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ORIGINAL ARTICLE – OPEN ACCESS

Assessment of Fungal Genital Infection Frequency, Antifungal Sensitivity, and the Impact of Hemoglobin A1c Levels on These Infections in Diabetic Children

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ABSTRACT

Objective: A positive relationship exists between high blood glucose levels and infection prevalence in patients with diabetes. Hyperglycemia may predispose to fungal infections. This study was conducted to compare the frequency of fungal infections and antifungal agent resistance of culture strains in children with type 1 diabetes mellitus (T1DM) with those in healthy controls and to assess the relationship between fungal infection and hemoglobin A1c (HbA1c) levels.

Materials and Methods: The study population included 67 girls with T1DM and 63 girls without T1DM, immunodeficiency, or chronic drug use. Blood and urine samples were collected, and genital smear sampling was performed. Samples were evaluated in a mycology laboratory, and fluconazole sensitivity of culture samples was determined.

Results: Genital complaints were more common among patients with diabetes. Fungal agents were isolated in 55.22% of patients with diabetes, where Candida glabrata was the most common strain isolated (46.0%). Meanwhile, Candida albicans was more common in the control group (40.0%). All strains were fluconazole-sensitive, as strains with native resistance were excepted. For serum HbA1c levels, a cutoff value of 8.9 was identified and was related to fungal growth with a reliability of 80%. Patients with diabetes for more than 12 months had a higher risk of fungal infection.

Conclusion: Patients with serum HbA1c levels of more than 8.9 and a diabetes duration of more than 12 months should be assessed for fungal infections, and genital smear samples should be obtained periodically during follow-up.

Keywords: Antifungal sensitivity, fluconazole, fungal genital infection, HbA1c, type 1 diabetes mellitus

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INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a chronic disease caused by immune-mediated destruction of beta cells of the pancreas (1–3). T1DM accounts for approximately 10%–15% of all patients with diabetes (4). The disruption of cells in diabetes and extracellular factors, such as hyperglycemia, hyperlipidemia, acidosis, and long-term complications of diabetes, also disturb immune mechanisms; thus, T1DM can be characterized as an autoimmune disease (5, 6). A positive correlation exists between high blood glucose levels and infection prevalence in patients with diabetes (7). Hyperglycemia may predispose patients to bacterial or fungal infections. Chemotaxis, adherence, phagocytosis, and intracellular microbial killing functions of polymorphonuclear leukocytes are destroyed, and serum chemotactic factor levels are decreased in children with diabetes; so fungal infections often occur in these patients (8, 9). Vaginal candidiasis is frequently observed in patients with long-term diabetes. Vaginal candidiasis caused by Candida albicans is the most frequently seen fungal infection (70%–90%) (10), but recently, infections caused by Candida glabrata have been notably increasing (11).

This study was conducted to compare the frequency of fungal infections and antifungal resistance of strains in children (<12 years old) and adolescents (12–18 years old) with T1DM with those in healthy controls by genital sampling, to assess the relationship between HbA1c levels and infection, and to standardize their treatment.

MATERIALS and METHODS

Study group

Sixty-seven female patients aged 3–18 years followed for T1DM in Erciyes University Medical Faculty between November 2015 and May 2016 were included in this case–control study. Patients with T1DM with concomitant chronic disease were excluded from the study. Sixty-three female patients without chronic diseases, long-term drug use history, and immune deficiencies were included in the control group. Detailed information on the study was given to the parents of the children, and signed informed consent forms were obtained. This study was approved by Erciyes University Medical Faculty Research Ethics Committee (reference number: 10135793).

