

Response to Reviewer #1

1. The prevalence of fungal infections in diabetic patients needs to be clarified

1. We would like to thank this reviewer for a positive outlook on our manuscript, as well as for valuable comments to improve its merit. Specific discussion on the prevalence of fungal infection has been addressed in the part of the manuscript "Types of urogenital candidiasis in patients with diabetes" (more specifically, in sections "Vulvovaginal candidiasis in women with diabetes", "Balanitis/balanoposthitis due to *Candida* spp. in men with diabetes" and "Candidiasis in the urinary tract of diabetic patients". For clarity purposes, we have also made a table highlighting specific prevalence rates in the literature, as a part of our response to the fourth query raised by this reviewer. Subsequently, this table has been included in the main manuscript.

2. How to source the literature, keywords and search time?

2. We searched the PubMed database until March 1, 2022, according to the keywords listed after the abstract (Balanitis; Balanoposthitis; *Candida*; Candidiasis; Diabetes; Pregnancy; Urogenital infections; Vulvovaginitis), and we also specified specific MeSH terms ("diabetes mellitus", "diabetes insipidus", "candida", "candidiasis", "balanitis", "vulvovaginitis", "urogenital system", "infections", "pathogenicity", and "pregnancy"). In addition, Scopus and Reference Citation Analysis (RCA) databases were also searched using the exact keywords.

Table 1 Keywords, database and search time

Keywords	MeSH term	Database
Balanitis	balanitis	PubMed, Scopus, RCA
Balanoposthitis	-	PubMed, Scopus, RCA
Vulvovaginitis	vulvovaginitis	PubMed, Scopus, RCA
Urogenital infections	urogenital system infections	PubMed, Scopus, RCA
Pregnancy	pathogenicity pregnancy	PubMed, Scopus, RCA
<i>Candida</i>	candida	PubMed, Scopus, RCA
Candidiasis	candidiasis	PubMed, Scopus, RCA
Diabetes	diabetes mellitus diabetes insipidus	PubMed, Scopus, RCA

RCA: Reference Citation Analysis

3. Why urogenital candidiasis is common in individuals with diabetes? possible mechanism

3. In our manuscript we highlighted how there is a myriad of host-related immune factors due to the intricate homeostatic relationship of fungi with the host's current immune status, which get disrupted during diabetes. We have also emphasized how the hyperglycemic environment,

rich in carbohydrates, serves as a source of energy indispensable for producing biofilms and matrices that protect fungal cells from external influences. Based on this point by the reviewer, we improved this discussion further. From a pathophysiological perspective, we find a suitable environment in diabetic patients for *Candida* multiplication and proliferation due to alteration of gut microbiota, dietary changes, reduced intestinal secretions and altered liver function, continued usage of antimicrobial agents (and other drugs), co-existing diseases, as well as the pervasive deficiency of key nutrients, as demonstrated in the literature.

4. Some literature studies can be shown graphically.

4. As this is a narrative review paper, it is challenging to choose which studies to show graphically because we have not assessed their quality. Selecting proper research that covers all essential aspects of urogenital candidiasis and diabetes is challenging, while randomly selecting some studies and showing only specific results can be misleading and lead to bias. However, we made a table (Table 3) in which we selected studies investigating the incidence or prevalence of urogenital candidiasis in patients with diabetes.

