




Candida albicans skin infection in patients with type 2 diabetes: a systematic review and meta-analysis

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Received: 7 January 2021 / Accepted: 6 April 2021 / Published online: 19 April 2021
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Abstract

Background Fungal infections including *Candida albicans* is one of the most important health concerns among type 2 diabetic patients. Therefore, this study aimed to determine the prevalence of *C. albicans* skin infection in patients with type 2 diabetes in a systematic review and meta-analysis.

Methods In this review study, data were extracted from national and international databases of SID, MagIran, IranMedex, IranDoc, Google Scholar, Cochrane, Embase, ScienceDirect, Scopus, PubMed, and Web of Science (WoS) with no time limit until January 2021. The random effects model was used for doing analysis and the I^2 index was used for assessing the heterogeneity of studies. Data were analyzed using Comprehensive Meta-Analysis (Version 2).

Results The prevalence of *C. albicans* skin infection in patients with type 2 diabetes was 11.4% (95% CI: 8.9%–14.4%) in 13 reviewed articles with a sample size of 1348. Regarding the heterogeneity based on meta-regression, there was a significant difference between the effect of sample size ($P < 0.05$) and the prevalence of *C. albicans* skin infection in patients with type 2 diabetes.

Conclusion The results of this study showed that *C. albicans* skin infection was high in type 2 diabetic patients in Iran. Therefore, to improve the aforementioned situation and to troubleshoot and monitor at all levels, appropriate policies should be adopted.

Keywords Skin infection · Diabetes · *Candida albicans* · Meta-analysis

Background

Candida albicans, a yeast-like fungus, and a limited number of other *Candida* species can cause infections in the skin, mucous membranes, and viscera. *C. albicans* and other *Candida* species are not considered normal skin flora [1].

Candida fungi coexist with the host, but due to predisposing factors, they can invade host tissues and cause disease, or make the person a carrier of *C. albicans*. The organism is found in the natural flora of the mouth, vagina, and intestine and reproduces by budding yeast forms. The fungus can cause infections leading to death in people with weakened immune

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systems, for example in people with AIDS, cancer, bone marrow transplants or organ transplants. Pregnancy, anti-pregnancy medication, antibiotic therapy, diabetes, long-term contact with water, treatment with topical steroids, some endocrine diseases, and factors involved in the weakening of cellular immunity may make this yeast pathogenic [2, 3]. People, despite having a complex immune system, are susceptible to infectious agents, including fungi that are ubiquitous [4].

Diabetes is the most common endocrine disease in the world, accounting for nearly 4 million deaths per year [5]. Diabetes is recognized not only as a disease, but also as a series of metabolic disorders caused by impaired insulin secretion or insulin function or both, and is characterized by elevated blood sugar [6]. Diabetes is an important and growing concern in public health [7, 8]. The major importance of diabetes is due to its high prevalence and its subsequent side effects. Diabetes is one of the most important health-care and social-economic problems in the world today [9]. According to the statistics and the growing trend of diabetes in the world, the World Health Organization (WHO) has declared it to be a hidden epidemic. In 2010, the global prevalence of diabetes was 6.4% for adults, which equals to 285 million people, in 2012, it was reported for 371 million people and by 2030, it is estimated to reach about 552 million people [5, 7, 8].

Type 2 diabetes is the most common type of diabetes, accounting for about 90% of the cases. The prevalence of type 2 diabetes is constantly increasing [10]. It is estimated that there are currently about 1.5 million diabetic patients in Iran [11]. In some people, infection with *C. albicans* is not recognized as the first symptom of diabetes. In a study in Pakistan, of 100 diabetic patients hospitalized for other causes, 27 showed symptoms of infection with *Candida* [12].

Many studies have reported that *Candida* species are the most common yeast isolated from diabetic foot ulcers. However, few studies have reported *C. albicans* as the most common species [13, 14]. Increased prevalence of fungal infections in the spaces between the fingers and nails in the diabetic foot leads to severe and profound inflammatory processes in the foot. Fungal infections among immunocompromised patients, especially diabetic patients, are one of the most important health concerns in the world today [14].

