Prevalence and risk factors for vaginal Candida colonization in women with type 1 and type 2 diabetes

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Abstract

Background: Diabetes mellitus increases the rate of vaginal colonization and infection with Candida species

Methods: We surveyed women with diabetes receiving care at either an urban or suburban diabetes clinic to examine the relationship between vaginal Candida colonization, diabetes type and duration, and HbA1c level. 101 participants completed the self-administered questionnaire and self-collected a vaginal swab for Candida culture. Candida colonization was similar by age and race.

Results: Type 1 diabetics were three times as likely as type 2 diabetics to be colonized with any Candida species (OR = 3.4; 95% CI: 1.03, 11.41; p = 0.04); even after adjusting for abnormal HbA1c, which had an independent effect (OR = 1.4; 95% CI: 1.04, 1.76; p = 0.02). Recent antibiotic use (OR = 4.5; 95% CI: 1.18, 16.79; p = 0.03), lifetime history of chlamydia (OR = 5.8; 95% CI: 1.09, 30.54; p = 0.04), and performing oral sex during the past 2 weeks (OR = 4.9; 95% CI: 0.84, 28.27; p = 0.08) were also associated with Candida carriage after adjusting for diabetic type and abnormal HbA1c. C. albicans was isolated from the majority of colonized type 1 participants (56%), while C. glabrata was the most common isolate among colonized type 2 participants (54%).

Conclusions: Improving glucose control and possibly modifying sexual behavior may reduce risk of Candida colonization, and potentially symptomatic infection, among women with diabetes.

Background

Diabetes mellitus predisposes individuals to bacterial and fungal infections, including those caused by Candida species. Many investigators have suggested that vulvovaginal candidiasis (VVC) occurs more frequently in diabetics [1–8]. Further, chronic recurring VVC may be a marker of diabetes [9]. Several studies report increased rates of asymptomatic vaginal carriage rates of Candida species and incidence of symptomatic infection in diabetic women, but results are inconsistent [5,10–14]. While some show no increase in carriage of vaginal Candida[5], those demonstrating increased Candida carriage in female diabetes patients do not examine the effect of glucose control or diabetes type [12,14]. However, in vitro studies demonstrating impaired host response directed against Candida in diabetics support the idea of increased rates of Candida...
colonization among diabetics [4,6,7]. Whether diabetes leads to more symptomatic and/or more recurrent VVC episodes is a subject of controversy.

Potential risk factors for VVC include diabetes type, severity, and degree of glucose control.[26–30] In addition to diabetes mellitus, a number of VVC risk factors have been identified, including African-American heritage [15–17], previous history of VVC [15], higher education degree, intermediate age, oral contraceptive pills [3,10,16,18], use of commercially available solutions for cleansing of external genitalia or vaginal douching, frequent sexual intercourse [17,19,10], sexual behavior (age at first intercourse, frequency of oral-genital contact) [20], contraception devices (diaphragm, vaginal contraceptive sponge, intravaginal device), and antibiotics [3,15,19]. Whether these factors increase risk of Candida colonization or symptomatic infection following colonization, or both, is unknown, however, it should be emphasized that a prerequisite for symptomatic vaginitis is vaginal colonization.

Few studies have addressed the relationship between Candida colonization, VVC, and diabetes; none we are aware of have examined the role of behavioral VVC risk factors for colonization among persons with diabetes. To evaluate the relationship between Candida colonization and hypothesized risk factors for vulvovaginal candidiasis colonization in diabetics, we conducted a cross-sectional study among female diabetes patients receiving care at one of two diabetes clinics. We describe the associations between Candida colonization, sociodemographics, health behaviors, diabetes type, diabetes severity, and Hemoglobin A1c level among women with type 1 and type 2 diabetes.