Table 1. Anthropometric measurements, ages, complaints, and genital inspection findings in the diabetes and control groups

	Diabetes group (n=67)	Control group (n=63)	p
Age (years)	11.7±3.64	12.7±2.93	0.083
Weight (kg)	44.02±18.60	53.15±16.96	0.004
Height (cm)	144.4±18.04	151.13±11.60	0.016
HbA1c (%)	9.59±2.41	–	–
Presence of genital complaints, n (%)			
Itching	23 (34.33)	27 (42.85)	0.318
Discharge	38 (56.71)	44 (69.84)	0.120
Dysuria	16 (23.89)	9 (14.29)	0.160
Genital inspection findings, n (%)			
Redness	27 (40.30)	24 (38.10)	0.790
Fetor	20 (29.85)	25 (39.70)	0.239
White plaque	22 (32.83)	11 (17.50)	0.044
Presence of genital bacterial infection, n (%)	9 (13.43)	10 (15.90)	0.920
Urinalysis, n (%)			
Pyuria	11 (16.41)	11 (17.46)	0.610
Nitrite (+)	5 (7.50)	1 (1.60)	0.200
Growth in urine culture, n (%)	9 (13.43)	2 (3.17)	0.030
Genital fungal infection in microscopic examination, n (%)	43 (64.18)	42 (66.70)	0.475

The Shapiro–Wilk test, chi-square test, and Student's t-test were used. Data were showed as mean±SD and n (%). SD: Standard deviation

Demographic and clinical data (age, duration of the disease, etc.) were recorded. The patients' urine complaints were also evaluated. Their histories of fungal infection, the period of their complaints, and their drug use were examined. Their weight and height were measured. To evaluate fungal infection, physical and genital examinations were performed in the presence of a healthcare provider and the patient's mother.

Laboratory Analyses

Urine samples were obtained for urine analysis and culture. Simultaneous venous blood samples were taken for hemoglobin A1c (HbA1c) levels. Genital swab samples were obtained using three standard culture swap bars, two of which were sent to the microbiology laboratory to assess fungal infection. They were inoculated using a standard identifying procedure. The third swab bar was sent to the bacteriology laboratory and inoculated using a standard procedure to evaluate the presence or absence of bacterial growth.

To isolate the fungal species C. albicans, ATCC 90028 was used as standard species. Isolates were confirmed using the API 20C AUX test system (Biomerieux, France). Identified species were studied to determine the minimum inhibitory concentration (MIC) of fluconazole. Fungal isolates of Candida species were examined for antifungal susceptibilities using microdilution assay using the "Clinical and Laboratory Standards Institute (CLSI) M27-A3 and M27-S4" reference method (12). MIC values were determined according to the criteria that the CLSI recommended. The lowest concentration of fluconazole that decreased the turbidity distinctly (~50%) was detected as the MIC value (13).

Statistical Analyses

Data were analyzed for normality using the Shapiro–Wilk test, histogram, and Q-Q plot graphics. The relationships between categorical variables were examined using the chi-square test. Student's t-test was used to compare numerical variables between groups. The threshold value of HbA1c to determine growth in the culture was analyzed using receiver operating characteristic (ROC) curve analysis. For all these data analyses, Statistical Package for the Social Sciences (version 22.0; IBM Corp., Armonk, NY, USA) and EasyROC 1.1 (www.biosoft.hacettepe.edu.tr/easyROC) were used (14). P-values of less than 0.05 were used to denote statistical significance.

RESULTS

Anthropometric measurements, age, complaints, and genital inspection findings of the diabetes and control groups are shown in Table 1. The mean age of the diabetes group was 12.7±2.93 years, and that of the control group was 11.7±3.64 years. No statistically significant difference in age was observed between the two groups (p=0.083). However, both weight and height levels in the diabetes group were lower than those in the control group (p=0.083 and p=0.04, respectively). Moreover, 67.2% of the 67 patients in the diabetes group have had diabetes for more than 1 year, 20.9% of them have had the disease for 6 months to 1 year, 11.9% of them have had diabetes for less than 6 months, and four were newly diagnosed at the beginning of the study. The mean HbA1c level was 9.50%±2.41% (Table 1).