Due to the influence of different factors on the prevalence of *C. albicans* skin disease in patients with type 2 diabetes and lack of general statistics in this regard, we decided to obtain general statistics on the prevalence of *C. albicans* skin disease in patients with type 2 diabetes by reviewing the literature in this area and doing statistical analysis of the results. Therefore, a structured review of all the documents and their combination can create a more complete picture of the dimensions of the problem and increase the use of the best and the highest quality documents available.

Methods

In this systematic review and meta-analysis study, the prevalence of *C. albicans* skin infection in patients with type 2 diabetes was evaluated based on the studies conducted in this area with no time limit until January 2021. To identify the related studies, searching was conducted online at the national databases of SID, MagIran, IranMedex, and IranDoc and the international databases of Google Scholar, ScienceDirect, Scopus, PubMed, and Web of Science (WoS) with Persian keywords and Latin keywords such as prevalence, type 2 diabetes, skin, *C. albicans*, derms, skin manifestations, and fungi infection. Finally, to access other relevant studies, the references used in the articles were also reviewed.

Each keyword in Persian and their English equivalents mentioned above were used to search with the Google Scholar search engine, and the AND, and OR operators were used to searching for articles in combination.

The selection criteria were observational (non-interventional studies) and full-text availability. For more information, the references of the articles reviewed for access to other articles.

Selection of studies

First, all articles related to the prevalence of *C. albicans* in diabetes were collected. At this stage, all studies having the aforementioned keywords in their titles or abstracts were included in the initial list, and other articles that did not address the prevalence of *C. albicans* in type 2 diabetes were excluded. Then, a checklist of the necessary study information including the article title, the place of study, the time of study, the sampling location, the sample size, the sample mean age, and the overall prevalence rate of *C. albicans* infection were prepared for final evaluation. Then, all articles referring to the prevalence of *C. albicans* in patients with type 2 diabetes were collected by the researchers and accepted based on the inclusion and exclusion criteria. Exclusion criteria included irrelevant issues, unavailability of prevalence rates, inadequate data, review studies, case reports, interventional studies, repeated studies, unclear methodology, and full-text unavailability. To reduce bias, searching for articles and extracting data were performed independently by three researchers, and if they disagreed on one article, it would be reviewed by the supervisor. Thirteen studies entered the third stage, quality assessment.

Quality assessment

The quality of the articles was evaluated based on the selected and related items of a 22-item STROBE checklist that could

be evaluated in this study (study design, background and literature review, place and time of study, outcome, inclusion criteria, sample size, and statistical analysis). They were also mentioned in the previous studies. Articles referring to 6 to 7 criteria were considered as high-quality articles, those that did not mention 2 items and more than 2 items from 7 items were considered as medium and low methodological quality articles, respectively.

Data extraction

All final articles entered into the meta-analysis process were prepared for extraction by a pre-prepared checklist. The checklist included the article title, the first author's name, the year of publication, the place of study, the sample size of women, the prevalence of *C. albicans* in men and women with type 2 diabetes, and the mean age.

Statistical analysis

Since the prevalence rate has a binomial distribution, prevalence variance was calculated using the binomial distribution variance formula and the weighted mean was used to combine the prevalence rate of different studies. To evaluate the heterogeneity of the selected studies, the I^2 test was used. Meta-regression analysis was used to investigate the relationship between the prevalence of *C. albicans* skin infection in type 2 diabetic patients with the year of study and sample size. The Egger test and a significance level of 0.05 were used to investigate the publication bias, and the Begg and Mazumdar test at the significant level of 0.1 and the corresponding Funnel plot were also used considering the high volume of samples included in the study. Sensitivity analysis was also used to evaluate the effect of individual studies on the final result. Data were analyzed using Comprehensive Meta-Analysis (Version 2) software.

Results

In this study, all studies regarding the prevalence of *C. albicans* skin infection in type 2 diabetic patients were reviewed systematically with no time limit based on the PRISMA guidelines. In the initial search, 800 articles were identified, of which 730 irrelevant articles and 44 duplicate articles were eliminated, 7 articles were removed due to lack of data access and poor quality, and 13 studies were finally entered the final analysis (Fig. 1) (Table 1).

