bind and adhere to acrylic surfaces, and dentures may act as a reservoir for these organisms, forming a bacterial-fungal biofilm layer that cannot be easily eradicated. Wearing dentures promotes the *Candida* species growth beneath denture, with low oxygen levels, an anaerobic environment, and a low pH. These conditions, together with a reduced salivary flow under the denture or poor oral and prosthetic hygiene, favor greater adherence of *Candida* species to the acrylic substrates of the denture [25]. All denture wearers, and especially diabetic, must maintain the highest level of oral health and remove the denture at night to sleep, to reduce the risk of candidal infection [10].

The oral distribution of the different *Candida* species between diabetics and non-diabetics was also established, without observing a statistically significant association ($p = 0.17$). The most prevalent *Candida* species in both groups was C. *albicans*, present in 78.1% of diabetics and 71.2% of non-diabetics. On the other hand, when *C. albicans* were compared with the rest of non-albicans *Candida* species, diabetics showed less frequent of *C. non-albicans* species oral detection, with statistically significant differences ($p = 0.04$). *C. tropicalis* and *C. parapsilosis* were the non-albicans species most commonly found in both diabetics and non-diabetics. Most of the studies [17, 21] state the percentage of detection of *C. albicans* in diabetics around 70%-85%, data that agrees with that indicated in this study. In the oral cavity of diabetics, the increase in sugar concentrations creates an ideal microenvironment for the colonization and proliferation of *C. albicans* [16].

Considering *C. non-albicans* species in diabetics, other studies [29], unlike the present one, place *C. glabrata* as the second *Candida* species detected in diabetics. There appears to be symbiotic cooperation between *C. albicans* and *C. glabrata*. The secretion of proteolytic and lipolytic enzymes by *C. glabrata* contributes to the invasiveness of the hyphae of *C. albicans* which, in turn, acts as a promotor for the invasion of *C. glabrata*, contributing to the increase in the pathogenesis of both species [25]. The pathogenic synergy among different *Candida* species, generating biofilms of mixed species, allows each other to benefit, resulting in the perpetuation of the infection, with greater difficulty in eradication and higher resistance to antifungal treatment [26].

5. CONCLUSIONS

In this meta-analysis, diabetics were three times more likely to be infected by *Candida* species (OR: 3.16, $p < 0.001$). Likewise, *Candida* species infections were more likely in patients with poor glycemic control (OR: 2.94, $p < 0.001$) and denture wearers (OR: 2.22, $p < 0.001$). In contrast, neither gender nor diabetes type conditioned fungal infections ($p > 0.05$). The most prevalent *Candida* species in both diabetics and controls were *C. albicans* and *C. tropicalis*. Diabetics had significantly fewer *Candida non-albicans* infections than non-diabetics ($p = 0.04$).

6. LIMITATIONS OF THE STUDY

The methods for sample collection (swab, rinse, smear, etc.), which could influence *Candida* counts, could not be assessed. Different criteria were also found to distinguish between being a *Candida* carrier without disease and having oral candidiasis.

The results of this meta-analysis should be interpreted with caution due to the high heterogeneity found in some comparisons. The studies differences may be conditioned by the study design type, the methods used to collect information, the type of analysis used or by the characteristics of the populations studied.

New studies are needed to evaluate the factors related to the increased susceptibility of diabetics to oral candidiasis.

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