ORIGINAL ARTICLE

UDC: 616.379-008.64:616.5
https://doi.org/10.2298/VSP190226073U

Association between skin manifestations and glycemic control in patients with type 2 diabetes mellitus

Povezanost između kožnih manifestacija i glikemijske kontrole kod bolesnika sa dijabetesom melitusom tipa 2

Sanja Umičević Šipka*, Jagoda Balaban*, Radojka Bijelić†

University Clinical Centre of the Republic of Srpska, *Skin and Venereal Diseases Clinic, Banja Luka, Republic of Srpska, Bosnia and Herzegovina; Health Center, †Family Medicine Service, Banja Luka, Republic of Srpska, Bosnia and Herzegovina

Abstract

Background/Aim. Diabetes mellitus (DM) can be associated with numerous skin diseases. This study aimed to determine the pattern and incidence of skin manifestations in patients with type 2 DM and their link to glycemic control. **Methods.** This cross-sectional study was conducted at the Skin and Venereal Diseases Clinic, University Clinical Centre of the Republic of Srpska in Banja Luka, Bosnia and Herzegovina, from January 2016 to January 2018. Adult patients of both genders suffering from type 2 DM and cutaneous manifestations participated in the study. Glycemic control was assessed according to the values of glycated hemoglobin (HbA1c) of 7%. **Results**. The mean age of 105 study participants (46% male and 54% female) was 68.4 ± 10 years, while the mean HbA1c was 8.3 ± 1.6%. Unsatisfactory glycemic control was found in 74.3% of patients with the mean HbA1c at 8.9 ± 1.4%, while satisfactory glycemic control was found in 25.7% of patients, with the mean HbA1c at 6.7 ± 0.2% ($p < 0.001$). Infections were the most frequent skin diseases (43.9%). Bacterial infections were most common (26.7%), followed by fungal infections (24.8%), xerosis (17.1%), psoriasis (15.2%), fibroma molle (14.3%), diabetic ulcer (7.7%), prurigo (6.7%), and stasis dermatitis (5.7%). Other skin manifestations were found at a lower rate. A significant association was found between unsatisfactory glycemic control and skin infections ($p = 0.009$). **Conclusion.** The most common skin manifestations in patients with type 2 diabetes are infections. They occurred more often in patients with unsatisfactory glycemic control.

Key words:
diabetes mellitus, type 2; skin manifestation; blood glucose; bosnia and herzegovina; infection.

Apstrakt

Uvod/Cilj. Dijabetes mellitus (DM) može biti udružen sa brojnim kožnim bolestima. Cilj naše studije bio je da se ustanovi uzorak i frekvencija kožnih manifestacija kod bolesnika sa DM tipa 2 i njihova povezanost sa glikemijskom kontrolom. **Metode.** Ova studija preseka sprovedena je na Klinici za kožne i polne bolesti, Univerzitetskog Kliničkog centra Republike Srpske, Banja Luka, Bosna i Hercegovina, u periodu od januara 2016. do januara 2018. godine. U studiju su bili uključeni odrasli bolesnici oba pola koji su imali kožne bolesti i DM tip 2. Glikemijska kontrola posmatrana je prema ciljnoj vrijednosti glikolizirranog hemoglobina (HbA1c) od 7%. **Rezultati.** U studiju je bilo uključeno 105 bolesnika (46% muškaraca i 54% žena), srednje dobi od 68,4 ± 10 godina, sa prosečnom vrednosti HbA1c od 8,3 ± 1,6%. Nezadovoljavajuća glikemijska kontrola utvrđena je kod 74,3% bolesnika koji su imali prosečnu vrednost HbA1c 8,9 ± 1,4%, a zadovoljavajuća kod 25,7% bolesnika sa prosečnom vrednosti HbA1c 6,7 ± 0,2% ($p < 0,001$). Među kožnim manifestacijama najzastupljenija je bila infekcija (43,4%). Bakterijska infekcija je bila najčešća (26,7%), a zatim gljivična infekcija (24,8%), kseroza kože (17,1%), psorijaza (15,2%), meki fibromi (14,3%), dijabetično stopalo (7,7%), prurigo (6,7%) i stazni dermatitis (5,7%). Druge kožne manifestacije uočene su sa manjom zastupljenošću. Utvrđena je značajna povezanost nezadovoljavajuće glikemijske kontrole sa infekcijama kože ($p = 0,09$). **Zaključak.** Najčešće kožne manifestacije kod bolesnika sa DM tipa 2 su infekcije. One su češće kod bolesnika sa nezadovoljavajućom glikemijskom kontrolom.

Ključne reči:
dijabetes melitus, insulin-nezavisni; koža, manifestacije; glikemija; bosna i hercegovina; infekcija.

Correspondence to: Sanja Umičević Šipka, University Clinical Centre of the Republic of Srpska, Skin and Venereal Diseases Clinic, Dvanaest beba, 78 000 Banja Luka, Bosnia and Herzegovina. E-mail: sanjaumicevic84@gmail.com

Introduction

Diabetes mellitus (DM) is the most common endocrine disorder with a broad spectrum of cutaneous manifestations [1]. Increased serum glucose causes damage to a wide range of cell types, including endothelial, neuron, and renal cells, but also keratinocytes and fibroblasts [2]. The overall prevalence of skin disorders in both types of DM varies from 51% to 97 % in different regions worldwide [3]. Most documented studies have shown that the incidence of cutaneous disorders associated with diabetes is between 30% and 71% [4].

