Original Investigation
Orijinal Araştırma

DOI: 10.4274/turkderm.galenos.2020.09216
Turkderm-Turk Arch Dermatol Venereol 2021;55:22-6

Cutaneous manifestations in children patients with type 1 diabetes mellitus

Tip 1 diabetes mellituslu çocuk hastalarda deri bulguları

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Abstract

Background and Design: Type 1 diabetes mellitus (T1DM) can cause significant changes in the skin. However, there are limited studies examining the skin findings in children with T1DM. The objective of this study is to determine the frequency of skin lesions in children with T1DM. Additionally, this study also evaluates the relationship of skin lesions with disease duration and hemoglobin A1c (HbA1c) levels.
Materials and Methods: This cross-sectional study enrolled 65 children with T1DM and 78 age- and sex-matched healthy children. Importantly, detailed skin examinations of the cases were conducted.
Results: The mean age at the onset of disease was 7.1±3.7 years, and the mean duration of T1DM was 45.9±40.4 months. The mean level of HbA1c in children with T1DM was determined as 8.0±1.6%. In total, 9 (13.8%) of the patients were using insulin infusion pump, whereas 56 of them were using multiple insulin injections therapy. At least one skin lesion related to insulin treatment was recorded in 54 patients (83%). Bruises (50.8%), lipohypertrophy (44.6%), and post-inflammatory hyperpigmentation (26.2%) were among the most observed skin reactions related to the insulin treatment. However, hypopigmented scar was the most frequently observed skin reaction related to the insulin treatment among the patients using insulin infusion pump (5/9, 55%). Only xerosis and rubeosis faciei diabeticorum were found to be significantly higher in the T1DM group, as compared to healthy controls. Xerosis was observed in 19 (29%) patients with DM and 8 (10.2%) healthy controls, whereas rubeosis faciei was observed in 6 (9.2%) patients with DM and 1 (1.3%) healthy control. Although not statistically significant, it was found that the disease duration was longer and HbA1c levels were higher in T1DM patients with rubeosis faciei or xerosis.
Conclusion: We believe that significant benefits can be provided for the management and prevention of skin findings in children with T1DM through the training of the patients and caregivers as well as by increasing the awareness of physicians.
Keywords: Children, insulin, lipodystrophy, type 1 diabetes mellitus

Öz

Amaç: Tip 1 diabetes mellitus (T1DM), çocukluk çağının en yaygın kronik hastalıklarından biri olup, önemli deri değişikliklerine neden olabilmektedir. T1DM'li çocuk hastalarda deri bulgularını inceleyen çalışmalar sınırlıdır. Çalışmamızda, T1DM'li çocuk hastalarda deri lezyonlarının sıklığını tanımlamak ve bu deri lezyonlarının hastalık süresi ve hemoglobin A1c (HbA1c) düzeyi ile ilişkisinin değerlendirilmesi amaçlandı.
Gereç ve Yöntem: Bu kesitsel çalışmada T1DM tanılı 65 çocuk hasta ve yaş ve cinsiyet olarak eşleştirilmiş 78 sağlıklı çocuk değerlendirildi. Çalışmaya alınan olguların ayrıntılı deri muayeneleri yapıldı.
Bulgular: T1DM'li çocukların ortalama hastalık başlangıç yaşı 7,1±3,7 ve ortalama hastalık süresi 45,9±40,4 aydı. DM'li çocukların ortalama HbA1c değeri 8,0±1,6 olarak saptandı. Hastaların 9'u (%13,8) insülin infüzyon pompası kullanırken, 56'sı multipl doz insülin enjeksiyon tedavisi uygulamaktaydı. Hastaların 54'ünde (%83) insülin tedavisi ile ilişkili en az bir deri reaksiyonu mevcuttu. Sırasıyla; ekimoz (%50,8), lipohipertrofi (%44,6) ve post-enflamatuvar hiperpigmentasyon (%26,2) en sıklıkla saptanan insülin tedavisi ilişkili deri reaksiyonlarıydı. Ancak insülin infüzyon pompası kullanan hastalar arasında en sık insülin tedavisi ilişkili deri reaksiyonu hipopigmente skar (5/9, %55) olarak bulundu. Sağlıklı kontrollerle karşılaştırıldığında, tip 1 DM'li grupta diyabet ile ilişki deri belirtilerinden sadece kserozis kutis ve rubeosis faciei diabetikorumun istatistiksel olarak anlamlı yüksek olduğu görüldü. Kserozis kutis DM'li hastalarda 19 (%29), sağlıklı kontrollerde 8 (%10,2), rubeosis faciei ise DM'li hastalarda 6 (%9,2), sağlıklı kontrollerde 1 (%1,3) olguda saptandı. Anlamlı bir ilişki gösterilememiş olsa da, rubeosis faciei veya kserozis kutisi olan hastaların, olmayanlara göre hastalık süresi daha uzun, HbA1c düzeyi daha yüksek bulundu.

