The prevalence of Oral Candidiasis among Smokers and Non-Smokers with and without Diabetic Mellitus

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Abstract: The aim of the present study was to assess the prevalence of oral *Candida* species among smokers and non-smokers with and without diabetes mellitus. Our result showed that, oral Candidiasis recorded higher frequency in age > 50 years in compared to age 30 and age 30-50 years in diabetic smokers, diabetic non-smokers, non-diabetic smokers and non-diabetic non-smokers. For age more than 50 years it recorded 62 (51.66%), 55 (52.38%), 53 (60.22%) and 41 (60.29%), respectively. *Candida albicans* recorded the highest diversity among all groups, the relative abundance (Pi) recorded 0.367, 0.371, 0.432 and 0.449, respectively. On the other hand *Candida glabrata* and *Candida guilliermondi* recoded the lowest diversity in diabetic smokers and diabetic non-smokers. Also, our data indicated a significant correlation between the frequency of Candidal isolates and HbA_1C level in diabetic smokers and non-smokers ($r = 0.999$, $p = 0.023$).
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1. Introduction

Candida albicans (*C. albicans*) is the most common fungal species that is isolated from the oral cavity of healthy individuals (Javed, *et al*., 2013). However, under opportunistic conditions, these fungi may become opportunistic pathogens (Javed, *et al*., 2009). Local risk factors have been associated with an increased oral *Candida* prevalence and carriage includes xerostomia, tobacco smoking, denture wearing and poor oral hygiene maintenance (Muzurovic, *et al*., 2012). Smoking is the largest preventable risk factor for morbidity and mortality in industrialized countries. World Health Organization (WHO) estimates that tobacco will become the largest single health problem by 2020, causing an estimated 8.4 million deaths annually (Vainio, *et al*., 2001). The global mortality toll is approximately 5 million annually and this is increasing (Garrett, *et al*., 2001).

The prevalence rates of tobacco smoking in the Kingdom of Saudi Arabia (KSA) were reported in several studies ranging from 2.4% to 52.3% (Bassiony, 2009; Al-Mohamed and Amin, 2010). Systemic diseases such as poorly-controlled diabetes mellitus, acquired immune deficiency syndrome and renal disorders have also been associated with an increased oral *Candida* carriage, which make immunosuppressed patients more susceptible to develop oral candidiasis as compared with their systemically healthy counterparts (Javed, *et al*., 2009; Chaves, *et al*., 2013; Javed, *et al*., 2014).

Several studies have reported that oral *Candida* carriage is significantly higher in patients with chronic hyperglycemia (such as those with poorly-controlled diabetes) than non-diabetic controls (Javed, *et al*., 2009; Al Mubarak, *et al*., 2013). These results may be explained by the fact that a dry oral environment (due to xerostomia in patients with poorly-controlled diabetes) facilitates *Candida* stagnation and growth on oral surfaces, most commonly the dorsal surface of tongue (Javed, *et al*., 2009; Khovidhunkit, *et al*., 2009). Moreover an immunocompromised state in patients with chronic hyperglycemia may also facilitate oral *Candida* growth and proliferation. Besides *C. albicans*, other species such *C. tropicalis*, *C. glabrata*, *C. krusei*, and *C. parapsilosis* are able to compete with the oral microbiota and become pathogenic.

Immunocompromised individuals are the most susceptible category of patients to *Candida* infections, a number of local oral factors can predispose to such infections in healthy individuals. These factors include persistent dry mouth, and oral appliances like dentures and fixed and removable orthodontic appliances (Daniluk, *et al*., 2006). Certain habits like high sugar diet and tobacco smoking (Soysa and Ellepola, 2005; Alanazi, *et al*., 2014) have also been implicated in the development of oral *Candida* infections. Chronic hyperglycemia and smoking are independent risk factors for increased oral *Candida* carriage; it is hypothesized that oral *Candida* carriage and species prevalence is significantly higher in diabetic and non-diabetic smokers as compared to non-smokers with and without diabetes mellitus. The aim of the present study was to assess the prevalence of oral *Candida* species among smokers and non-smokers with and without diabetic mellitus**.**

2. Materials and Methods

2.1. Study participants

Three hundred eighty one (One hundred twenty diabetic smokers, 105 diabetic non-smokers, 88 non-diabetic smokers and 68 non-diabetic non-smoking systemically healthy individuals) were involved in this study. These individuals were recruited from private dental clinics and were examined at oral healthcare centers in Ha'il province, Saudi Arabia. In all patients with diabetes had been diagnosed in accordance with the criteria proposed by the American Diabetes Association (2013).