Methods

Study population

Female diabetes patients seen at an outpatient academic diabetes practice of Wayne State University Division of Endocrinology, Department of Internal Medicine, were eligible for study. The practice included an urban (University Health Center, Detroit, MI) clinic and a suburban clinic (Hechtman Clinic, Bingham Farms, MI). Patients were diagnosed with type 1 and type 2 diabetes on clinical presentation by a board certified endocrinologist. Potential participants were approached in the clinic waiting room and consent obtained. As an incentive for participation, subjects were rewarded with video rental gift certificates (value $5). Participants consented to a medical record review which included abstraction of total glycated hemoglobin levels obtained at the enrollment visit, completed a self-administered questionnaire and self-collected a vaginal swab. The questionnaire addressed the following variables: sociodemographic (age, race, marital status, insurance status, highest education completed, occupation); diabetes duration, type, severity, and abnormal glucose level; lifetime history of physician diagnosed VVC episodes; recent antibiotic use, by type; sexual history; health behaviors. For the diabetes section we used questions from the Diabetes Care Profile, an instrument developed and validated by the Michigan Diabetes Research and Training Center [21,22]. The study protocol was approved by the Institutional Review Boards at the University of Michigan and Wayne State University.

Of 155 women approached, 105 (67.7%) consented. One woman was ineligible because her vaginal sample was lost. Two women decided to stop participating during the study; one did not understand the questionnaire, while the other felt the questionnaire was too intrusive, leaving a final sample size of 101 participants.

Laboratory methods

All vaginal specimens were cultured for yeast. Specimens were placed on plates with media selective for Candida growth (Sabouraud’s dextrose agar). Suspected mixed samples, as determined by colony type and microscopic characteristics, were plated on plates with media showing species-specific colony color change (Chromagar, CHROMagar, Paris, France). C. albicans and C. glabrata were identified by chlamydospore and germ tube tests; all other species were identified by carbohydrate assimilation tests (API-20C AUX).

Data analysis

We described the distributions of hypothesized variables among participants, using simple descriptive statistics, and the associations between hypothesized risk factors and Candida colonization using odds ratios (OR) and Cornfield 95% confidence intervals (CI). After a detailed stratified analysis, to assess confounding and effect modification, we fit a logistic regression model for Candida carriage. We calculated ORS and 95% CIs for the bivariate analyses using Epilinfo [23]; all other analyses and data management were done using SAS [24]. Several variables strongly associated with Candida colonization had small numbers of missing values, particularly for oral sex (13%) and douching (9%) (others did not exceed 5%). In this case, for the multivariate analyses, we inferred that a missing response was equivalent to a negative response. If we are wrong in this inference, the resulting estimates will be biased towards the null hypothesis of no effect. Excluding the missing responses from the relevant analyses only modestly changed the point estimates.

Results

Demographic characteristics by clinic

Fifty-nine participants were recruited from UHC; forty-two were recruited from Hechtman. Mean age among UHC participants was 52.3 years, while mean age among
HbA1c at time of enrollment. Type 1 subjects had a higher overall, only 20 of 101 participants (19.8%) had normal study population was 7.91, with a range of 4.4–15.7. Antibiotic use in the past 2 weeks, lifetime were not significantly associated with age, race, marital status, education, and employment each diabetic type tended to have longer duration of diabetes, although those who were colonized in each diabetic type tended to have longer duration of diabetes (mean duration diabetes, colonized v. not: type 1: 15.7 v. 20.2 y, p = 0.34; type 2: 9.8 v. 16.1 y, p = 0.28). Average duration of diabetes among colonized women did not differ by type (type 1: 20.2 v. type 2: 16.1; p = 0.53).

Age, race, marital status, education, and employment were not significantly associated with Candida colonization (Table 1). Antibiotic use in the past 2 weeks, lifetime history of chlamydia, douching, and report of both performing and receiving oral sex in the last two weeks were strongly associated with Candida colonization, whereas vaginal-penile sex had only a modest and not statistically significant association with Candida colonization. When stratified by oral sex, there was no association between vaginal sex and colonization status. However, the effect of oral sex remained after stratification by vaginal sex.