The probability of publication bias was evaluated by funnel plot and Egger test (Fig. 2), indicating that the publication bias was not statistically significant ($p = 0.283$). Also, the results of the Begg and Mazumdar test at a significant level of 0.1

showed that there was no publication bias in the present study ($p = 0.143$).

Based on the results of the I^2 test ($I^2 = 57.7$) and due to the heterogeneity of the selected studies, the random effects model was used to combine the studies and jointly estimate the prevalence of type 2 diabetes. The total sample size of the study was 1384 persons, ranging from 87 to 18 years of age. The specifications of the selected articles are presented in Table 1. The lowest and the highest sample size was, respectively, related to a 2001 study by Heald et al. in Manchester, England [25], and a 2009 study by Rashidi et al. in Urmia, Iran [21]. The highest and the lowest prevalence rate of *C. albicans* skin infection was related to Heald et al.'s study in 2001 in Manchester, England with 29.4% (95% CI: 12.8–54.2%) [25], and Somolinos et al.'s study in 1991 in Puerto Rico with 5% (95% CI: 2.1–11.5%) [23], respectively. According to the results of this study, the overall prevalence rate of *C. albicans* skin infection in patients with type 2 diabetes was 11.4% (95% CI: 8.9–14.4%), The middle point of each line segment shows the prevalence of *C. albicans* skin infection in patients in each study, and the diamond mark shows the prevalence *C. albicans* skin infection in patients with type 2 diabetes in Iran for the total studies. (Fig. 3).

The relationship between the year of study and the sample size with the prevalence of *C. albicans* skin infection in type 2 diabetic patients was investigated using meta-regression analysis. As shown in Fig. 4, the prevalence of *C. albicans* skin infection decreased with increasing the sample size, which was significantly different ($P < 0.05$). Also, as shown in Fig. 5, the prevalence of *C. albicans* skin infection increased as the year of study increased, which was not significantly different ($P = 0.681$).

Discussion

The present study is the first systematic review and meta-analysis study conducted on the prevalence of *C. albicans* in patients with type 2 diabetes. This study has been formulated using the most optimal secondary analysis methods out of 13 eligible primary studies. The articles used in this study ranged from 1991 to 2019. A total of 1384 samples aged 18–87 years were included in the study data. The overall prevalence rate of *C. albicans* skin infection in patients with type 2 diabetes was 11.4% (95% confidence interval: 8.9–14.4%) in this study.

Individuals of all ages and all social and economic strata are affected by diabetes mellitus. The number of type 2 diabetic patients in 2000 was 171 million. It is likely to reach 366 million by 2030 [27].

Diabetes is an important factor for fungal infections. It has significant morbidity and mortality. Most of the infections in diabetic patients are due to high blood sugar, which causes defects in cellular and humoral immunity [16]. Swings in

Table 1 Characteristic of included studies

Author, year, [Reference]	Age (years)	city	Sample size	Prevalence %
Abilash S,2015 [14]	31–72	India	100	16
Saba Fata,2010 [15]	32–86	Iran	120	9.1
Varsha T. Kalshetti, 2017 [16]	32–73	India	80	7.5
Hiten Kareliya,2019 [17]	42–76	India	100	16
Ghulam Hussain Baloch,2008 [18]	40–80	Pakistan	90	22.2
Maryam Roudbary,2014 [19]	38–74	Iran	57	8.8
Omid Raiesi,2016 [20]	–	Iran	122	10.6
Toraj Rashidi,2009 [21]	–	Iran	200	10
J. Nithyalakshmi,2014 [22]	38–67	India	142	9.8
Aida Lugo-Somolinos,1991 [23]	18–83	Puerto Rico	100	5
Jayaraman Selvaraj,2016 [24]	50–70	India	100	6
A. H. Heald,2001 [25]	43–87	England	17	29.4
Haji Khan Khoharo,2009 [26]	33–76	Pakistan	120	10

blood sugar and hypoxia and poor blood circulation may impair the ability of white blood cells to kill pathogenic bacteria and fungi [28]. Diabetic patients are more at risk for bacterial

and fungal infections and are also prone to increased skin and soft tissue infections. In these patients, soft tissue and lower extremity bone infections are the most common cause of