2.2. Data collection

A trained interviewer gathered information regarding age, gender, brushing frequency (less than once daily, once daily, more than twice daily) and dental status (dentate and denture wearer) from diabetic smokers, diabetic non-smokers, non-diabetic smokers and non-diabetic non-smoking systemically healthy individuals.

2.3. Sample collection and cultivation

Three hundred eighty one Candidal isolates were obtained from three hundred eighty one individuals (One hundred twenty diabetic smokers, 105 diabetic non-smokers, 88 systemically healthy smokers and 68 non-smokers systemically healthy). Sample collection was performed after a period of 2 hours that participants did not eat or drink anything. Samples were mainly collected from the buccal mucosa, tongue and hard palate by using sterile cotton swabs. These swabs were cultivated on the Sabouraud dextrose agar (SDA) plates and placed in the incubator for 48-72 hr. at 37 °C. The growth was stained and identified.

2.4. Identification of isolates

Candidal isolates were identified by classical methods using the following biochemical tests: Fermentation of D-glucose, assimilation of carbohydrates D-galactose, maltose, sucrose, cellobiose, trehalose, raffinose, melezitose, soluble starch, L-arabinose and germ tube formation (Brown and Gow, 1999), hyphae/pseudohyphae (Kurtzman and Fell, 1998) and chlamydospores production (Taschdjian, 1957). Carbohydrate fermentation and urea hydrolysis were carried out by subculture of 2-3 representative colonies on CHROMagar *Candida* medium (CHROMagar, Paris, France). The plates were incubated at 37°C for 48-72 hr. Also, the identification of Candidal isolates was confirmed by using the API 20C *Candida* identification system (Bio-Merieux, Marcy I'Etoile, France).

2.5. HbA_1C level

HbA_1C level was determined in capillary whole blood or venous whole blood to diabetic smokers and diabetic non-smokers individuals using an immunoturbidimetric assay (DCA 2000 HbA_1C System, Bayer. Denmark). The validity of this assay has previously been tested (Mortensen *et al*., 1994).

2.6. Statistical analysis

Statistical analysis was performed using a software program (SPSS, Version 15, Chicago, IL. USA). The difference between values was analyzed by ANOVA test at 5% significance level. The confidence interval used for all statistical analyses was 95%. *P*-values less than 0.05 were significant. Pearson's correlation was done in order to assess correlation between the frequency of oral candidiasis and HbA_1C level in diabetic smokers and non-diabetic smokers. Diversity of Candidal isolates in diabetic smokers, diabetic non- smokers, non-diabetic smokers and non-diabetic non-smokers were analyzed by Shannon-Wiener Index of Diversity (H').

2.7. Ethical Consent

Each participant was asked to sign a written ethical consent during the questionnaire's interview, before the obtaining of the specimen. The informed ethical consent form was designed and approved by the ethical committee of the College of Medicine (University of Hail, KSA) Research Board.

3. Results

Three hundred eighty one Candidal isolates were obtained from Three hundred eighty individuals (One hundred twenty (31%) diabetic smokers, 105 (28%) diabetic non-smokers, 88 (23%) non- diabetic smokers and 68 (18%) non-diabetic non-smokers) (Fig. 1**)**.

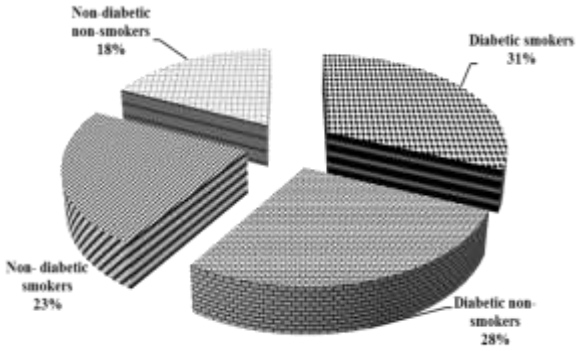

Fig (1): Study Population

3.1. Association between the frequency of oral candidiasis and some risk factors

Groups were matched to age, gender, brushing frequency, dental status and HbA_1C level **(**Table 1).

