The Correlation between Oral *Candida* albicans and Interlukine-23 in Diabetic Patients in Hilla City, Iraq

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Abstract

Background: Candidiasis is the most common opportunistic fungal infection in the oral cavity. Because of immunosuppression and other physiological changes, diabetes makes people more susceptible to *Candida* infections. *Candida* infections have become more frequent through the years. Interleukins are a significant class of cytokines that control immunological processes and are produced by immunocompetent cells. **Objective:** Identification and molecular detection of *Candida albicans* and determination of interlukine-23 (IL-23) concentration and studying the correlation between oral *C. albicans* and IL-23 in diabetic patients. **Materials and Methods:** 100 study samples (60 patients; 40 control), 43 were male patients and 57 were female patients, the age ranging from 20 to 70 year. The oral swabs of all samples were identified by real-time polymerase chain reaction (PCR), blood samples were obtained from all patients and control in order to determine hemoglobin A1c (HbA1c) and IL-23. IL-23 level was detected by enzyme-linked immunosorbent assay. **Results:** The current study revealed a higher prevalence of oral *C. albicans* colonization in diabetic patients than in control and found increase of significant differences in age >60 in the sample study between diabetic patients and control with oral *C. albicans*. An increase in the serum level of IL-23 was found among diabetic patients with oral *C. albicans* when compared with healthy controls. There is negative correlation between IL-23 and HbA1c in diabetic patients. **Conclusion:** Oral *C. albicans* were more prevalent in diabetic patients in comparison with healthy subjects, identified by specific primer by real-time PCR, along with a significant increase in IL-23 concentration between patients and controls with oral *C. albicans* was noted. Oral *C. albicans* were more prevalent in diabetic patients in comparison with healthy subjects, identified by specific primer by real-time PCR.

Keywords: *Candida albicans*, diabetes mellitus, interleukin-23, oral candidiasis

Introduction

Diabetes is one of the world's most common endocrine illnesses and one of the four top non-communicable illnesses according to the International Diabetes Federation.[1] Diabetes has a considerable unfavorable impact on diabetics' general health (particularly from vascular, cardiac, renal, ophthalmic, or neurological complications).[2] *Candida* species colonize the human oral cavity commensally, with a high prevalence of carriage (>70%). It induces opportunistic infections in immunocompromised individuals, allowing the infection to spread throughout the bloodstream, culminating in severe infection with significant morbidity and mortality.[3] Diabetics are more likely to develop candidiasis, which is linked to poor glycemic control. This propensity is also caused by xerostomia, which can be caused by high glucose levels in the oral fluids or immunological dysregulation.[4] Other oral changes often seen in diabetes include xerostomia, burning mouth syndrome, and increased incidence of fungal (*Candida albicans*) infections.[5]

The oropharyngeal cavity is frequently colonized by *C. albicans*, a common commensal fungus, mostly because of its capacity to attach to biotic and abiotic surfaces and enter tissues.[6] *Candida albicans* pathogenicity is mediated by a number of virulence mechanisms, including adhesion and biofilm development on human tissue as well as

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medical equipment.[7] The majority of the first encounter between *C. albicans* and the host is believed to include yeast, and subsequent contact leading to the production of germ tubes and hyphae.[8] There are many virulence factors of *C. albicans* and several hydrolytic enzymes, including proteinase, lipase, and phospholipase, are secreted by *C. albicans*.[9] Biofilms are one of the most crucial virulence characteristics because they exhibit a high tolerance to the antifungal medications used to treat fungal infections,[10] millions of microorganisms attack the mucosal surfaces of the human body. Together with these microbes, the host and microorganisms have evolved plastic mechanisms that control the equilibrium between preserving healthy germs and eliminating infections.[11] By secreting cytokines and chemokines that draw leucocytes to the infection site and subsequently prime them for increased antifungal activity, the oral epithelium directs the early antifungal response to infection.[12] Interleukins are a significant class of cytokines that control immunological processes and are produced by immunocompetent cells[13] Two subunits, p19 and p40, make up the pro-inflammatory cytokine interleukin-23 (IL-23). The identification of cytokine (IL-23) has a significant impact on hypotheses regarding chronic inflammation and autoimmune disease.[14] Along with IL-12, IL-27, IL-35, and IL-39, IL-23 belonged to the IL-12 family. Dendritic cells and activated macrophages both produce IL-23.[15]

Materials and Methods

This study included 100 samples (60 samples are diabetic patients which include 25(41.6%) males and 35 (58.3%) females with type 1 and type 2 diabetes mellitus , age range (20-70) years) , and 40 sample of control (healthy individuals without medical illness) which include19 (47%) males and 21 (52.5%) females with age range (20-70) years. This study is conducted in the diabetes center of Mirjan medical city and Al-Sadiq hospital in Hilla city from September 2022 to February 2023.