Skin diseases can appear as the first sign of diabetes or may develop at any time in the course of the illness [5]. In dermatology, a great number of findings on skin diseases have been associated with diabetes, some demonstrating a stronger connection than others. Some of them have various health implications ranging from those that are concerning from the aesthetic point of view to those that may be life-threatening [6]. Awareness of cutaneous manifestations of DM can provide an insight into the present or prior metabolic status of patients. Recognition of such findings may aid in diagnosing diabetes or may be monitored as a marker of glycemic control [7]. Good metabolic control may prevent some of these manifestations and support treatment [8]. There is considerable uncertainty around the pathogenesis of many cutaneous conditions affecting diabetic patients because of insufficient understanding of the metabolic basis of DM itself [9]. There is no strict classification of skin lesions related to DM, but academic literature usually classifies them into four categories: skin lesions with strong-to-weak association with diabetes (necrobiosis lipoidica, diabetic dermopathy, diabetic bullae, yellow skin, eruptive xanthomas, perforating disorders, acanthosis nigricans, oral leucoplakia, lichen planus), infections (bacterial, fungal), cutaneous manifestations of diabetic complications (microangiopathy, macroangiopathy, neuropathy), and skin reactions to diabetic treatment (sulphonylurea or insulin). Some authors also add endocrine syndrome with skin changes and diabetes as the fifth group [7, 10].

Glycated hemoglobin (HbA1c) has been used as an objective marker of average glycemic control for many years. Recommendations for clinical practice by the American Diabetes Association (ADA) suggest that maintaining HbA1c value closer to normal levels may be beneficial for patients. The target value for prevention of microvascular complications is < 7% [11]. Since dermatological patients often have diabetes, the aim of this study was to determine the pattern and incidence of skin manifestations in patients with type 2 DM and their link with glycemic control.

Methods

This cross-sectional study included 105 adult patients of both genders treated at the Skin and Venereal Diseases Clinic, University Clinical Centre of the Republic of Srpska in Banja Luka, Bosnia and Herzegovina, from January 2016 to January 2018. The study was approved by the Ethics Committee University Clinical Centre of the Republic of Srpska in Banja Luka.

Patients with skin diseases and diabetes mellitus were referred to a hospital or outpatient treatment by their family doctor. Referral factors for outpatients included adult patients of both genders with type 2 DM diagnosed by an endocrinologist and with the value of HbA1c tested within the last two weeks. Glycated hemoglobin test for hospital patients was carried out during the diagnostic examination. Based on the ADA recommendations for the target value of HbA1c of 7% for glycemic control, patients were divided into two groups. The first group included patients with satisfactory and the second group included patients with unsatisfactory glycemic control [11]. Satisfactory glycemic control was defined as HbA1c $\leq$ 7%. Unsatisfactory glycemic control was defined as HbA1c $\geq$ 7%. Detailed medical history was obtained from the study participants including diabetes duration and treatment method for diabetes. The diabetes duration was observed over four time periods: 1) less than one year, 2) between 1 and 9 years, 3) between 10 and 19 years, and 4) 20 years and over. The treatment method for diabetes was observed based on insulin dependency, i.e. insulin-dependent and insulin-independent.

Clinical diagnosis of dermatological findings was established after a detailed general, systemic and cutaneous examination. In addition to clinical findings, this study used relevant laboratory blood tests, bacteriological, mycological, immunological, or other necessary laboratory investigations where required in order to confirm the diagnosis of skin diseases. The study respondents were divided into three groups based on skin manifestations. The first group included patients with skin manifestations related to diabetic complications (i.e. complications of infectious, microangiopathy, or neuropathic origin). The second group included patients with skin diseases known as commonly associated with diabetes. The third group involved patients with other skin manifestations which are not commonly associated with diabetes.

Statistical analyses were carried out using SPSS 22 software package. The data were described by mean values and standard deviations (SD) for continuous variables and incidence and percentages (%) for categorical variables. The differences between subgroup mean values were analyzed by the *t*-test and the one-way analysis of variance (ANOVA) depending on the number of groups. The chi-squared test (χ^2) was used to determine whether there was a significant difference between the incidences of categorical variables. *P*-values lower than 0.05 were considered significant.

Results

The study included 105 adult patients with different skin diseases and type 2 DM. There were 54.2% of women and 45.8% of men at the mean age of 68.4 ± 10.7 years and with the mean HbA1c 8.3 ± 1.6%. Participants were divided into two groups according to their glycemic control. Satisfactory glycemic control (HbA1c 6.7 ± 0.2%) was observed in 25.7% of patients (mean age 70.4 ± 8.1 years). Unsatisfactory glycemic control (HbA1c 8.9 ± 1.4%) was observed in

74.3% of patients (mean age 67.6 ± 11.4 years). Most patients in this study had unsatisfactory glycemic control ($p < 0.001$). There was no statistically significant difference in relation to gender ($p = 0.547$) or the mean age ($p = 0.192$) between the two groups. Most participants with unsatisfactory glycemic control (77%) had a long duration of diabetic disease (between 10 and 19 years). Even 95% of patients with diabetes duration > 20 years had unregulated glycemic control. Duration of diabetes differed significantly between the two groups ($p < 0.001$) (Table 1).