Frequency of oral candidiasis was higher in age > 50 years in compared to age 30 and age 30-50 years in diabetic smokers, diabetic non-smokers, non-diabetic smokers and non-diabetic non-smokers. For age more than 50 years it recorded 62 (51.66%), 55 (52.38%), 53 (60.22%) and 41 (60.29%), respectively, while for

age 30 and age 30-50 years recorded 17 (14.16%), 41 (34.16%); 14 (13.33%), 36 (34.28%); 2 (2.27%), 33 (37.50%) and 1 (1.47%), 26 (38.23%); respectively. Also, for dental status, the frequency of oral candidiasis was higher in dentate than denture wearer. Our data recorded 86 (71.66%), 34 (28.33%); 78 (74.28%), 27 (25.71%); 63 (71.59%), 25 (28.40%) and 62 (91.17%), 6 (8.82%); respectively. In diabetic individuals have poor control HbA_1c level the frequency of oral candidiasis was higher than good control one. In both diabetic smokers and diabetic non-smokers the frequency of oral candidiasis recorded 66 (55.00%), 21 (17.50%); 58 (55.23%), 18 (17.14%). Statistically, the frequency of oral candidiasis is significantly difference between diabetic smokers, diabetic non-smokers, non-diabetic smokers and non-diabetic non-smoking individuals (P-value < 0.05).

Table (1): Association between the frequency of oral candidiasis and some risk factors

Parameters	Frequency of oral candidiasis								P- value
	Diabetic smokers		Diabetic non-smoker		Non-diabetic smokers		Non-diabetic non-smokers		
	No.	%	No.	%	No.	%	No.	%	
Age (Years)									
< 30	17	14.16	14	13.33	2	2.27	1	1.47	
30- 50	41	34.16	36	34.28	33	37.50	26	38.23	0.022
> 50	62	51.66	55	52.38	53	60.22	41	60.29	
Gender									
Male	76	63.33	52	49.52	55	62.50	60	88.23	0.000
Female	44	36.33	53	50.47	33	37.50	8	11.76	
Brushing frequency									
< 1/ day	23	19.16	22	20.95	4	4.54	0	0.00	
Once/ day	39	32.50	33	31.42	32	36.36	19	27.94	0.001
> 2/ day	58	48.33	50	47.61	52	59.09	49	72.05	
Dental status									
Dentate	86	71.66	78	74.28	63	71.59	62	91.17	0.012
Denture wearer	34	28.33	27	25.71	25	28.40	6	8.82	
HbA_1c level									
Good control (6.5-7.5 %).	21	17.50	18	17.14	ND		ND		
Fair control (8 -9.5 %).	33	27.50	29	27.61					0.023
Poor control (> 9.5 %).	66	55.00	58	55.23					
Total	120	100%	105	100%	88	100%	68	100%	--

(ND): Not detected.

Table (2): Frequency of the Candidal isolates among smokers and non-Smokers with and without Diabetic Mellitus

Candidal isolates	Frequency of the Candidal isolates								P- value
	Diabetic smokers		Diabetic non-smoker		Non-diabetic smokers		Non-diabetic non-smokers		
	No.	%	No.	%	No.	%	No.	%	
Candida albicans	44	36.66	39	37.14	38	43.18	31	45.58	
Candida famata	32	26.66	29	27.61	27	30.68	18	26.47	
Candida tropicalis	19	15.83	17	16.19	17	19.31	9	13.23	
Candida parapsilosis	11	9.16	9	8.57	6	6.81	5	7.35	0.031
Candida krusei	7	5.83	5	4.76	0	0.00	4	5.88	
Candida glabrata	4	3.33	3	2.85	0	0.00	1	1.47	
Candida guilliermondi	3	2.50	3	2.85	0	0.00	0	0.00	
Total	120	100%	105	100%	88	100%	68	100%	--

3.2. Frequency of the Candidal isolates among smokers and non-Smokers with and without Diabetic Mellitus

The isolated pathogens were *Candida albicans, C. famata, C. tropicalis, C. parapsilosis, C. krusei, C. glabrata and C. guillermondii,* respectively. Our data showed that the frequency of *Candida albicans* was highest among diabetic smokers, diabetic non-smokers, non-diabetic smokers and non-diabetic non-smokers followed by *Candida famata* and *Candida tropicalis.* It recorded 44 (36.66%), 32 (26.66%), 19 (15.83%); 39 (37.14%), 29 (27.61%), 17 (16.19%); 38 (43.18%), 27 (30.68%), 17 (19.31%) and 31 (45.58%), 18 (26.47%), 9 (13.23%); respectively (Table 2).