We evaluated the symptoms of the study subjects: 56.71% of the patients in the diabetes group and 69.84% of the individuals in the control group had genital discharges, 34.33% of the patients in the

Table 2. Fungal growth and fluconazole sensitivity/resistance of the culture samples obtained from the study groups

	Patient group n (%)	Control group n (%)	p
Growth in fungal culture	37 (55.22)	15 (23.80)	<0.001
Candida spp.			
C. glabrata	17 (46.00)	4 (26.70)	<0.001
C. albicans	13 (35.13)	6 (40.00)	<0.001
C. krusei	5 (13.50)	3 (20.00)	0.349
C. parapsilosis	1 (2.70)	0 (0.00)	0.273
C. kefyr	1 (2.70)	2 (13.33)	0.468
Sensitivity to fluconazole	31/6	11/4	
Sensitive/resistant	(83.80/16.20)	(73.30/26.70)	0.448
MIC (µg/mL)			
≤2 (sensitive)	15 (41.00)	8 (53.30)	
≤32 (dose-related sensitivity)	17 (46.00)	4 (26.70)	0.477
≥64 (resistant)	5 (13.00)	3 (20)	

MIC: Minimum inhibitory concentration; *: Chi square test was used

Table 3. Comparison of HbA1c levels and culture results within the diabetes group

	Fungal growth (+) (n=37) Mean±SD	Fungal growth (-) (n=30) Mean±SD	p
HbA1c (%)	10.51±2.11	8.45±2.28	<0.001

SD: Standard deviation; Student's t-test was used

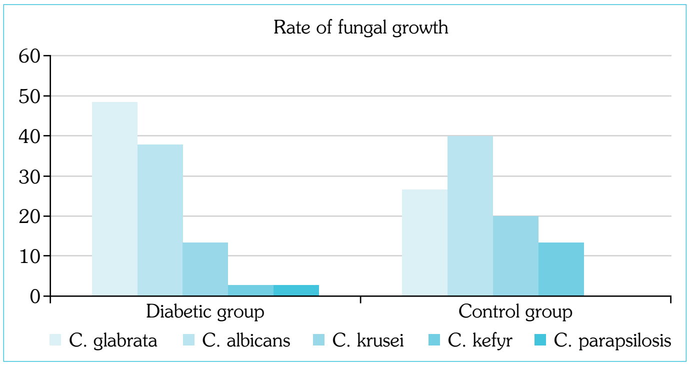

Figure 1. Candida spp. growth in the genital swab samples of the diabetes and control groups

diabetes group and 42.85% of the individuals in the control group had itching, and 23.89% of the patients in the diabetes group and 14.29% of the individuals in the control group had dysuria. No statistically significant differences in the prevalence of discharges, itching, and dysuria was observed between the two groups (p=0.120, p=0.318, and p=0.160, respectively). Genital inspection showed that 40.30% of the patients in the diabetes group and 38.10% of the control subjects had redness (p=0.79). Moreover, 32.83% of the patients in the diabetes group and 17.50% of the control subjects had white plaques (p=0.044). No statistically significant differences in terms of pyuria (>5 leucocyte) and positive nitrite in urine (p=0.05) were observed between the two groups. Furthermore, 13.43% of the patients in the diabetes group and 3.17% of the control subjects had growth in urine culture (p=0.03). Forty-three (64.18%) patients and 42 (66.70%) control subjects had genital fungal infection. However, no statistically significant difference was observed between the two groups (p=0.475) (Table 1).

Fungal growth was observed in the genital swap samples of 37 patients (24.80%) and 15 control subjects (23.80%), and we found a statistically significant difference between the two groups (p<0.001) (Table 2).

The most common Candida species isolated were C. glabrata (46%) in the diabetes group and C. albicans (35.13%) in the control group. No significant differences in terms of other Candida species, such as Candida krusei, Candida parapsilosis, and Candida kefyr, were observed between the two groups (Fig. 1).