(16.2%). Other bacterial infections such as impetigo, furunculous, erysipelas, erythrasma, and folliculitis had low incidence. Fungal infections caused by *Candida* spp. were found in 15.2% of patients, while infections caused by dermatophytes were found in 9.5% of patients. The mean HbA1c in patients with these skin disorders was 8.9 ± 1.8%. The highest value of HbA1c was found in patients with cellulitis (10 ± 1.9%), while the lowest one was in patients with Schamberg's disease, i.e. 7.5 ± 1.3%. Satisfactory glycemic control had 25.9% of patients, while 55.1% of patients had unsatis-

Table 1

Characteristics of the study population

Variables	Total patients n (%)	Glycemic control		*p*-value
		satisfactory n (%)	unsatisfactory n (%)	
	105 (100)	27 (25.7)	78 (74.3)	0.000
Age (years), mean ± SD	68.36 ± 10.72	70.44 ± 8.08	67.64 ± 11.45	0.192
Gender, n (%)				
male	48 (45.8)	11 (22.9)	37 (77.1)	0.547
female	57 (54.2)	16 (28.1)	41 (71.9)	
HbA1c (%), mean ± SD	8.32 ± 1.57	6.67 ± 0.21	8.88 ± 1.43	0.000
Duration of diabetes (years)				
< 1	8 (7.6)	3 (37.5)	5 (62.5)	0.480
1–9	33 (31.4)	13 (39.4)	20 (60.6)	0.223
10–19	44 (41.9)	10 (22.7)	34 (77.3)	0.000
≥ 20	20 (19.0)	1 (5.0)	19 (95.0)	0.000
Insulin dependency, n (%)				
dependent	60 (57.1)	11 (18.3)	49 (81.7)	0.000
independent	45 (42.9)	16 (35.6)	29 (64.4)	0.053

HbA1c – glycated hemoglobin; SD – standard deviation.

Table 2

Skin manifestations related to diabetic complications and glycemic control

Skin manifestations	Total patients (n = 105) n (%)	HbA1c (%) mean ± SD	Glycemic control		*p*-value
			satisfactory (n = 27) n (%)	unsatisfactory (n = 78) n (%)	
All skin infections	46 (43.9)	8.98 ± 1.86	6 (22.2)	40 (51.3)	0.009
Bacterial infections	28 (26.7)	9.30 ± 2.03	5 (18.5)	23 (29.4)	0.267
cellulitis	17 (16.2)	10.07 ± 1.92	1 (3.7)	16 (20.6)	0.029
impetigo	3 (2.8)	7.13 ± 0.47	1 (3.7)	2 (2.6)	
furunculous	3 (2.8)	9.50 ± 2.36	1 (3.7)	2 (2.6)	
erysipelas	2 (1.9)	9.10 ± 0.28	0 (0.0)	2 (2.6)	
erythrasma	2 (1.9)	6.60 ± 0.00	2 (7.4)	0 (0.0)	
folliculitis	1 (0.9)	8.00 ± 0.00	0 (0.0)	1 (1.3)	
Fungal infections	26 (24.8)	9.00 ± 1.62	1 (3.7)	25 (32.0)	0.003
candidiasis	16 (15.2)	9.48 ± 1.80	0 (0.0)	16 (20.6)	0.197
dermatophytosis	10 (9.5)	8.71 ± 1.47	1 (3.7)	9 (11.6)	
Viral infections	2 (1.9)	8.85 ± 1.34	0 (0.0)	2 (2.6)	0.401
Diabetic foot ulcer	8 (7.7)	8.28 ± 0.89	0 (0.0)	8 (10.2)	0.083
Schamberg's disease	2 (1.9)	7.55 ± 1.34	1 (3.7)	1 (1.3)	0.428
Total patients	50 (47.6)	8.91 ± 1.82	7 (25.9)	43 (55.1)	0.009

For abbreviations see under Table 1.

Skin disorders related to diabetic complications were found in 47.6% of patients. The most common disorders in this group were skin infections (43.9%). Bacterial infections were found in 26.7% of cases and fungal in 24.8% of cases. Foot ulcers were found in 7.7% of participants, while viral infections and Schamberg's disease were low (both by 2.1%). The most common bacterial infection was cellulitis

factory glycemic control. The difference in the occurrence of skin manifestations related to diabetic complications between patients with unsatisfactory and satisfactory glycemic control was statistically significant ($p = 0.009$) (Table 2).

In this study, 51.4% of participants had aggravated or skin diseases commonly associated with diabetes. The most recurrent skin disease in this group was xerosis (17.1%),

followed by psoriasis (15.2%) and fibroma molle (14.3%). Other diseases detected with a lower incidence were dermopathia diabeticorum (8.6%), pruritus (6.7%), granuloma annulare (5.7%), and scleredema diabeticorum (2.8%). The mean HbA1c in this group was 8.4 ± 1.7%. The highest HbA1c value of 10.1 ± 2.7% was found in patients with scleredema diabeticorum and the lowest value of 7.6 ± 1.2% was found in patients with annular granuloma. Satisfactory glycemic control had 41.8% and unsatisfactory 52.6% of these patients. There was no significant difference in the occurrence of skin diseases aggravated or commonly associated with diabetes according to glycemic control between the two groups (Table 3).