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Sonuç: Hasta ve bakım verenlerin eğitimi, bilinçlendirilmesi ve hekimlerin farkındalığının artırılması ile T1DM'li çocuklarda, deri bulgularının yönetimi ve önlenmesi için oldukça önemli faydalar sağlanacağını düşünüyoruz.
Anahtar Kelimeler: Çocuk, insülin, lipodistrofi, tip 1 diabetes mellitus

Introduction

Type 1 diabetes mellitus (T1DM) is a type of diabetes that develops because of the destruction of insulin-producing pancreatic beta cells and requires exogenous insulin replacement. Although T1DM can be diagnosed at any age, it is one of the most common chronic diseases of childhood. The incidence and prevalence of T1DM vary significantly among countries[1]. In our country, the nationwide incidence and prevalence of T1DM among children aged under 18 years have been reported as 10.8/100,000 and 0.75/1,000, respectively[2]. Recent years have seen a global and continual increase in the incidence and prevalence of this disease[3]. A regional study conducted in our country demonstrated that a significant increase trend of T1DM in children was detected in the total 10-year observation period (between; 2009 and 2019); the average annual percent change was 7.8%[4].

Skin changes are among the most common symptoms of DM. Abnormal carbohydrate metabolism, atherosclerosis, microangiopathy, neuron degeneration, and impaired host mechanisms are possible factors contributing toward the pathogenesis of skin findings. Additionally, patients with T1DM more frequently develop autoimmune type of cutaneous lesions[2,5]. In the literature, there are limited studies examining the skin findings in children with T1DM, and there are no studies on this subject in Turkey.

The purpose of this cross-sectional study is to determine the frequency of skin lesions in children with T1DM and compare it with healthy controls. Additionally, this study aims to evaluate the relationship of skin lesions with the disease duration and hemoglobin A1c (HbA1c) levels.

Materials and Methods

Ethical approval was received from the Aydın Adnan Menderes University Faculty of Medicine, Non-interventional Clinical Research Ethics Committee (approval number: 2017/1058, date: January 19, 2017).

This study included 65 children with T1DM who were followed up in the Outpatient's Clinic of Pediatric Endocrinology in Aydın Adnan Menderes University Faculty of Medicine between June 2017 and June 2018 together with 78 age- and sex-matched healthy non-obese children. Written informed consent form was obtained from all the participants. Detailed skin examinations of this study's cases were performed by the same dermatologist. Furthermore, Wood's lamp and mycological examinations were conducted whenever necessary. Demographic data of the participants were also collected. Importantly, HbA1c values measured during routine examinations and disease-related data of children with T1DM were also evaluated.

Statistical Analysis

SPSS 18 software program was used for statistical analysis. Descriptive analysis, chi-square test, and t-test were used in data analysis. P<0.05 value was considered as statistically significant for data analysis.