Antifungal sensitivities of the fungal species in culture samples were evaluated, and we found that fluconazole sensitivity was 83.80% and resistance was 16.20% in the diabetes group. In the control group, fluconazole sensitivity was 73.30% and resistance was 26.70%. No statistically significant differences in terms of fluconazole sensitivity or resistance (p=0.448) were observed between the two groups. In vitro study of MIC80 levels of fluconazole was conducted. C. krusei was isolated in five patients with diabetes (13%), which was fluconazole-resistant with MIC80 levels of ≥64 µg/mL. C. glabrata was isolated in 17 (46%) patients with diabetes, which was sensitive to fluconazole in a dose-related manner with MIC80 levels of ≤32 µg/mL. Other species (i.e., C. albicans and C. kefyr) had MIC80 levels of ≤2 µg/mL, indicating sensitivity to fluconazole. In the control group, C. krusei was isolated in three (20%) participants, which was resistant to fluconazole with MIC80 levels of ≥64 µg/mL. C. glabrata was isolated in four (26.70%) control subjects with MIC80 levels of ≤32 µg/mL, indicating dose-related sensitivity. C. albicans and C. kefyr that were isolated in eight control subjects had MIC80 levels of ≤2 µg/mL, indicating sensitivity to fluconazole.

Patients with diabetes with and without fungal growth were compared with each other in terms of their HbA1c levels: patients without fungal growth had a mean HbA1c level of 8.45%±2.28% and those with fungal growth had a mean HbA1c level of 10.51%±2.11%. A statistically significant difference in the mean HbA1c level was observed between the two groups (Table 3). Because of the statistically significant difference between the two subgroups of patients with diabetes, we performed ROC analysis according to Youden's method. For HbA1c, the cutoff point was 8.9%, and the area under the curve (AUC) was 0.769 (Table 4). In patients with diabetes with HbA1c levels of more than 8.9%, fungal growth can be detected with 77% reliability (Fig. 2).

Simultaneous urine samples were obtained from all participants using a genital swab, and complete urinalysis and urine culture were performed and evaluated. We did not find a statistically significant difference in terms of pyuria (>5 leucocytes) and nitrite positive results between the diabetes and control groups. However, a statistically significant difference in culture (p=0.030) was ob-

Table 4. Youden's method, cutoff value of HbA1c levels, and statistical evaluation

Optimal cutoff	8.9
Optimal criterion	0.5108108
SEN (95%CI)	0.811 (0.648–0.920)
SPE (95%CI)	0.700 (0.506–0.853)
PPR (95%CI)	0.769 (0.594–0.900)
NPR (95%CI)	0.750 (0.564–0.882)
LR+(95%CI)	2.703 (1.531–4.771)
LR-(95%CI)	0.270 (0.133–0.548)

CI: Confidence interval; SEN: Sensitivity; SPE: Specificity; PPR: Positive predictive rate; NPR: Negative predictive rate; LR-: Negative likelihood ratio; LR+: Positive likelihood ratio

served between the groups with and without fungal growth. The patients' genital swab samples were bacteriologically evaluated, and we did not find a significant difference between the subgroups (p=0.920). Among 37 patients with diabetes, 30 (81.10%) were fungal culture-positive and have had diabetes for more than 12 months; three (8.10%) have had diabetes for 6–12 months; and four (10.80%) have had diabetes for less than 6 months. A statistically significant difference was observed between the three subgroups (p=0.01) (Table 5).

DISCUSSION

In this study, 37 (55.22%) of the 67 patients with diabetes had fungal growth in their genital swab culture samples, whereas only 23.80% in the control group had fungal growth. Atabek et al. (15) have reported that 39% of patients with diabetes had fungal growth in their study. Goswami et al. (16) have reported that the incidence of vaginal Candida infections is 46% in adult patients with diabetes, and another study has shown that this rate is 42% (17). A recent study by Willems et al. (18) has reported that diabetes is a risk factor for vulvovaginal candidiasis, but did not increase the risk in patients with diabetes. No study abroad involving pediatric patients with diabetes has been conducted; thus, we could not compare our results. Our results were higher than the results stated by a study from our country (15), and we concluded that the frequency of fungal infection has increased in years.

The mean HbA1c level in the diabetes group was 9.59%±2.41%. Kendirci et al. (10) have reported that the mean HbA1c level was 10.6%±2.2% in their study, and Atabek et al. (15) have reported that the mean HbA1c level was 9.5%±2.49%. According to these results, the patients' glycemic control was nearly similar in the three aforementioned studies.