Multivariate Analyses
To simultaneously adjust for variables independently associated with Candida colonization in the crude analyses, we fit a logistic regression model predicting Candida carriage (Table 2). Because of the small sample size, we created a base model including age, diabetes type, abnormal HbA1c, recent antibiotic use, and performing oral sex. We assumed for this analysis that those who did not respond to questions about oral sex did not engage in oral sex. Receiving oral sex was not associated after adjustment for performing oral sex (OR = 1.07; 95% CI: 0.12, 9.42, p = 0.95) and thus was excluded from the base model. Other variables associated in the bivariate analyses were added one at a time to the base model. After adjustment, older age, having type 1 diabetes, an abnormal HbA1c level, and report of antibiotic use during the previous 2 weeks were statistically significantly associated with Candida colonization. Performing oral sex was associated with an almost fivefold increase in colonization, but the association was not statistically significant (p = 0.08). When added individually to the base model, lifetime history of chlamydia (OR = 5.8; 95% CI: 10.9, 30.54) but not douching (OR = 2.2; 95% CI: 0.68, 7.00) remained strongly associated with colonization. Four participants positive for Candida also had a previous chlamydia diagnosis and reported douching. When entered simultaneously into the model, the estimates were unstable, thus, they were entered separately. Douching and history of chlamydia were also strongly associated with performing oral sex; adding each of these variables reduced the parameter estimate and statistical significance of the association with performing oral sex. Pregnancy history had no association with colonization after adjustment (OR = 0.97; 95% CI:0.26, 3.66).

Discussion
Among women with diabetes, Candida carriage increased with older age, type 1 diabetes, abnormal HbA1c level, oral antibiotic use in the previous two weeks, and ever history of chlamydia. Other VVC risk factors, including African American descent, lifetime history of VVC, higher education, oral contraceptive use, and frequency of vaginal intercourse were not significantly associated with Candida colonization after adjustment for other variables. These data suggest that behavioral factors, as well as HbA1c, are important determinants of Candida colonization among women with diabetes.
| Characteristic                              | Not Colonized | Colonized | OR     | 95% CI     | p-value |
|--------------------------------------------|---------------|-----------|--------|------------|---------|
| **Diabetes Type**                          |               |           |        |            |         |
| Type 1                                     | 23            | 16        | 2.62   | (0.99, 6.98) | 0.03    |
| Type 2                                     | 49            | 13        |        |            |         |
| **Hemoglobin A1c**                         |               |           |        |            |         |
| Normal (4–6.4%)                            | 17            | 3         |        |            |         |
| Abnormal (> 6.4%)                          | 55            | 26        | 2.68   | (0.68, 15.39) | 0.13    |
| **Duration (miss = 5)**                    |               |           |        |            |         |
| < 5 years                                  | 24            | 9         |        |            |         |
| 6–14 years                                 | 26            | 4         | 0.41   | (0.08, 1.74) | 0.17    |
| > 14 years                                 | 19            | 14        | 1.96   | (0.63, 6.32) | 0.20    |
| **Age**                                    |               |           |        |            |         |
| 18–44                                      | 24            | 7         |        |            |         |
| 45–59                                      | 21            | 15        | 2.45   | (0.75, 8.45) | 0.10    |
| 60+                                        | 27            | 7         | 0.89   | (0.23, 3.46) | 0.85    |
| **Race (miss = 1)**                        |               |           |        |            |         |
| White                                      | 38            | 13        |        |            |         |
| Black                                      | 32            | 15        | 1.37   | (0.52, 3.64) | 0.48    |
| Asian                                      | 1             | 1         | 2.92   | (0.03, 234.35) | 0.44    |
| **Marital Status (miss = 6)**              |               |           |        |            |         |
| Never married                              | 11            | 6         |        |            |         |
| Married, living with spouse                | 30            | 12        | 0.73   | (0.19, 3.00) | 0.61    |
| Married, not living with spouse and/or separated spouse | 5 | 2 | 0.73 | (0.05, 6.55) | 0.75 |
| Widowed or divorced                        | 22            | 7         | 0.58   | (0.13, 2.69) | 0.42    |
| **Education (miss = 4)**                   |               |           |        |            |         |
| High school or less                        | 25            | 6         |        |            |         |
| Vocational/Associate/ Some college          | 26            | 15        | 2.40   | (0.72, 8.72) | 0.11    |
| Bachelor’s degree and higher               | 19            | 6         | 1.32   | (0.30, 5.78) | 0.67    |
| **Employed (miss = 8)**                    |               |           |        |            |         |
| Not employed                               | 30            | 15        |        |            |         |
| Part-time                                  | 14            | 3         | 0.43   | (0.07, 1.91) | 0.22    |
| Full-time                                  | 22            | 9         | 0.82   | (0.26, 2.44) | 0.69    |
| **Insurance (miss = 10)**                  |               |           |        |            |         |
| No                                         | 0             | 3         |        |            |         |
| Yes                                        | 64            | 24        | --     | (0.0, 0.98) | 0.02*   |
| **Antibiotics (oral only)**                |               |           |        |            |         |
| None                                       | 65            | 20        |        |            |         |
| Taken in last two weeks                    | 7             | 9         | 4.18   | (1.19, 14.84) | 0.01*   |
| **Lifetime history of Chlamydia (miss = 5)**|           |           |        |            |         |
| No                                         | 65            | 23        |        |            |         |
| Yes                                        | 3             | 5         | 4.71   | (0.83,32.12) | 0.04*   |
| **Douche (miss = 9)**                      |               |           |        |            |         |
| No                                         | 48            | 15        |        |            |         |
| Yes                                        | 17            | 12        | 2.26   | (0.79, 6.37) | 0.09    |
| **Oral sex in past 2 weeks (miss = 13)**   |               |           |        |            |         |
| None                                       | 58            | 17        |        |            |         |
| Perform only                               | 1             | 1         | 3.41   | (0.04,272.31) | 0.42*   |
| Receive only                               | 3             | 1         | 1.14   | (0.02, 15.23) | 1.00*   |
| Perform and Receive                        | 2             | 5         | 8.53   | (1.22,93.93) | 0.02*   |
| **Vaginal-penile sex in past 2 weeks (miss = 8)**| |           |        |            |         |
| No                                         | 45            | 22        |        |            |         |
| Yes                                        | 15            | 11        | 1.50   | (0.53,4.17) | 0.39    |