Other different skin manifestations either not commonly associated or unassociated with diabetes were found in 48.5% of patients. The most common was seborrheic keratosis (20%). Other skin diseases detected in a lower incidence in the descending order included the following: prurigo (6.7%), stasis dermatitis (5.7%), urticaria/angioedema (4.8%), drug-induced exanthema (3.3%), pemphigus (3.3%), parapsoriasis (2.8%), erythroderma (2.8%), and bullous pemphigoid (1.2%). The mean value of HbA1c in this group of skin disorders was 8.3 ± 1.7%. The highest value of HbA1c was in patients with nodular prurigo (10 ± 2.4%). The lowest value was in patients with exanthema (6.9 ± 0.7%) and urticaria/angioedema (6.9 ± 0.5%). There was no significant difference in the occurrence of skin diseases not commonly associated with diabetes between the two groups according to glycemic control (Table 4).

Discussion

The study found that patients with type 2 diabetes had a wide range of different skin manifestations. Among them, the most common were skin infections of bacterial and fungal origin. Skin infections were more frequent in patients with unsatisfactory glycemic control.

There was no gender difference among the study participants (p = 0.547). The result was similar to the report presented by Bhat et al. [12]. However, some authors reported that dermatological manifestations were more common in women since a higher number of women visit doctors, which indicates a higher disease burden and health awareness among the females [13]. On the other hand, some authors have shown a preponderance among men [14, 15]. The mean age of the study participants was 68 ± 11 years. This result was higher than in the findings by various similar studies in which the age of patients with type 2 DM and skin manifestations was usually between 50 and 60 years [13–16]. The mean age for DM presentation indicated that the majority of patients had longstanding diabetes, and the study confirmed this with the findings on diabetes duration, which was between 10 and 19 years in 42% of patients and more than 20 years in 20% of patients. Diabetes lasted longer ($p < 0.001$) in patients with poor glycemic control. Nevertheless, in similar studies, some authors found diabetes duration < 10 years among a higher number of respondents [4, 12]. The majority of patients (74%) had poorly controlled diabetes, with the mean HbA1c at 8.9 ± 1.4%. This was considerably higher than the target value recom-

Table 3

Skin manifestations aggravated or commonly associated with diabetes and glycemic control

Skin manifestations	Total patients (n = 105) n (%)	HbA1c (%) mean ± SD	Glycemic control		*p*-value
			satisfactory (n = 27) n (%)	unsatisfactory (n = 78) n (%)	
Xerosis	18 (17.1)	8.97 ± 2.08	4 (14.8)	14 (17.9)	0.710
Psoriasis	16 (15.2)	7.80 ± 1.04	5 (18.5)	11 (14.1)	0.582
Fibroma molle	15 (14.3)	8.87 ± 1.99	3 (11.1)	12 (15.4)	0.584
Diabetic dermopathy	9 (8.6)	9.45 ± 2.15	0 (0.0)	9 (11.6)	0.065
Pruritus	7 (6.7)	9.00 ± 1.83	1 (3.7)	6 (7.7)	0.474
Granuloma annulare	6 (5.7)	7.66 ± 1.21	2 (7.4)	4 (5.1)	0.660
Scleredema diabeticorum	3 (2.8)	10.13 ± 2.67	0 (0.0)	3 (3.8)	0.301
Total patients	54 (51.4)	8.45 ± 1.68	13 (48.1)	41 (52.6)	0.692

For abbreviations see under Table 1.

Table 4

Skin manifestations not commonly associated with diabetes and glycemic control

Skin manifestations	Total patients (n = 105) n (%)	HbA1c (%) mean ± SD	Glycemic control		*p*-value
			satisfactory (n = 27)	unsatisfactory (n = 78)	
Keratosis seborrhoica	21 (20.0)	8.57 ± 1.47	4 (14.8)	17 (21.8)	0.435
Prurigo	7 (6.7)	10.08 ± 2.40	1 (3.7)	6 (7.7)	0.474
Stasis dermatitis	6 (5.7)	7.88 ± 1.16	2 (7.4)	4 (5.1)	0.660
Urticaria/angioedema	5 (4.8)	6.96 ± 0.54	3 (11.1)	2 (2.6)	0.072
Exanthema	4 (3.8)	6.95 ± 0.76	3 (11.1)	1 (1.3)	0.021
Pemphigus	4 (3.8)	8.15 ± 1.76	0 (0.0)	4 (5.1)	0.230
Parapsoriasis	3 (2.8)	7.50 ± 0.84	1 (3.7)	2 (2.6)	0.759
Erythroderma	3 (2.8)	7.20 ± 0.51	2 (7.4)	1 (1.3)	0.100
Pemphigoid bullous	2 (1.2)	7.50 ± 0.84	1 (3.7)	1 (1.3)	0.428
Total patients	51 (48.5)	8.38 ± 1.70	14 (51.8)	37 (47.4)	0.692

For abbreviations see under Table 1.

mended by the ADA [11]. However, the results of this study corresponded to the findings of Furquana et al. [13], who found that 68% of patients with unsatisfactory glycemic control had the mean HbA1c at 8.6 ± 1.5%. Foss et al. [17] found HbA1c at 12.7% in type 2 diabetic patients with inadequate metabolic controls. Ahmed et al. [18] reported an incidence of 93% of uncontrolled diabetes in a similar series of patients. In this study, 60% of patients were on insulin therapy very often in combination with oral antidiabetics. A higher number of patients with unsatisfactory glycemic control were insulin-dependent. The results in the incidence of insulin dependency vary from one study to another [13, 18, 19]. This probably depended on a number of factors, including diabetes duration and patients' age.