Results

Of the 65 children with T1DM, 43 (66.1%) were females and 22 (33.8%) were males. Of the 78 healthy children, 50 (64.1%) were females and 28 (35.8%) were males. The mean age of the patient group was 11±3.4 years (minimum-maximum: 3-17 years), and the mean age of the control group was 9.9±4 years (minimum-maximum: 2-17 years). There was no statistically significant difference between the two groups in terms of age and gender. The mean age of disease onset was 7.1±3.7 (minimum-maximum: 6 months-15 years old) and the mean duration of T1DM was 45.9±40.4 (minimum-maximum: 1-156 months) months. The mean HbA1c level in children with T1DM was determined as 8.0±1.6%. Although children with obesity were not included in the control group, the number of children with obesity in T1DM group was 10 (15.3%). Additionally, body mass index (BMI) and BMI percentile values were statistically significantly higher in the T1DM group than that in the healthy control group. Table 1 shows the demographic data of the patients and healthy controls.

Although 9 (13.8%) of the patients were using insulin infusion pump (continuous subcutaneous insulin infusion), 56 of them were using multiple insulin injections therapy. At least one skin lesion related to insulin treatment was present in 54 patients (83%). Bruises (50.8%), lipohypertrophy (44.6%), and post-inflammatory hyperpigmentation (26.2%) were among the most observed skin reactions related to insulin treatment. However, hypopigmented scar was the most frequently observed skin reaction related to the insulin treatment among the patients using insulin pump (5/9, 55%). Table 2 shows the details of skin reactions associated with insulin therapy. Although patients with lipoatrophy had a longer disease duration than those without lipoatrophy (156 months vs 44.2±38.3 months) (p=0.005), there was no statistically significant difference between skin reactions associated with insulin therapy and the disease duration or HbA1c values.

Table 1. Characteristics of children with type 1 diabetes mellitus and healthy controls

	Children with T1DM (n=65)	Healthy controls (n=78)	p
Age (years) (mean ± SD)	11±3.4	9.9±4	0.099
Sex (male/female)	22/43	28/50	0.798
Duration of diabetes (months) (mean ± SD)	45.9±40.4	-	-
Age at T1DM onset (years) (mean ± SD)	7.1±3.7	-	-
HbA1c (%) (mean ± SD)	8.0±1.6	-	-
BMI (kg/m^2) (mean ± SD)	20.41±4.76	17.66±3.06*	**<0.001**
BMI percentile (mean ± SD)	63.4±28.8	39.1±27.5*	**<0.001**
Obesity	10 (15.3%)	0 (0%)*	**<0.001**

*Children with obesity were not included in the control group, T1DM: Type 1 diabetes mellitus, SD: Standard deviation, BMI: Body mass index

Table 2. Skin reactions associated with insulin therapy

	Insulin therapy (n=65) n (%)	Multiple daily insulin injections (n=56) n (%)	Insulin pump therapy (n=9) n (%)
Lipohypertrophy	29 (44.6%)	27 (48.2%)	2 (22%)
Lipoatrophy	1 (1.5%)	1 (1.7%)	0 (0%)
Post-inflammatory hyperpigmentation	17 (26.2%)	14 (25%)	3 (33%)
Scar	10 (15.4%)	5 (8.9%)	5 (55%)
Erythema	11 (16.9%)	10 (17.8%)	1 (11%)
Bulla	0 (0%)	0 (0%)	0 (0%)
Local infection	0 (0%)	0 (0%)	0 (0%)
Bruise	33 (50.8%)	33 (58.9%)	0 (0%)
Insulin pump-related contact dermatitis	1 (1.5%)	0 (0%)	1 (11%)

Only xerosis and rubeosis faciei diabeticorum were found to be significantly higher in the group of T1DM, as compared to healthy controls. Xerosis was observed in 19 (29%) patients with DM and 8 (10.2%) healthy controls, whereas rubeosis faciei was observed in 6 (9.2%) patients with DM and 1 (1.3%) healthy control. Table 3 shows the details of skin findings in the patients and healthy controls. Although not statistically significant, it was found that the disease duration was longer and HbA1c levels were higher in T1DM patients with rubeosis faciei or xerosis. Additionally, it was observed that the BMI of T1DM patients with rubeosis faciei diabeticorum was significantly higher than those without rubeosis (Table 4).