In this study, genital complaints of patients with diabetes were not different from those of the control group. In the diabetes group, the most common complaint was genital discharge (56.71%), whereas itching and dysuria were less common. These symptoms and their rates were similar to those in the control group. Atabek et al. (15) have reported that 82.6% of their patients had at least one genital symptom. Kendirci et al. (10) have reported that itching was the most prevalent symptom in the diabetes and control groups in their

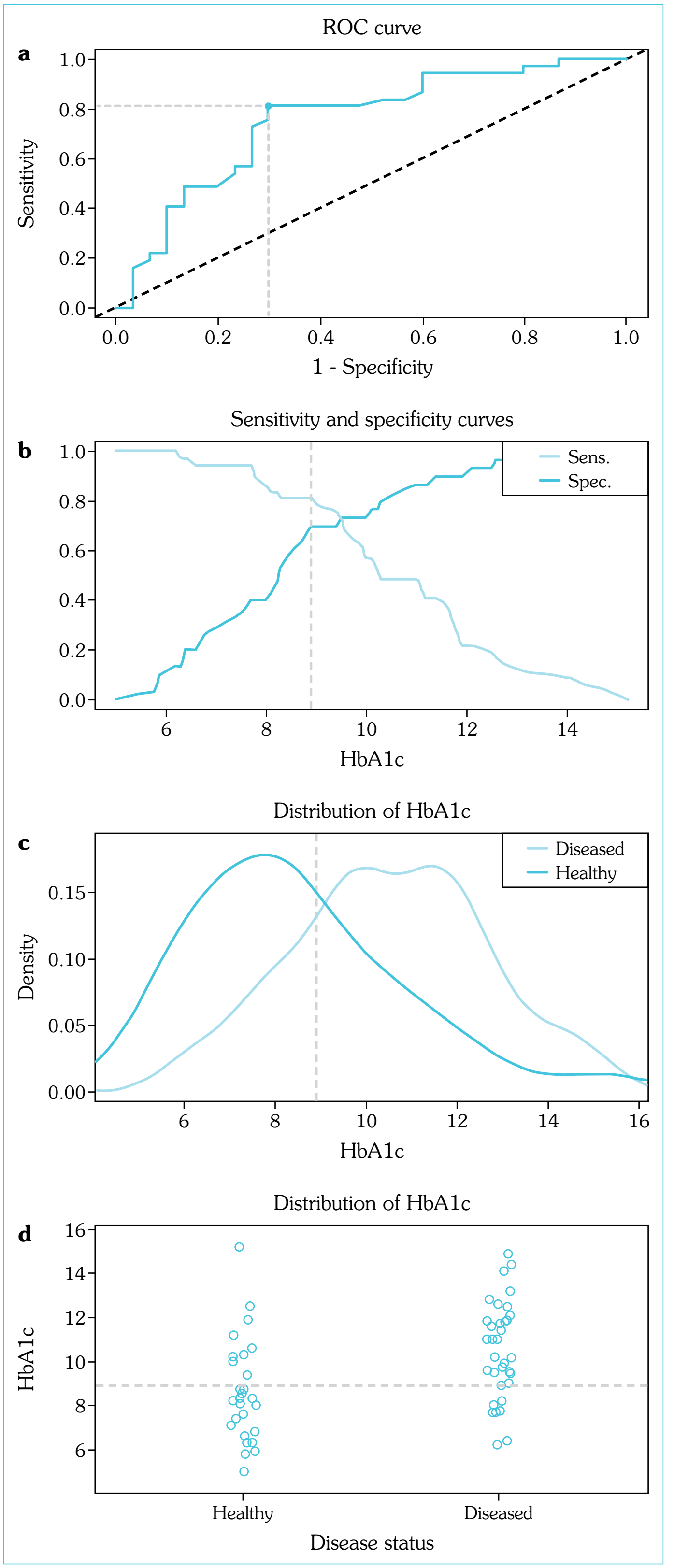

Figure 2. Evaluation of the effects of HbA1c levels on fungal growth using ROC analysis. (a) The ROC curve of HbA1c in patients with diabetes; the HbA1c cutoff point was 8.9%; area under curve (AUC) was 0.769. (b) Sensitivity and specificity curves of HbA1c in patients with diabetes. (C, d) Distribution of HbA1c in the diabetes and healthy groups