Skin infections, as disorders related to diabetic complications, were the most common skin manifestation (44%) found in the study. The study findings were consistent with the academic literature data, according to which the overall incidence of skin infections varied between 20–50% [20–22]. The data depended on the study design, eligibility criteria of the involved patients, and regional affiliation [3]. Many patients with infections had poorly regulated glycemic control. Bacterial infections were found in 27% of the study participants, with the mean HbA1c at 9.3 ± 2.0%. The most common bacterial infection was cellulitis (16.2%). The study participants with cellulitis had the highest mean value of HbA1c (10 ± 1.9%) of all patients with infections. Other bacterial infections such as impetigo, furunculus, erysipelas, erythrasma, and disseminate folliculitis had a low incidence. Furquana et al. [13] have reported similar results (26%). Other authors found a higher incidence of bacterial infections, while there were studies in which bacterial infection had a much smaller incidence [23, 24]. Fungal infections were found in 24.8% of patients. Almost all of these patients had unsuccessful diabetic control ($p = 0.003$). The average value of HbA1c in these patients was 9.0 ± 1.6%. Among fungal infections, 15% of the study participants had candidiasis. Mucocutaneous infections with *Candida* spp. are considered to be an early indicator of an undiagnosed DM or inadequately controlled glycemia [25]. Dermatophytosis was found in 9% of respondents. Some authors considered that fungal infections in patients with type 2 DM were more prevalent than bacterial [3]. This was confirmed by studies with a high incidence of dermatophytosis [17, 23, 24]. Viral infections had a very low incidence in the study. This study has registered only two patients with herpes zoster. Otherwise, viral infections in diabetic patients or with low participation in similar studies were rarely mentioned [3].

We found diabetic foot ulcers in 7.7% of patients. All patients had unsuccessful diabetic control, and the mean HbA1c at 8.3 ± 0.8%. The diabetic neuropathic ulcer was the most frequently recognized complication in diabetics. Zhang et al. [26] found that global diabetic foot ulcer prevalence was 6.3%, while this value was 5.1% in Europe. Some studies from different parts of the world present different data. Foss et al. [17] and Yosipovitch et al. [27] cited a very low incidence of HbA1c at 0.7% and 0.8%. In a community-based study in the Northwestern United Kingdom, the incidence of active foot ulcers identified at screening among persons with diabetes was 1.7% [28]. Some Indian authors found a higher incidence of diabetic foot ulcers [29].

We found a small incidence of Schamberg's disease (progressive pigmentary dermatosis). Only two patients (1.9%) with the average value of HbA1c at 7.5 ± 1.3% had a progressive type of this disease. Results of this study were consistent with the data according to which Schamberg's disease is rare and usually associated with diabetes mellitus, rheumatoid arthritis, or systemic lupus erythematosus [30, 31].

In the group of skin manifestations commonly associated with DM, the most frequent were xerosis, psoriasis, and fibroma molle. Other diseases were less frequent. There was no significant difference between skin manifestations and glycemic control in this group ($p > 0.05$). Xerosis had an incidence of 17% among patients in this study, with the mean HbA1c at 9.0 ± 2.0%. Xerosis was reported in several studies, and rates showed high heterogeneity. Bhardwaj et al. [24] have reported an incidence of 10.3%, while in the study of Goyal et al. [4], xerosis accounted for the most common skin manifestation (44 %).

Psoriasis was found in 15% of the study participants, with the mean HbA1c at 7.8 ± 1%. Studies by Cvitanović et al. [10] and Sasmaz et al. [31] identified 11% of patients with psoriasis vulgaris. Vahora et al. [20] found a lower incidence of psoriasis (3%). On the other hand, some authors indicated that psoriasis was not associated with diabetes [32]. However, it is known that psoriasis, as a multisystemic inflammatory disease, is related to an increased cardiometabolic risk and that DM is a major contributor to cardiovascular morbidity and mortality [33]. Some authors supported a view that psoriasis had the strongest association with metabolic syndrome among all skin diseases [34]. Several studies have shown that psoriasis is associated with diabetes and its complications. Khalid et al. [35], in a Danish nationwide cohort study, concluded that psoriasis was associated with increased incidence rates of the new-onset type 2 DM. Armstrong et al. [36] also noted that psoriasis was associated with an increased prevalence and incidence of diabetes and that association may be the strongest among the patients with severe psoriasis.