*Note: HbA1c calculated from a linear regression formula using total glycated hemoglobin values. Cut points based on local laboratory values. *2-tailed Fisher’s Exact Test
We found a borderline significant association with performing oral sex associated with an almost five-fold increase in vaginal colonization with Candida. Receiving but not performing oral sex has been previously reported as a risk factor for VVC [15]. Oral sex may facilitate transmission of yeast, as Candida often colonizes the oral cavity [15,33]. Diabetics may be more likely to carry Candida in the oral cavity than their sex partner; thus, performing oral sex on their sex partner prior to vaginal intercourse may serve to inoculate the vaginal cavity. Douching has also been previously associated with Candida colonization [17,19,20]. The practice is hypothesized to disrupt vaginal flora; vaginal symptoms may also lead a woman to douche so the direction of effect is unclear. The association we observed with chlamydia is probably a marker of sexual behavior rather than a causal factor; for example, women who reported a history of chlamydia were more likely to douche and to report engaging in oral sex, although it is possible that chlamydia carriage adversely affects the vaginal flora increasing the chance of Candida colonization. Recent antibiotic use is a well-described correlate of symptomatic Candida vaginitis [3,15–18,34]. While asymptomatic infection is not equivalent to disease, antibiotic use may act to alter the vaginal microenvironment to facilitate Candida colonization in the same way it is hypothesized to promote VVC.

Women aged 45 years and older in our study were more likely to be colonized with Candida species. We are unaware of colonization studies in women of comparable age; most have emphasized women of childbearing age [8,35,36]. Whether our observation is a real finding or a reflection of our age distribution (18–84) or unknown selection biases which led to inclusion in our study requires further investigation. However, incidence of symptomatic infection is higher in younger (18–44) women [15].