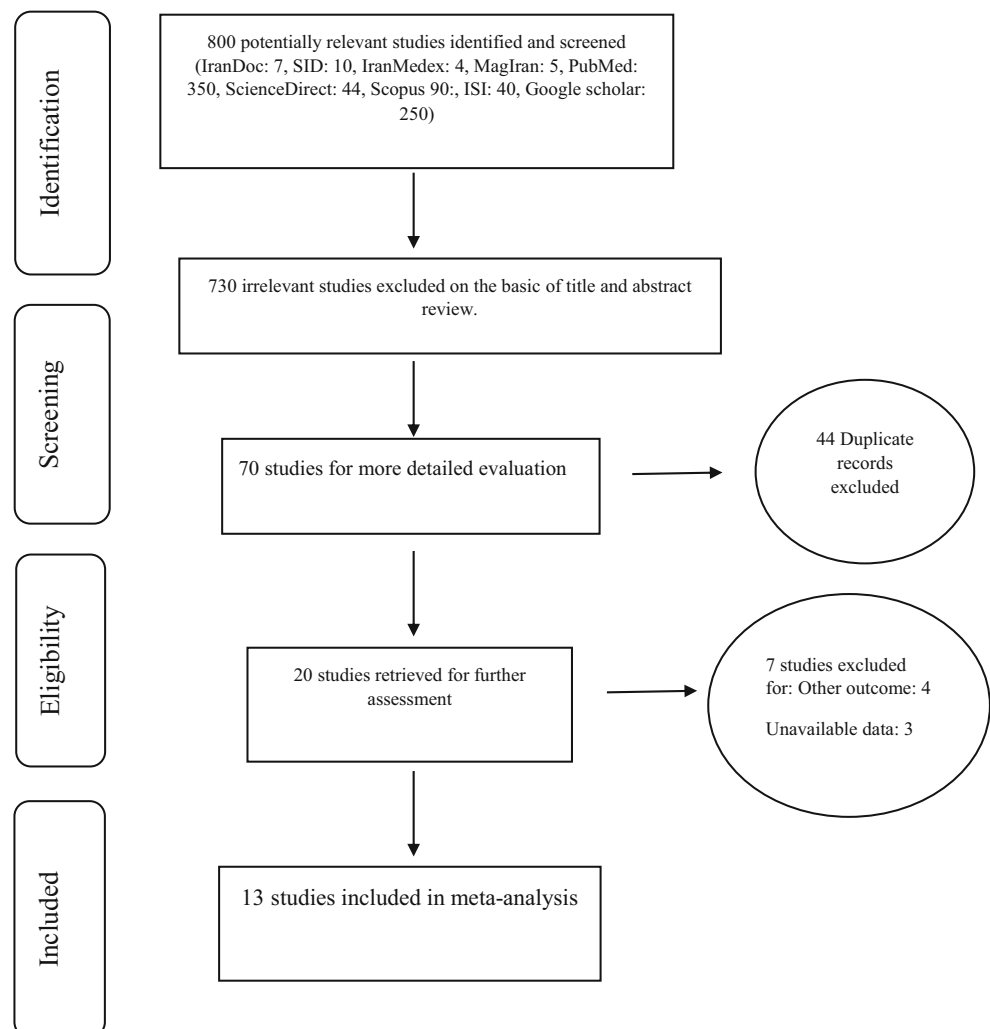
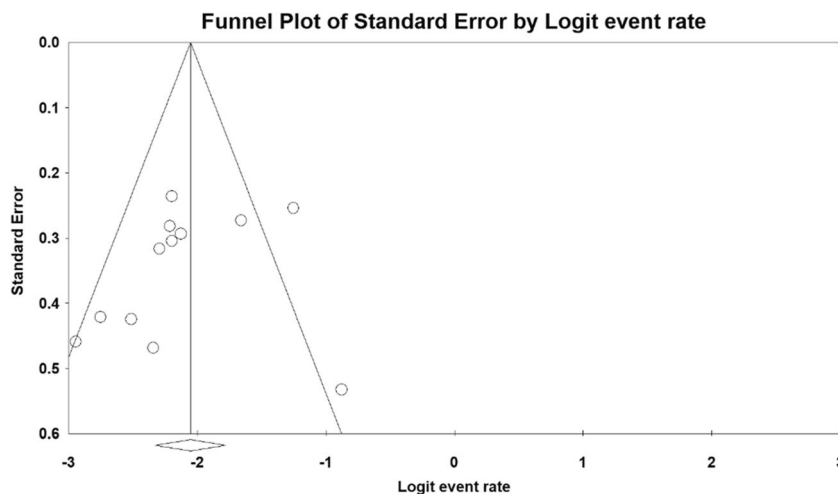
Fig. 1 Flow diagram of study selection