Table 3 Studies of the prevalence of candidiasis in individuals with diabetes

Author	Year	Study Population	Study outcome
Goswami et al. [64]	2000	n=78 diabetics, n=88 non-diabetics	A total of 46% of diabetic patients showed vaginal <i>Candida</i> sp. and 23% healthy subjects demonstrated <i>Candida</i> spp.
Goswami et al. [65]	2006	n=85 diabetics, n=62 non-diabetics	A total of 67.1% of diabetic patients showed vaginal <i>Candida</i> spp. and 47.3% healthy subjects demonstrated <i>Candida</i> spp. following fluconazole treatment
Gunther et al. [30]	2014	n=48 diabetics; n=669 non-diabetics	A total of 18.8% of diabetics showed vaginal <i>Candida</i> spp. and 11.8% healthy subjects demonstrated <i>Candida</i> spp.
Yokoyama et al. [5]	2019	65 diabetic patients	A total of 36.9% of diabetic patients converted to a positive vaginal <i>Candida</i> spp.
Halteet et al. [62]	2020	550 diabetic patients	A total of 15.6% of diabetics showed vaginal <i>Candida</i> spp.
Lisboa et al. [71]	2010	n=38 diabetics; n=440 non-diabetics	A total of 26.2% of men had <i>Candida</i> spp. and 18% of men had balanitis; 13.8% of diabetic patients had balanitis
Kofteridis et al. [84]	2009	n=88 diabetics; n=118 non-diabetics	A total of 12.7% of diabetic patients showed urinary tract <i>Candida</i> spp. and 1.7% healthy subjects demonstrated <i>Candida</i> spp.

Yismaw et al. [90]	2013	422 diabetic patients; n=387 with asymptomatic UTI; n=35 with symptomatic UTI	A total of 17.1% of symptomatic diabetic patients showed significant candiduria and 7.5% of asymptomatic diabetic patients
Falahati et al. [91]	2016	305 diabetic patients	A total of 12.5% of diabetic patients were positive for candiduria
Esmailzadeh et al. [89]	2018	400 diabetic patients	A total of 10% of diabetic patients showed <i>Candida</i> spp. in urinary tract
Gharanfoli et al. [92]	2019	500 patients with UTI; n=106 diabetics; n=394 non-diabetics	A total of 21.1% of diabetic patients showed <i>Candida</i> sp. in urinary tract and 4.2% of UTI patients were positive for <i>Candida</i> sp.

UTI: urinary tract infections; n: number of patients

5. What has previously been published on this topic and what does this work add to the existing literature?

5. Reviews on the topic have been deficient, which is why decided to pursue and in-depth analysis of the current state of knowledge on the topic. All research studies that deal with this issue have been cited (with the crux of them shown in the table), as well as reviews that were published before our manuscript (we would kindly refer the reviewer to references 21, 28, 68, 85 and 86). However, we believe our approach resulted in the most comprehensive review of the topic, as it discusses both pathophysiological and clinical consideration, and includes all relevant conditions (relevant for both men and women) in a single manuscript. Research studies that contribute to this topic have been summed up in a table that is now included as a part of this manuscript.

6. This reviewer would expect to see some points regarding how to translate these observations to help address this public health concern.

6. We would like to thank the reviewer for this valuable comment. In our conclusion section, we have already emphasized the importance of establishing and preserving euglycemia, alongside any introduced antifungal treatment approaches, if our end-goal is to successfully manage urogenital candidiasis in affected individuals with diabetes. We have also added that, in order to minimize this high burden of yeast infections in individuals with diabetes, it is pivotal to identify those at high risk for developing type 2 diabetes mellitus and forestall the rise of complications; consequently, many lifestyle interventions (such as dietary changes, exercise and weight reduction) have much better impact than pharmacologic treatment. If the condition arises and the patient is faced with urogenital *Candida* infections, early and appropriate treatment regimen should be introduced, especially to avoid several complicated conditions which we have described.

Response to Reviewer #2

This is a contradicting statement. In fact, reference number 4 indicates candida balanitis to be very common in uncircumcised men.

We agree with this comment and would like to thank the reviewer for pointing this out. Therefore, this has been revised.

'Of note, balanitis is rarely seen in circumcised men, as the moist space beneath the foreskin represents an ideal environment for facilitated yeast proliferation^[4].'

This should be expanded to indicate what treatment options are available for the two species (*C. krusei* and *C. glabrata*)

We wish to thank this reviewer for this valuable comment. The discussion on treatment options regarding these two species has been expanded.

'Exceptions are infections caused by *C. krusei* and *C. glabrata*, where amphotericin B deoxycholate is often used (due to inadequate urine concentrations of other azole antifungals and echinocandins)'

Include duration of treatment.

Thank you for this important observation. The duration of treatment has been included.

'The standard treatment regimen is two weeks.'