On the other hand *Candida guilliermondi* showed the lowest frequencies among diabetic smokers and diabetic non-smokers. It recorded 3 (2.50%) and 3 (2.85%); respectively and not detected in both non-diabetic smokers and non-diabetic non-smokers individuals. Statistically, the frequency of oral Candidal isolates is significantly difference between diabetic smokers, diabetic non-smokers, non-diabetic smokers and non-diabetic non-smoking individuals (P-value = 0.031). Also, estimated marginal mean of Candidal isolates was significantly different. It recorded 2.408, 2.362, 1.898 and 2.059, respectively (Fig. 2).

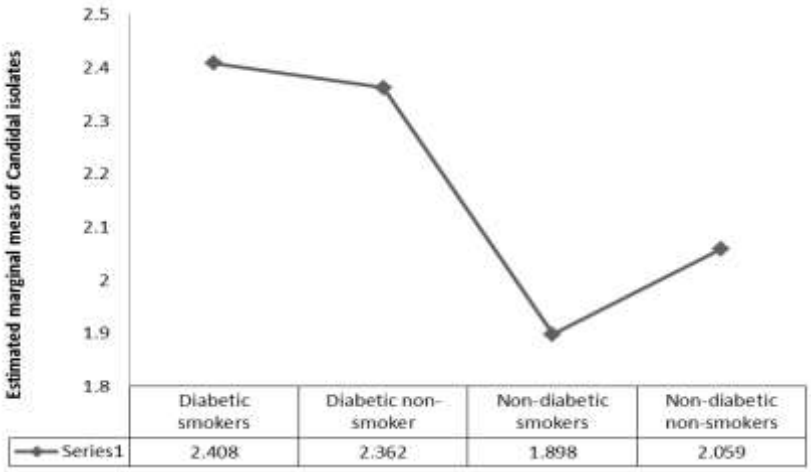

Fig (2): Estimated marginal mean of Candidal isolates

3.3. Diversity of Candidal isolates among diabetic smokers, diabetic non-smokers, non-diabetic smokers and non-diabetic non-smokers

Table 3 & Fig. 3 represented the diversity of candidal isolates among diabetic smokers, diabetic non-smokers, non-diabetic smokers and non-diabetic non-smokers. Our result showed that *Candida albicans* recorded the highest diversity among diabetic smokers, diabetic non-smokers, non-diabetic smokers and non-diabetic non-smokers. The relative abundance (Pi) recorded 0.367, 0.371, 0.432 and 0.449, respectively. On the other hand *Candida glabrata* and *Candida guilliermondi* recoded the lowest diversity among diabetic smokers and diabetic non-smokers. The relative abundance (Pi) recorded 0.025 and 0.029, respectively and not detected in non-diabetic smokers.

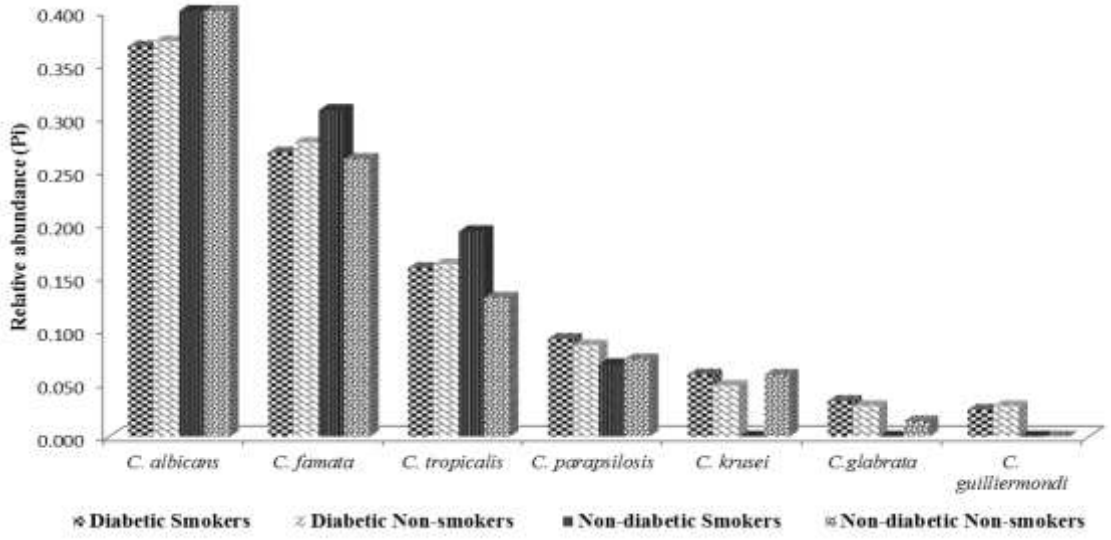

Fig (3): Diversity of Candidal isolates among diabetic smokers, diabetic non-smokers, non-diabetic smokers and non-diabetic non-smokers