Fig. 2 Funnel plot of the results of the prevalence of *C. albicans* skin infection in patients with type 2 diabetes



hospitalization. Sometimes, it causes amputation in the lower extremity [15, 19, 29].

From various skin disease studies, it can be concluded that diabetes is the most common systemic disease associated with multiple skin complications [26]. In the study by Farshchian et al., it was found that cutaneous infections were the most common skin disease in diabetic patients, among which fungal infections with 37.9% being the most common fungal causes [30]. Also, in Dr. Darjani et al.’s study, 28.6% of the lesions were infectious, 24% of which were fungal causes [31]. In the study of Kaushik V. Phulari et al., infectious lesions and fungal infections were seen in 61% and 39.5% patients, respectively [32].

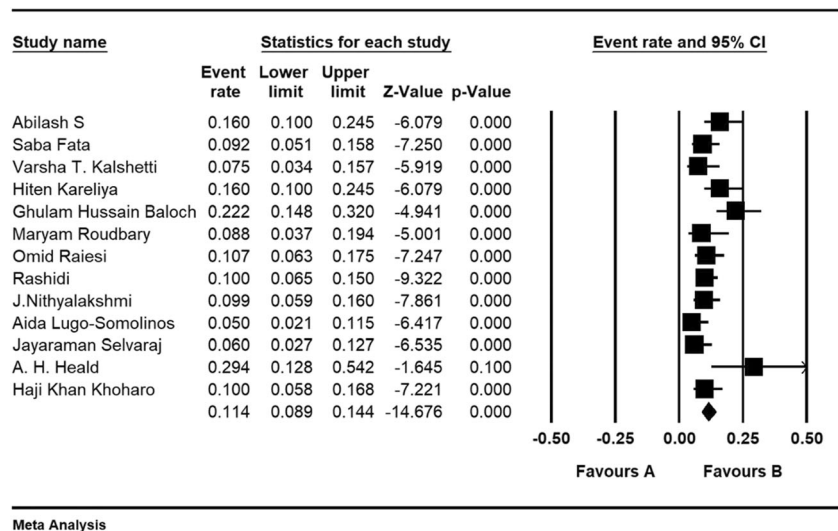
Fungal infections, especially Candida fungus, are common in most diabetic patients. Occasionally, Candida infection has not been recognized as an early symptom of diabetes [33]. Fungal infections in patients with diabetes can lead to fatal complications such as foot amputation if not treated on time [16].

Most people control the growth and propagation of this opportunistic fungus with physiological defense mechanisms and a healthy immune system. Under certain conditions and despite predisposing factors as controllers such as diabetes, immune deficiency, and widespread use of antibiotics, an opportunity is created for *C. albicans* to transform from symbiotic to pathogenic, capable of infecting different tissues and causing fatal systemic disease [34–36].

In a 2015 study aimed to determine the prevalence of fungal infection in diabetic foot ulcers, Abilash S et al. stated that out of 100 patients studied, 18% had a positive evaluation of fungal culture, the most frequent of which was the strain of *C. albicans* with 16% followed by *Candida tropicalis* with 2% [14].