Specimen collection methods

The samples were taken from patients and control, and oral swabs were obtained, by adding phosphate buffer to it, to detect oral *C. albicans* by real-time polymerase chain reaction (PCR). From all subjects, blood samples were collected for the detection of hemoglobin A1c (HbA1c) and IL-23 (serum). IL-23 was detected by enzyme-linked immunosorbent assay (ELISA).

Genomic identification of *Candida albicans*

After collecting the swabs from the oral cavity, those were kept in phosphate buffer saline in a molecular lab. Genomic DNA was extracted using modified protocols described by the manufacturer. *Candida albicans* isolates were confirmed by RT-PCR using specific pair of CA1F/R[16] to amplify 354 bp DNA fragment with F: 5′TTTATCAACTTGTCACACCAGA3′, R: 5′GGTCAAAGTTTGAAGATATACGT3′. The primer in this study was prepared according to the manufacturer of the primer's instructions (Macrogen, Seoul, Republic of Korea). The qPCR Master Mix contain the following: primer (upstream) (1 µL), primer (downstream) (1 µL), nuclease-free water (25 µL), EVA green (2.5×) (20 µL), purity DNA (2 µL), and $MgCl_2$ (1 µL). The thermocycle conditions for PCR are as follows: 94°C for 1 min, 1 cycle, followed by 40 cycles of 94ºC, 10 s, 60°C for 30 s and 72°C for 30 s and melt 60–95ºC, 1ºC for each step, 5 s.

Detecting of IL-23 by enzyme-linked immunosorbent assay technique

The technique was carried out in accordance with the manufacturer's instructions. On the micro ELISA plate, contained in this kit, a human IL-23-specific antibody has already been pre-coated. Standards or samples are put into the wells of the micro ELISA plate, together with the particular antibody. Then each well of the microplate is gradually filled with an Avidin-Horseradish Peroxidase (HRP) combination and a biotinylated detection antibody specific for human IL-23. Free elements are removed by washing. Each well receives a dose of the substrate solution. Only the wells that also contain an Avidin-HRP conjugate and a biotinylated detection antibody for human IL-23 will show blue color. By adding stop solution, the enzyme-substrate reaction is stopped, and the color changes to yellow.

HbA1c Te

Test principle

Proteases extensively digest the lysed whole blood sample releasing amino acid-like glycated valines from the Hb beta chain. The recombinant fructosyl valine oxidase enzyme then acts on the glycated valine, cleaving them in the N-terminal sites producing hydrogen peroxide. Measurement made by using a horseradish peroxidase catalyzed reaction and a suitable chromogen.

Test procedure

Accordance to the user's instructions, blood samples were collected, and then 20 µL of the whole blood was taken and added it to 2000 µL of hemolysis reagent in a test tube. It was mixed and allowed to stand for 5 min. Again it was mixed and measured it by Biorex device.[17]

Statistical analysis

Data were processed and examined using the Statistical Analysis System (SAS 2018), (Version 9.6th ed. SAS. Inst. Inc., Cary, North Carolina). This program examined the impact of the patient and control groups on parameters of study. To significantly compare between means, the *t* test was utilized. Chi-square test was utilized to statistically compare percentages. Statistics are considered significant if the *P* value is less than 0.05.[18]

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Ethical approval

The study was conducted in accordance with the Helsinki Declaration's ethical guidelines. Before taking the sample, the patients verbal and analytical consent were obtained. To obtain this permission, a local ethics committee evaluated and approved the study protocol, subject information, and consent form using document number 6275 (containing the number and date in December 14, 2022).

Results

Distribution oral *Candida* albicans among diabetic patients and control

Table 1 shows significant differences in the distribution of oral *C. albicans* among diabetic patients and control ($P \leq 0.05$).

Distribution of oral *Candida albicans* among patients and control in relation to age

In Table 2, the results showed an increase in significant differences in age >60 in the sample study between diabetic patients and control with oral *C. albicans* ($P \leq 0.0001$), and significant differences in age (<30–39) in the sample study between diabetic patients and control with oral *C. albicans* ($P \leq 0.05$).