Fibroma molle (skin tags, acrochordons) as a feature of diabetes was also found in 14.3% of the study participants, and they had the mean HbA1c at 8.9 ± 1.9%. Since fibroma molle is highly prevalent among the general population, increasing in incidence with patient's age, this study considered only multiple forms (more than 30 skin tags). Vahora et al. [20] have reported a similar result (13.3%). The possible association of skin tags with DM was first mentioned in 1951. Since then, a few clinical studies have been conducted in order to examine this hypothesis and they have come up with conflicting results. Multiple skin tags have been associated with abnormalities in the glucose metabolism, specifically type 2 diabetes, hyperinsulinemia, and insulin resistance [37].

Diabetic dermopathy had an incidence of 8.6% among patients who participated in this study. All patients had unsatisfactory glycemic control, with the mean HbA1c at 9.4 ± 2.1%. Furquana et al. [13] came up with the same result. It has

been reported that diabetic dermopathy occurs in variable percentages between 9% and 55% of patients with diabetes [38]. However, some authors found a very low incidence of this disease in diabetics, like Morgan and Schwartz [39] (0.2%) and Foss et al. [17] (1.2%). This distribution may result from variations among sample sizes and ethnicities of the study groups.

As a feature of diabetes, pruritus was also found in 6.7% of the study participants. All patients except one had poor glycaemic control with the mean HbA1c at 9.0 ± 1.8%. Five of seven patients had localized, while two had generalized pruritus. Pruritus is well known to be associated with diabetes mellitus, as reported by the past academic literature. The findings of this study correspond to the results by Cvitanović et al. [10] (7%), but other authors have found a higher incidence in a similar study [40].

Granuloma annulare (GA) was found in 5.7% of the study participants, with the mean HbA1c at 7.6 ± 1.2%. Three patients had a localized, and three patients had a disseminated form of the disease. GA may be an idiopathic entity. However, GA is persistently described within the setting of a variety of systemic diseases. DM and hyperlipidemia are most commonly reported. Some papers support while others disprove the existence of an association between GA and DM. George and Walton [41] had reported that this association is 4%, while others found a lower incidence of GA among diabetic patients [10]. Nobari et al. [42] emphasized that in this type of skin lesion, particularly in disseminated forms, the clinicians are supposed to carry out a diabetic evaluation of all patients, even those without symptoms. On the other hand, Cheng et al. [43] considered that an association between GA and DM remains controversial. Nebesio et al. [44] did not find an association between type 2 diabetes mellitus and GA.

Scleredema diabeticorum was found in 2.8% of the study participants. All three patients had strikingly poor glycemic control, and the mean HbA1c at 10.1 ± 2.6%. Scleredema diabeticorum is a rare cutaneous manifestation of DM. Results of this study were in accordance with the data presented by Draznin et al. [45]. A few studies reported an incidence of scleredema diabeticorum between 2.5% and 14% [46].

In the group of skin diseases unassociated with diabetes, this study found various skin manifestations mainly occurring at an older age. The most frequent skin manifestation in this group was seborrheic keratosis (20%). The result corresponded with the data according to which seborrheic keratosis is the most common benign cutaneous neoplasm occurring in at least 20% of older adults [47].

As a feature of diabetes, prurigo nodularis was also found in 6.7% of the study participants. These patients had the highest mean value of HbA1c in the group of skin manifestations (10.0 ± 2.4%). Foss et al. [17] came to a similar result, while Sasmaz et al. [31] found prurigo among 9.9% of patients in their study. There is a deficiency in epidemiological data regarding the incidence and prevalence of prurigo nodularis, but it seems that elderly people are most frequently affected, usually as patients with chronic kidney disease [48]. We found stasis dermatitis in 5.7% of patients. Stasis dermatitis is also most common in people > 50 years old, with an overall disease prevalence of 6–7% [49]. Urticaria was found in 4.8% of the study participants. All of them had satisfactory glycemic control. One of five patients had urticaria associated with non-steroidal anti-inflammatory drugs. Two patients had isolated angioedema caused by antihypertensive drugs from the group of angiotensin-converting enzyme (ACE) inhibitors, and two patients had chronic idiopathic urticaria. Other skin diseases found in low incidence were the following: exanthema, pemphigus, parapsoriasis, erythroderma, and bullous pemphigoid. In this group of skin diseases, there was no significant difference between patients with satisfactory and unsatisfactory glycemic control ($p > 0.05$), except for exanthema ($p = 0.021$). Other similar studies found extremely different skin manifestations which are either not commonly associated or are associated with diabetes, such as actinic degeneration, pigmentation disorders, benign skin tumors, eczemas, nail dystrophy, and peripheral hypotrichia [3]. The pattern of skin manifestations depends on regional affiliation, study design, age of study respondents, and diabetes duration.

Conclusion

Skin infections of bacterial and fungal origin are the most frequent skin manifestations in patients with type 2 DM. Other different skin disorders are comparatively less common. This study confirmed that skin infections in type 2 DM highly correlate with unsuccessful diabetic control. Achieving appropriate glycemic control in patients with diabetes can reduce skin infections and other skin manifestations related to diabetic complications. Early detection and adequate treatment of not only elevated glycemia but also of skin disorders in diabetics may reduce morbidity, complications, and hospital visits and improve the quality of life of diabetics. Since skin manifestations in diabetics are common and easily visible, dermatologists have to emphasize the importance of the multidisciplinary and team approach to diabetes.