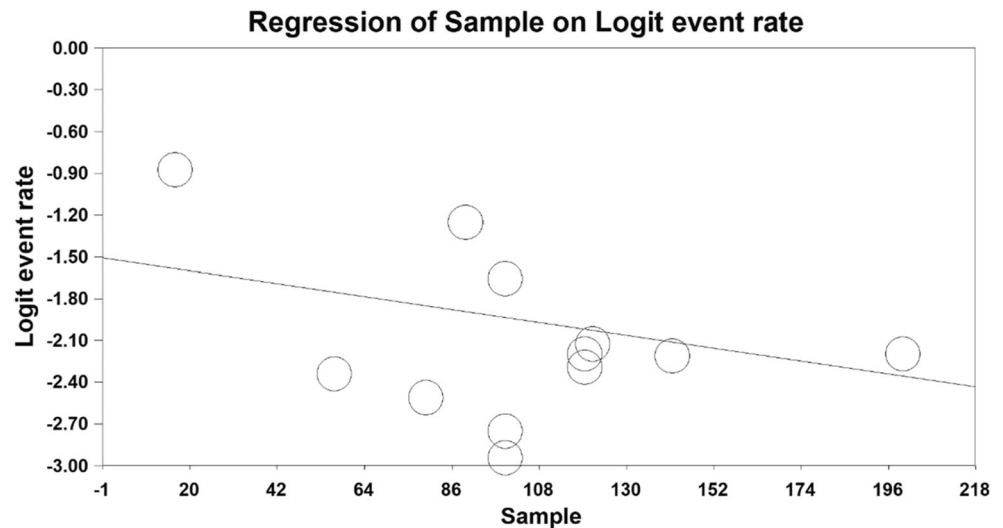
The results obtained from the prevalence of *C. albicans* skin infection in this meta-analysis are close to the results of Rashidi et al.’s study. In this study, which aimed to evaluate the *C. albicans* skin infection in type 2 diabetic patients, they stated that out of 200 specimens infected, 180 (90%) had a

Fig. 3 Overall prevalence of *C. albicans* skin infection in patients with type 2 diabetes and a 95% confidence interval in Iran



Meta Analysis

Fig. 4 Meta-regression of the relationship between the sample size and the overall prevalence of *C. albicans* skin infection in patients with type 2 diabetes



negative culture of *albicans*, and 20 (10%) had a positive culture. In this article, the rate of *Candida* infection was reported to be relatively higher in older patients and men. The infection rate in poorly-controlled diabetes was significantly higher than in well-controlled diabetes. The rate of infection in people with type 1 diabetes was higher than in people with type 2 diabetes. No relationship has been found between the infection and duration of diabetes in this study [15].

Comparing the results of this study with other studies, it should be noted that the prevalence of *C. albicans* skin infection in our study was higher than that of Saba Fata et al.'s (2010) study in Mashhad (11.4% vs. 9.1%) and lower than that of Varsha T. Kalshetti et al.'s (2017) study in Dhule (11.4% vs. 42.85) [15, 16].

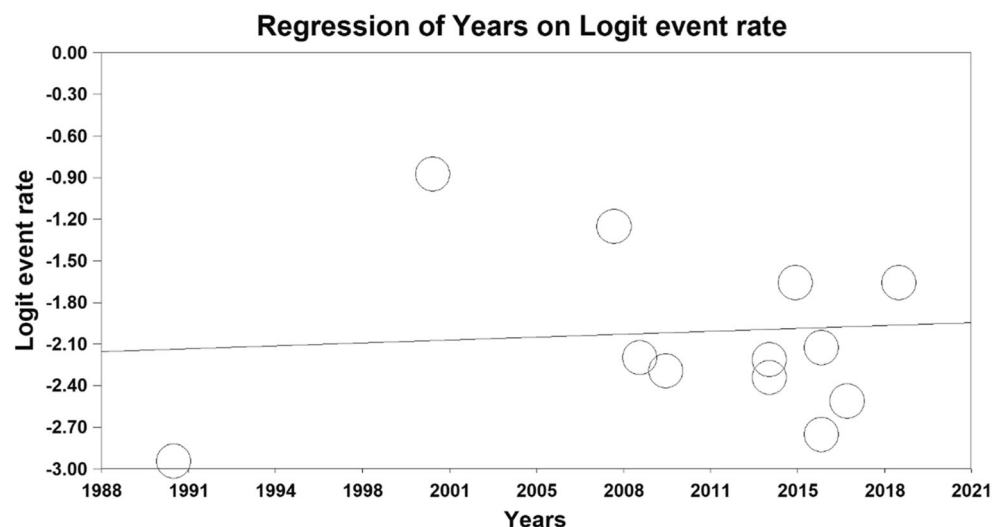
The prevalence of *C. albicans* skin infection increased with increasing the year of study, which was not significantly different ($P = 0.681$). In a study by Hiten Kareliya et al. in July 2019 on 100 patients with type 2 diabetes, the prevalence of *C. albicans* skin infection was reported to be 16% which