Relationship of oral *Candida* albicans and IL-23 in patients and control groups

In Table 3, the findings revealed higher significant differences in IL-23 concentration between patients and controls with oral *C. albicans*.

Detection of *Candida albicans* by the detection of specific gene

Candida albicans were identified using real-time PCR methods by using specific gene CA1F/R, and 100 samples of sample study are detected by real-time PCR and the result showed there were 48 samples were positive of oral *Candida* albicans which showed as red curve as in Figure 1.

The correlation coefficient between study parameters of diabetic patients

In this step, we measure the correlation between the concentration of cytokines IL-23 and HbA1c in diabetic patients. The results show there is no significant correlation between them in this study, as shown in Table 4.

Discussion

In our findings, diabetic patients have a higher rate of oral candidiasis than healthy controls, as shown in Table 1.

Table 1: Distribution oral *C. albicans* among diabetic patients and control

Group	Oral *Candida albicans*	Total *N* (%)	*P*-value
Patients (*N* = 60)	Positive	33 (55.00%)	0.0084**
	Negative	27 (45.00%)	
Control (*N* = 40)	Positive	15 (37.50%)	
	Negative	25 (62.50%)	

** $P \leq 0.01$, highly significant

Table 2: Distribution of oral *Candida* albicans among patients and control in relation to age

Group	Oral *Candida albicans*	<30 *N* (%)	30–39 yr. *N* (%)	40–49 yr. *N* (%)	50–59 yr. *N* (%)	≥60 yr.
Patients (*N* = 60)	Positive	2 (3.33%)	1 (1.67%)	6 (10.00%)	8 (13.33%)	16 (26.67%)
	Negative	2 (3.33%)	5 (8.33%)	5 (8.33%)	7 (11.67%)	8 (13.33%)
Control (*N* = 40)	Positive	0 (0.00%)	7 (17.50%)	4 (10.0%)	4 (10.0%)	0 (0.00%)
	Negative	9 (22.50%)	3 (7.50%)	3 (7.50%)	6 (15.00%)	4 (10.0%)
P-value	–	0.0016**	0.0338 *	0.411 NS	0.319 NS	0.0001 **

* $P \leq 0.05$

** $P \leq 0.01$

Table 3: Relationship of oral *C. albicans* and IL-23 in group of patients and control

Group	Oral *Candida albicans*	Mean ± SE IL-23 (pg/mL)	LSD value	*P*-value
Patients	Positive	55.08 ± 11.47[a]	23.904*	0.03
	Negative	52.15 ± 15.26[a]		
Control	Positive	20.57 ± 5.21[b]		
	Negative	23.24 ± 5.67[b]		

Means that had various letters in the same column varied significantly

* $P \leq 0.05$

** $P \leq 0.01$

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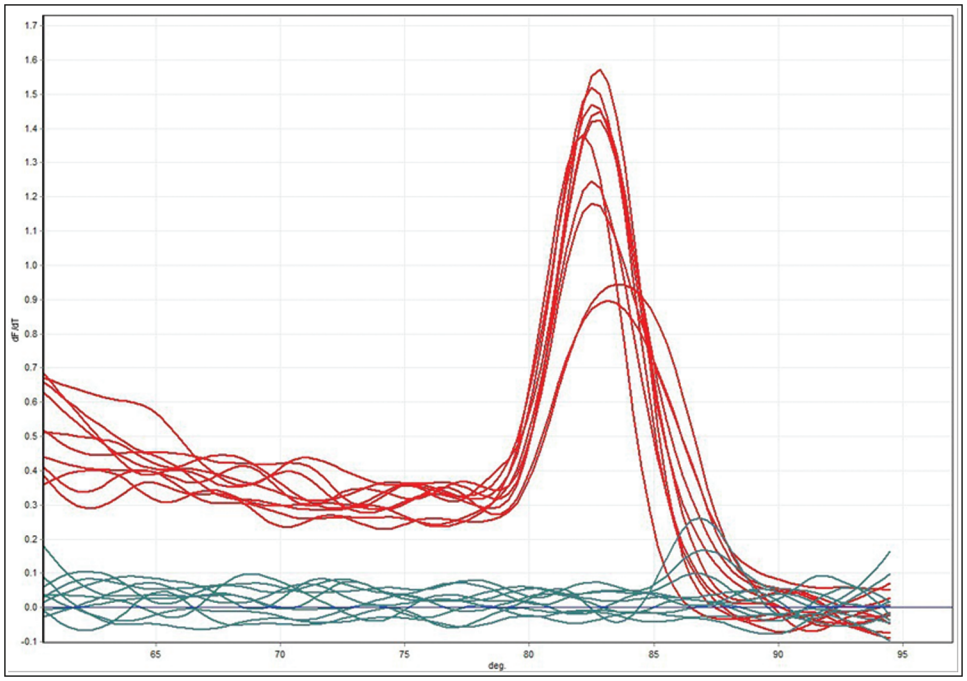