Table 5. Comparison of fungal growth and duration of diabetes in the diabetes group

Duration of diabetes	Fungal growth (-) (n=30)		Fungal growth (+) (n=37)		Total (n=67)		p
	n	%	n	%	n	%	
<6 months	4	13.33	4	10.80	8	11.90	
6–12 months	11	36.67	3	8.10	14	20.90	0.010
12 months	15	50	30	81.10	45	67.20	

The chi-square test was used

study. We suggest that in all patients with diabetes with and without symptoms, genital fungal infection should be considered and assessed. In adult patients with diabetes, the vulvovaginal flora is different; therefore, for us, adult patients with diabetes should not be compared with pediatric patients with diabetes. White plaques were mostly observed in patients with diabetes, and fungal growth was also detected in the same patients. Therefore, white plaque should be considered an important symptom of fungal infection. To evaluate the cause of the patients' complaints, that is, urinary tract infection or genital fungal infection, we performed urinalysis and found no difference in both groups. However, the urine culture results in the diabetes group were significantly different from those in the control group, and this difference could be attributed to the fact that patients with diabetes are prone infection.

In this study, the most frequent isolated fungal species was C. glabrata (48.6%) in the diabetes group and C. albicans (40%) in the control group. Kendirci et al. (10) have reported that the most isolated agent was C. albicans (72.7%) in their study. Atabek et al. (15) have found that the incidence of fungal infection was 39% in pediatric patients with diabetes, and the most isolated fungal agent was C. albicans (50%). Grigoriou et al. (19) have reported in their study that the most common isolated fungal agent was C. albicans, and the second most isolated organism was C. glabrata on vulvovaginal examination of patients followed for T1DM. Adult patients with diabetes had C. albicans (53%) in the study in Yemen by Abdullah Al-Mamari et al. (17).

In this study, except for C. krusei, all isolated species from the diabetes and control groups were sensitive to fluconazole (C. krusei has natural resistance to fluconazole). C. glabrata was sensitive to fluconazole in patients with higher MIC80 levels. Sensitivity to fluconazole was 83.7% considering all species.

In this study, we measured the HbA1c levels in patients with diabetes and compared them between patients with and without fungal growth. The mean HbA1c level was 10.51%±2.11% in patients with fungal growth and 8.45%±2.28% in patients without fungal growth. This difference between participants showed that poorly controlled glycemia had expressive effects on the development of genital fungal infection. We performed ROC analysis and found a cutoff value for HbA1c levels in patients with diabetes. The incidence of fungal growth was significantly higher in the genital swab samples of patients with HbA1c levels of more than 8.9%. Considering this level, the positive predictive value was measured as 0.796 with 80% reliability. Patients with HbA1c levels higher than 8.9%, fungal growth might be observed.

Obesity is a risk factor for fungal infections (20–22), and poorly controlled glycemia increases this risk (23). However, in this study, we did not find a significant difference in the weight and height between the diabetes groups with and without fungal growth.

We determined that genital itching and discharge were more frequent in patients with positive genital fungal growth, but dysuria was insignificant. According to this result, we highlighted the necessity of evaluating patients' complaints carefully. We conclude that especially patients who have had diabetes for more than 12 months and with poorly controlled glycemia should be screened occasionally for genital fungal infection.

Ethics Committee Approval: The Erciyes University Clinical Research Ethics Committee granted approval for this study (date: 09.04.2015, number: 10135793).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – BE, MK; Design – BE, NÇ, IÇ, ANK, MK; Supervision – BE, NÇ, IÇ, ANK, MK; Resource – BE, NÇ, IÇ, ANK, MK; Materials – BE, MK; Data Collection and/or Processing – BE, MK; Analysis and/or Interpretation – BE, MK; Literature Search – BE, NÇ, IÇ, ANK, MK; Writing – BE, NÇ, IÇ, ANK, MK; Critical Reviews – BE, NÇ, IÇ, ANK, MK.

Conflict of Interest: The authors have no conflict of interest to declare.

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