Table (3): Diversity of Candidal isolates among smokers and non-Smokers with and without Diabetic Mellitus

Candidal isolates	Relative abundance (Pi) of Candidal isolates			
	Diabetic smokers	Diabetic non-smoker	Non-diabetic smokers	Non-diabetic non-smokers
C. albicans	0.367	0.371	0.432	0.449
C. famata	0.267	0.276	0.307	0.261
C. tropicalis	0.158	0.162	0.193	0.130
C. parapsilosis	0.092	0.086	0.068	0.072
C. krusei	0.058	0.048	0.000	0.058
C. glabrata	0.033	0.029	0.000	0.014
C. guilliermondi	0.025	0.029	0.000	0.000

3.4. Correlation between diabetic smokers and non-smokers

Our data recorded that a significant correlation between the frequency of Candidal isolates and HbA_1C level in diabetic smokers and non-smokers (r = 0.999, p = 0.023) (Table 4 & Fig 4). The Pearson's correlation coefficient between the frequency of Candidal isolates and HbA_1C level in diabetic smokers and non-smokers (0.999*), the p-value of the correlation (0.023), this correlation is significant because the p-value is less than 0.05.

Table (4): Pearson's correlation coefficient between the frequency of Candidal isolates and HbA_1C level in diabetic smokers and non-smokers

	Diabetic smokers	Diabetic non-smokers
Diabetic smokers		
Pearson's Correlation	1	0.999*
Sig. (2 tailed)		0.023
N	3	3
Diabetic non-smokers		
Pearson's Correlation	0.999*	1
Sig. (2 tailed)	0.023	
N	3	3

***Correlation is significant at 0.05 level (2 tailed).**

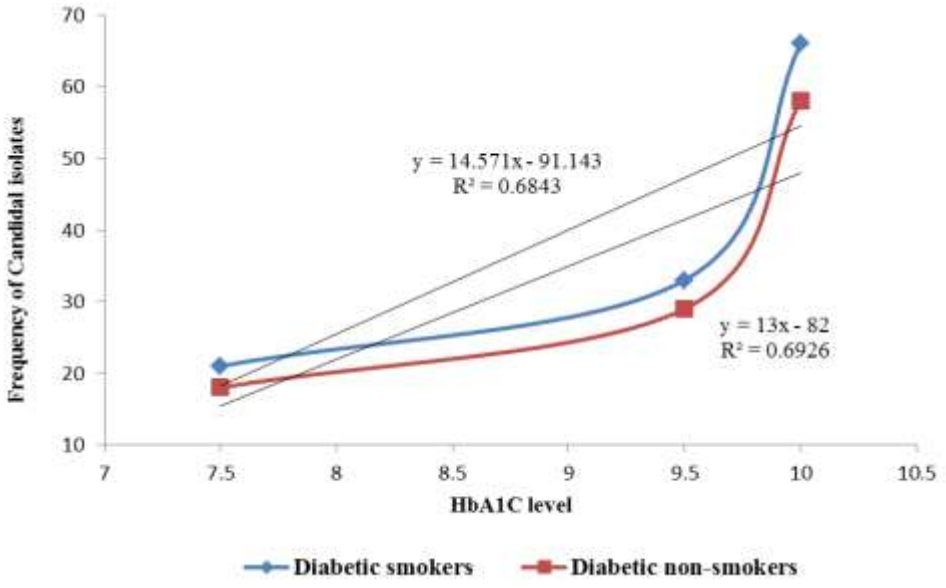

Fig (4): Correlation between the frequency of Candidal isolates and HbA_1C level in diabetic smokers and non-smokers (r = 0.999, p = 0.023)