Figure 1: Samples melting curves, detection of *Candida albicans* by real-time polymerase chain reaction (red curves represent positive samples)

Table 4: The correlation coefficient between study parameters of diabetic patients

Parameters study	Correlation coefficient-*r*	*P*-value
IL-23 and HbA1c	–0.06 NS	0.678

NS: non-significant

The patient's poor glycemic control is one of these contributing variables, and these results correspond with Dehghan *et al.*[19] who found, that xerostomia and changes in physiological variables such as glucose and pH levels may rise *Candida* proliferation inside the mouth. These features are regarded to be important risk factors for oral candidiasis in diabetics. Candida infestation is more prevalent in the oral cavity. These results coincide with results obtains by Zarei *et al.*[20] which found *C. albicans* was the most common causal agent isolated from diabetes patients and nondiabetic healthy people. It is widely recognized that immunosuppressive conditions, such as diabetes mellitus can have a greater impact on *Candida* colonization and thus advance the infection in host tissue. The results in this study were similar to Shenoy *et al.*[21] who found oral candidiasis was more prevalent among individuals with uncontrolled diabetes mellitus. This patient group also has a complex infection course. The kind and length of the condition, as well as the degree of glycemic control, have all been linked to oral yeast carriage in diabetes patients. Amin *et al.*[22] found high significant difference between patients and control in the colonization of oral *C. albicans.*

The change of *C. albicans* to hyphal development improves its penetration into tissue and increases its pathogenicity.[23] Elevated salivary glucose levels, decreased salivary flow, and decreased neutrophil candidacidal activity in patients are all known host factors for candida colonization and infection.[24] Premkumar[23] gave the reason for the high prevalence of oral *Candida* in diabetic patients that the immunocompromised circumstances altered the oral flora. Candidal density appears to be a good predictor of the development of oral candidiasis. This is due to immunocompromised states altering the oral flora.

The high prevalence of *C. albicans* colonization was observed in diabetic cases older than 60 years as shown in Table 2. These results correspond with the results obtained by Belazi *et al.*[25] who found the same relationship. He integrated the findings and discovered a significant increase in candidal development in diabetics over the age of 60. Numerous factors may contribute to the development of candida in the oral cavity in older adults, including medical conditions, increased use of prescription and over-the-counter medications, poor oral hygiene practices, poor dietary decisions, and increased dental issues.[25] Our findings agreed on with Al Mubarak *et al*[26] who found that *C. albicans* are higher in age (40–50) years. Other studies[27] disagree with these results. Our study corresponded with Nguyen *et al.*[28] which found the likelihood of developing candidiasis increases with age and length of diabetes treatment.

Diabetic patients with oral candida in this study had significant differences in IL-23 concentration in comparison with the control group. This result is corresponding with the results obtained by other study.[29,30] Conti *et al.*[29] showed that IL-23 and IL-17RA are necessary for

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successful oral candidiasis resistance; as a result, IL-23 is necessary to avoid invasive oral candidiasis and to enable a strong PMN response). IL-23p19 defective individuals developed severe oral candidiasis, minimal fungal loads and no overt illness in those lacking (IL-12p35). This study also agreed with, Nur *et al*.[31] who discovered IL-23's unique function in antifungal defense. Nur *et al*.[31] discovered that the crucial novel cytokine IL-23 controls the innate immune system's reaction to fungal infection through a complicated network of cytokines, which is extremely sensitive to systemic infection with *C. albicans*. There were no significant differences in patient groups between IL-23 and HbA1c, so this result disagree with other studies[32-35] but found positive correlation between two parameters.

Conclusion

Oral *C. albicans* were more prevalent in diabetic patients in comparison with healthy subjects. *C. albicans* was highly prevalent in ages >60 than in other age group. There were significant differences in IL-23 concentration between patients and controls with oral *C. albicans* (*P*-value = 0.03).

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Conflicts of interest

There are no conflicts of interest.

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