was close to the results of this meta-analysis with a prevalence rate of 11.4% (95% confidence interval: 8.9–14.4%) [17].

The results of the present study also report that the prevalence of *C. albicans* increases with the years of research, which can be due to the increase in diagnostic methods as well as increasing awareness of diabetics about oral infections, including *Candida* [37].

The results of this study show that different outbreaks of *Candida* have been reported in different regions due to racial differences, economic and social status and cultural level of different societies [15], in various studies, the carriage rate of *C. albicans* in the oral cavity was different. It could be due to different methods of sampling. In the oral cavity of diabetic patients, the carriage rate of *Candida* is claimed to be higher. Increased *C. albicans* density has been shown to be associated with increased concentration of salivary glucose [37]. Other investigators have also observed that increased *C. albicans* reflects increased salivary glucose levels. [37, 38]

Fig. 5 Meta-regression of the relationship between the year of study and the overall prevalence of *C. albicans* skin infection in patients with type 2 diabetes



Skin infections in diabetic patients can cause many problems for patients. It costs a great deal of money for the patient and society. Based on the findings, it can be said that fungal infections in the skin are observed in diabetic patients, among which, *C. albicans* fungal infection is more prevalent than other lesions. Skin care and ongoing cutaneous examination are of clinical importance. In this regard, the familiarity of physicians and medical personnel with cutaneous symptoms and fungal infections in patients with diabetes is of importance as well. Education of diabetic patients and their families with cutaneous manifestations, especially infectious and fungal causes should be considered. Encouraging faster referral for treatment and observing health issues can reduce the progression of lesions and help reduce personal, social, and economic complications.

Limitations

The main limitation of the present study was the lack of access to the full text of the articles and the poor quality of some of the studies reviewed.

Conclusion

Our findings showed an 11.4 prevalence of *C. albicans* skin infections in patients with diabetes. Careful attention to the likelihood of fungal infection incidence, early diagnosis, and appropriate treatment will rapidly improve and eliminate the risk of amputation and minimize the mortality rate and costs. Given the high prevalence of *C. albicans* in type 2 diabetic patients, health policy-makers need to take the necessary measures to effectively control the disease, including periodic skin examination for diabetic patients.

Abbreviations *Candida albicans*, *C. albicans*; WHO, World Health Organization; SID, Scientific Information Database; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology for cross-sectional Study; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

Acknowledgements The authors thank the student research committee, Kermanshah University of Medical Sciences.

Authors' contributions SHR and SHSH and NS contributed to the design, MM and RJ statistical analysis, participated in most of the study steps. SHR and AVR prepared the manuscript. RJ and MM and NS assisted in designing the study, and helped in the, interpretation of the study. All authors have read and approved the content of the manuscript. **Availability of data and materials** Datasets are available through the corresponding author upon reasonable request.

Funding By Deputy for Research and Technology, Kermanshah University of Medical Sciences (IR) (3010843). This deputy has no role in the study process.

Declarations

Ethics approval and consent to participate Ethics approval was received from the ethics committee of deputy of research and technology, Kermanshah University of Medical Sciences (3010843).

Consent for publication Not applicable.

Competing interests The authors declare that they have no conflict of interest.

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