REFERENCES

1. *Farshchian M, Farshchian M, Fereydoonnejad M, Yazdanfar A, Kimyai-Asadi A.* Cutaneous manifestations of diabetes mellitus: a case series. Cutis 2010; 86(1): 31–5.
2. *Lima AL, Illing T, Schliemann S, Elsner P.* Cutaneous Manifestations of Diabetes Mellitus: A Review. Am J Clin Dermatol 2017; 18(4): 541–53.
3. *De Macedo GMC, Nunes S, Barreto T.* Skin disorders in diabetes mellitus: an epidemiology and physiopathology review. Diabetol Metab Syndr 2016; 8: 63.
4. *Goyal A, Raina S, Kaushal SS, Mahajan V, Sharma NL.* Pattern of cutaneous manifestations in diabetes mellitus. Indian J Dermatol 2010; 55(1): 39-41.

5. *Duff M, Demidova O, Blackburn S, Jay Shubrook J.* Cutaneous Manifestations of Diabetes Mellitus. Clin Diabetes 2015; 33(1): 40–8.
6. *Han G.* A new appraisal of dermatologic manifestations of diabetes mellitus. Cutis 2014; 94(1): E21–6.
7. *Rosen J, Yosipovitch G.* Skin Manifestations of Diabetes Mellitus. [updated 2018 Jan 4]. In: *Feingold KR, Anawalt B, Boyce A, Chrousos G, Dungan K, Grossman A,* et al, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000. Available from: http://www.ncbi.nlm.nih.gov/books/NBK481900/
8. *Van Hattem S, Bootsma AH, Bing Thio H.* Skin manifestations of diabetes. Review. Cleve Clinic Med 2008; 75(11): 772, 774, 776–7, 780–7.
9. *Sreeedevi C, Car N, Pavlić-Renar I.* Dermatologic lesions of diabetes mellitus. Review. Diabetol Croat 2002; 31(3): 147–59.
10. *Cvitanović H, Jančić E, Knežević E, Kuljanac I.* Skin changes in patients with diabetes mellitus in Karlovac county. Acta Med Croat 2009; 45(4): 370–80.
11. *Kojić Damjanov S, Đerić M, Eremić Kojić N.* Glycated hemoglobin A1c as a modern biochemical marker of glucose regulation. Med Pregl 2014; 67(9–10): 339–44.
12. *Bhat YJ, Gupta V, Kudyar RP.* Cutaneous manifestations of diabetes mellitus. Int J Diabetes Dev Ctries 2006; 26: 152–5.
13. *Furquana N, Bashir F, Shams N, Shaikh Z, Ahmed I.* Cutaneous manifestations of diabetes mellitus type 2: prevalence and association with glycemic control. J Pak Assoc Dermatol 2016; 26 (1): 4–11.
14. *Phulari YJ, Kaushik* V. Study of cutaneous manifestations of type 2 diabetes mellitus. Int J Res Dermatol 2018; 4(1): 8–13.
15. *Furqan S, Kamani L, Jabbar A.* Skin manifestations in diabetes mellitus. J Ayub Med Coll Abbottabad 2014; 26(1): 46–8.
16. *Ghos K, Das K, Ghos S, Chakraborty S, Jatua SK, Bhattacharya A,* et al. Prevalence of skin changes in diabetes mellitus and its correlation with internal diseases: a single center observational study. Indian J Dermatol 2015; 60(5): 465–9.
17. *Foss NT, Polon DP, Takada MH, Foss-Freitas MC, Foss MC.* Skin lesions in diabetic patients. Rev Saude Publica 2005; 39(4): 677–82. (Portoguese)
18. *Ahmed K, Muhammad Z, Qayum I.* Prevalence of cutaneous manifestations of diabetes mellitus. J Ayub Med Coll Abbottabad 2009; 21(2): 76–9.
19. *Mahajan S, Koranne RV, Sharma SK.* Cutaneous manifestation of diabetes mellitus. Indian J Dermatol Venereol Leprol 2003; 69(2): 105–8.
20. *Vahora R, Thakkar S, MarfatiaY.* Skin, a mirror reflecting diabetes mellitus: A longitudinal study in a tertiary care hospital in Gujarat. Indian J Endocr Metab 2013; 17(4): 659–64.
21. *Chatterjee N, Chattopadhyay C, Sengupta N, Das C, Sarma N, Pal SK.* An observational study of cutaneous manifestations in diabetes mellitus in a tertiary care hospital of Eastern India. Indian J Endocr Metab 2014; 18(2): 217–20.
22. *Demirseren DD, Emre S, Akoglu G, Arpacı D, Arman A, Metin A,* et al. Relationship between skin diseases and extracutaneous complications of diabetes mellitus: clinical analysis of 750 patients. Am J Clin Dermatol 2014; 15(1): 65–70.
23. *Vani G, Reddy VN.* A clinical study of diabetic dermatological manifestations at a tertiary care hospital in South India. Int J Res Dermatol 2018; 4(3): 293–7.
24. *Bhardwaj N, Roy S, Jindal R, Ahmad S.* Cutaneous manifestations of diabetes mellitus: a clinical study. Int J Res Dermatol 2018; 4(3): 352–6.
25. *Piérard GE, Seité S, Hermanns-Lê T, Delvenne P, André Scheen, Piérard-Franchimont C.* The skin landscape in diabetes mellitus. Focus on dermocosmetic management. Clin Cosmet Investig Dermatol 2013; 6: 127–35.