Table 2: Logistic regression models predicting Candida colonization among 101 women with type 1 or type 2 diabetes (2000)

| Variable Name                              | Parameter Estimate | p-value | Odds Ratio (95% CI) |
|--------------------------------------------|--------------------|---------|---------------------|
| Age 45 and older                           | 1.92               | 0.001   | 6.8 (1.64, 28.37)   |
| Diabetes type 1                            | -1.23              | 0.04    | 3.4 (1.03, 11.41)   |
| Glycemia (% HbA1c)*                        | 0.30               | 0.02    | 1.36 (1.04, 1.76)   |
| Antibiotics in past 2 weeks (oral only)    | 1.49               | 0.03    | 4.5 (1.18, 16.79)   |
| Perform oral sex in past 2 weeks           | 1.59               | 0.08    | 4.9 (0.84, 28.27)   |
| Douching                                   | 0.78               | 0.19    | 2.2 (0.68, 7.00)    |
| Lifetime history of chlamydia              | 1.75               | 0.04    | 5.8 (1.09, 30.54)   |

* HbA1c (%) > 6.4. HbA1c calculated from a linear regression formula using total glycated hemoglobin values. Cut points based on local laboratory values. NOTE: All models included age, diabetes type, HbA1c, antibiotic use, and oral sex.

Women with type 1 diabetes had higher Candida colonization rates than those with type 2, even after adjusting for age, behavioral factors and HbA1c. One possible explanation is difference in duration of Candida carriage: women with type 1 and type 2 diabetes may be equally likely to acquire Candida, but those with type 1 may be less able to clear it. Similar to previous reports, C. albicans was isolated from the majority of colonized type 1 participants, while C. glabrata was the most common isolate in type 2 participants, but our numbers are small [1]. Whether this is due to diabetes type or reflects different distributions of Candida species by age or both is uncertain.

The observation that hyperglycemia in type 1 diabetes increases risk for Candida colonization is consistent with previous reports [1,5,6,31]. A New Zealand study of 124 women with type 1 diabetes found 7 of 7 women with elevated glycated hemoglobin reported vaginal symptoms for the previous year, compared with 60% overall [10]. Hyperglycemia limits neutrophil function among persons with type 1 diabetes, including neutrophils’ ability to phagocytose and kill Candida organisms. With the oxidative killing ability of neutrophils hindered, diabetics may not be able to clear pathogens as well as non-diabetics [1,6,7,31]. Hyperglycemic individuals may also have increased risk for Candida colonization because their secretions contain glucose, which can act as nutrients for Candida organisms. Sobel and colleagues reported a fucose (6-deoxy-galactose) vaginal epithelial cell receptor that aids in adhesion of Candida to vaginal epithelial cells [32]. Since fucose contains an isomer of glucose and acts as one form of receptor site for Candida adhesion, it is possible that increased Candida colonization is proportional to glucose level. Receptor avidity may be a reflection of increased glucose levels in the blood and tissues. Glycemia, however, does not fully explain the observed increased risk of Candida colonization.
This study is small and was intended to be hypothesis generating. The study population is in no way representative of all females with diabetes, although the age and racial distribution of participants reflected that of the participating clinics. Although it is possible that women with a history of symptomatic infection might have been more likely to participate, we have no reason to believe that women differentially participated by both symptomatic history and other variables under study which would have biased our results. Further, as women were unaware of whether they carried Candida at the time of completing the questionnaire, it seems unlikely that a differential recall of behaviors among colonized and non-colonized might have occurred. A final concern is that Candida colonization, while the first step toward VVC, is not equivalent to symptomatic infection. Larger, more definitive studies, which include a non-diabetic control group and prospective follow-up, are planned.

Conclusions
We found strong, statistically significant associations between vaginal Candida colonization and antibiotic use, lifetime history of chlamydia, diabetes type and HbA1c level and a borderline significant association with performing oral sex. More non-albicans species were observed among women with type 2 diabetes. Improving glucose control and possibly modifying sexual behavior may reduce risk of Candida colonization, and potentially symptomatic infection, among women with diabetes.

Competing interests
None declared.

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