4. Discussion

The present study was based on the hypothesis that that, the frequency of oral candidiasis is higher in diabetic smokers as compared with diabetic non-smokers, non-diabetic smokers and non-diabetic non-smokers. Interestingly, the present results showed comparable outcomes in terms of the frequency of oral candidiasis between smokers and non-Smokers with and without diabetic mellitus. An explanation in this regard may be derived from the fact that all diabetic individuals (regardless of their smoking status) were hyperglycemic. Our results indicated that, the frequency of oral candidiasis was higher in age > 50 years in compared to age 30 and age 30-50 years in diabetic smokers, diabetic non-smokers, non-diabetic smokers and non-diabetic non-smokers. For age more than 50 years it recorded 62 (51.66%), 55 (52.38%), 53 (60.22%) and 41 (60.29%), respectively, while for age 30 and age 30-50 years recorded 17 (14.16%), 41 (34.16%); 14 (13.33%), 36 (34.28%); 2 (2.27%), 33 (37.50%) and 1 (1.47%), 26 (38.23%); respectively. Also, for dental status, the frequency of oral candidiasis was higher in dentate than denture wearer. Our data recorded 86 (71.66%), 34 (28.33%); 78 (74.28%), 27 (25.71%); 63 (71.59%), 25 (28.40%) and 62 (91.17%), 6 (8.82%); respectively.

In diabetic individuals have poor control HbA_1c level the frequency of oral candidiasis was higher than good control one. The frequency of oral candidiasis recorded 66 (55.00%), 21 (17.50%); 58 (55.23%), 18 (17.14%), respectively in both diabetic smokers and diabetic non-smokers. Statistically, the frequency of oral candidiasis is significantly difference between all groups (P-value < 0.05). Our data showed that the most predominant isolate in all groups was *Candida albicans* followed by *Candida famata*. It recorded the highest diversity among diabetic smokers, diabetic non-smokers, non-diabetic smokers and non-diabetic non-smokers. The relative abundance (Pi) recorded 0.367, 0.371, 0.432 and 0.449, respectively. On the other hand *Candida glabrata* and *Candida guilliermondi* recoded the lowest diversity among diabetic smokers and diabetic non-smokers. The relative abundance (Pi) recorded 0.025 and 0.029, respectively and not detected in non-diabetic smokers.

Similarly Hamit *et. al.*, (2015) they found that, the prevalence of *Candida* carriage was similar between cigarette and maras powder (MP) users (P = 0.854). The most frequently isolated species was *Candida albicans* at a rate of 30% in the cigarette users' group, 28.3% in the MP users' group and at a rate of 18.3% in the controls. Also, Fahad and Fawad (2015) found that, Candida species were isolated from all smokers and non-smokers with T2DM. *Candida* species were isolated from 100% non-diabetic smokers 56.7% non-diabetic non-smokers. *Candida albicans* (*C. albicans*) was the most commonly isolated yeast species in all groups. *C. albicans* carriage was significantly higher in non-diabetic smokers as compared with non-smokers.

The current study is consistent with numerous previous studies, which have shown that the frequency of oral candidiasis was higher in diabetic than in non-diabetic individuals (Azmi *et al.* (2010); Taheri *et al*., 2010; Becker *et al*., 2015; Najla *et al.*, 2016; Ajrish and Muralidhran, 2017; Sanja *et al*., 2018). This is also in agreement with numerous previous studies, which have all indicated that diabetes mellitus enhances *Candida* colonization and proliferation (Kumar *et al.*, 2005; Gupta *et al.*, 2007; Khovidhunkit *et al.*, 2009; Mohammad *et al.*, 2009; Sashikumar and Kannan 2010; Radmila *et al.*, 2011; Guoqin *et al*., 2017).

Similar work was carried by Ghadah *et.al.* (2016), they found that the predominant isolate was Streptococcus sp. in both groups but with higher percentage in non-smokers (42.6%) compared to smokers (31.6%). Anaerobic bacteria showed a higher percentage (36.2%) in smokers compared to non-smokers (22.8%) at P < 0.05. Gram negative bacilli showed higher significant percentage in smokers (32.7%) compared to non-smokers (12.9%) (P < 0.05). Our data recorded that a significant correlation between the frequency of Candidal isolates and HbA_1C level in diabetic smokers and non-smokers (r = 0.999, p = 0.023). The Pearson's correlation coefficient between the frequency of Candidal isolates and HbA_1C level in diabetic smokers and non-smokers (0.999*), the p-value of the correlation (0.023), this correlation is significant because the p-value is less than 0.05.

5. Conclusion

In diabetics, the prevalence of oral candidiasis is governed by hyperglycemia and the role of tobacco smoking in this regard seems to be rather secondary risk factor.

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