26. *Zhang P, Lu J, Jing Y, Tang S, Zhu D, Bi Y.* Global epidemiology of diabetic foot ulceration: a systematic review and meta-analysis (†). Ann Med 2017; 49(2): 106–6.
27. *Yosipovitch G, Hodak E, Vardi P, Shraga I, Karp M, Sprecher E,* et al. The prevalence of cutaneous manifestations in IDDM patients and their association with diabetes risk factors and microvascular complications. Diabetes Care 1998; 21(4): 506–9.
28. *Armstrong DG, Boulton AJM, Bus SA.* Diabetic Foot Ulcers and Their Recurrence. N Engl J Med 2017; 376(24): 2367–75.
29. *Chandrashekar SM, Suraj Muralidhar S.* A study on the prevalence of risk factors and presence of diabetic foot ulcers in T2DM patients in K. R. Hospital. Int Surg J 2017; 4(9): 2983–6.
30. *Hussain SM, Ahmed SI.* Schamberg Purpura - A Rare Complication of Skin associated with Type 2 Diabetes Mellitus. Journ Rawalp Med College (JRMC) 2014; 18(1): 163.
31. *Sasmaz S, Buyukbese M, Cetinkaya A, Celik M, Arican O.* The Prevalence of Skin Disorders in Type-2 Diabetic Patients. Int J Dermatol 2004; 3: 1.
32. *Casagrande SS, Menke A, Cowie CC.* No Association between Psoriasis and Diabetes in the U.S. Population. Diabetes Res Clin Pract 2014; 104(3): e58–60.
33. *Dinić MŽ, Zečević RD, Hajduković Z, Mijušković M, Djurić P, Jović Z,* et al. Psoriasis is the independent factor for early atherosclerosis: A prospective study of cardiometabolic risk profile. Vojnosanit Pregl 2016; 73(12): 1094–101.
34. *Karadag AS, Ozly E, Lavery MJ.* Cutaneous manifestations of diabetes mellitus and the metabolic syndrome. Clin Dermatol 2018; 36(1): 89–3.
35. *Khalid U, Hansen PR, Gislason GH, Lindhardsen J, Kristensen SL, Winther SA,* et al. Psoriasis and new-onset diabetes: a Danish nationwide cohort study. Diabetes Care 2013; 36(8): 2402–7.
36. *Armstrong AW, Harskamp CT, Armstrong EJ.* Psoriasis and the risk of diabetes mellitus: a systematic review and meta-analysis. JAMA Dermatol 2013; 149(1): 84–91.
37. *Maluki AH, Abdullah AA.* Metabolic Associations with Skin Tags. Int J Dermatol Clin Res 2016; 2(1): 3–11.
38. *George MS, Walton S.* Diabetic dermopathy. Br J Diabetes Vasc Dis 2014; 14(3): 95–7.
39. *Morgan AJ, Schwartz RA.* Diabetic dermopathy: A subtle sign with grave implications. J Am Acad Dermatol 2008; 58(3): 447–51.
40. *Babakinejad P, Walton S.* Diabetes and pruritus. Br J Diabetes 2016; 16: 154–5.
41. *George MS, Walton S.* Granuloma annulare. Br J Diabetes 2016; 16: 58–61.
42. *Nobari NN, Ghalamkarpour F, Gheisari M, Iranmanesh B.* Multiple granuloma annulare as presenting sign of asymptomatic diabetes mellitus in a child. J Dermatol Dis 2018; 5: 274.
43. *Cheng YW, Tsai WC, Chuang FC, Chern E, Lee CH, Sung CH* et al. A retrospective analysis of 44 patients with granuloma annulare during an 11-year period from a tertiary medical center in south Taiwan. Dermatol Sin 2016; 34(3): 121–5.
44. *Nebesio CL, Lewia C, Chuang TZ.* Lack association between granuloma annulare and type 2 diabetes mellitus. Br J Dermatol 2002; 146(1): 122–4.
45. *Draznin M, Eison R, Maverakis E, Huntley A.* Cutaneus manifestations of diabetes mellitus. In: *Bowker J, Pfeifer M,* editor. Levin and O'Neal's The Diabetic Foot with CD-ROM. 7th ed. Mosby 2008. P. 185–97.
46. *Shrestha B, Sharma E, Mukhtar O, Kaler J, Thapa S, Khalid M.* Scleredema Diabeticorum with Superimposed Cellulitis and

Abscess Formation. Case Rep Endocrinol 2018: 2018: 9513768.

47. *Del Rosso JQ*. A Closer Look at Seborrheic Keratoses: Patient Perspectives, Clinical Relevance, Medical Necessity, and Implications for Management. J Clin Aesthet Dermatol 2017; 10(3): 16–25.
48. *Mettang T, Vonend A, Raap U*. Prurigo nodularis: its association with dermatoses and systemic disorders. Hautarzt 2014; 65(8): 697–703. (German)
49. *Sundarsen S, Migden MR, Silapunt S*. Stasis dermatitis: Pathophysiology, Evaluation and Management. Am J Clin Dermatol 2017; 18(3): 389–90.

Received on February 26, 2019.
Revised on May 17, 2019.
Accepted June 17, 2019.
Online First June, 2019.