Discussion

Various skin findings such as xerosis, rubeosis faciei diabeticorum, limited joint mobility, scleroderma-like skin changes, and infections may develop during the course of the disease in patients with T1DM[5,6]. Xerosis cutis is one of the most common diabetes-related skin findings in patients with T1DM[7,8]. It has been objectively determined that there is a reduced hydration state of the stratum corneum together with a decreased sebaceous gland activity without any impairment of the stratum corneum barrier function in patients with DM[9]. Our study determined that the most common skin manifestation, in accordance with the literature, was xerosis cutis (29.2%). A previous study showed that xerosis cutis was strongly correlated with HbA1c, which is an indicator of glycemic control[10]. In our study, a significant relationship could not be shown, even though when the HbA1c level was higher in T1DM patients with xerosis cutis. Because of the increased risk of xerosis cutis in pediatric patients with T1DM, we believe that patients and their caregivers should be made aware of this subject and appropriate moisturizers should be recommended to the patients.

Rubeosis faciei diabeticorum, which is characterized by facial rashes in patients with diabetes, is caused by the dilatation of small vessels in the cheeks[7]. In different studies performed in patients with T1DM, rubeosis faciei was found in 0-8.75% of the cases[8,10-12]. Our study found that the frequency of rubeosis faciei diabeticorum was higher (9.2%) than the previous studies. In earlier studies, the development

Table 3. Skin findings in patients with type 1 diabetes mellitus and healthy controls

	Patients with T1DM (n=65) n (%)	Healthy controls (n=78) n (%)	p
Skin infections			
***Bacterial**			
Folliculitis	13 (20%)	7 (8.9%)	0.058
Other bacterial infections	0 (0%)	0 (0%)	-
*Fungal	0 (0%)	0 (0%)	-
***Viral**			
Wart	3(4.6%)	6 (7.6%)	0.511
Herpes virus infection	1(1.5%)	0 (0%)	0.455
Skin manifestations associated with diabetes			
Limited joint mobility	1 (1.5%)	0 (0%)	0.455
Scleroderma-like skin changes	1 (1.5%)	0 (0%)	0.455
Xerosis cutis	19 (29.2%)	8 (10.2%)	**0.004***
Acquired ichthyosis	0 (0%)	0 (0%)	-
Rubeosis faciei diabeticorum	6 (9.2%)	1 (1.2%)	**0.047***
Diabetic bullae	0 (0%)	0 (0%)	-
Necrobiosis lipoidica	0 (0%)	0 (0%)	-
Diabetic dermopathy	0 (0%)	0 (0%)	-
Keratosis pilaris	14 (21.5%)	14 (17.9%)	0.590
Acanthosis nigricans	4 (6.1%) (3 cases are obese)	1 (1.2%)	0.177
Acrochordons	0 (0%)	0 (0%)	-
Granuloma annulare	0 (0%)	0 (0%)	-
Other dermatoses			
Psoriasis	0 (0%)	0 (0%)	-
Atopic dermatitis	0 (0%)	0 (0%)	-
Vitiligo	1 (1.5%)	0 (0%)	0.455
Alopecia areata	0 (0%)	0 (0%)	-
Dermatitis herpetiformis	0 (0%)	0 (0%)	-
Perforating dermatoses	0 (0%)	0 (0%)	-
Lichen planus	0 (0%)	0 (0%)	-
Seborrheic dermatitis	8 (12.3%)	6 (7.6%)	0.355
Acne vulgaris	18 (27.6%)	21 (26.9%)	0.918
Striae	13 (20%)	15 (19.2%)	0.908
Hirsutism	1 (1.5%)	0 (0%)	0.455
Ingrown nails	1 (1.5%)	0 (0%)	0.455
Geographic tongue	1 (1.5%)	0 (0%)	0.455
Pruritus	1 (1.5%)	0 (0%)	0.455
Miliaria rubra	1(1.5%)	0 (0%)	0.455
Pityriasis alba	5 (7.6%)	1 (1.2%)	0.092
Spider angioma	1 (1.5%)	1 (1.2%)	1
Intertrigo	0 (0%)	1 (1.2%)	1
Pediculosis capitis	5 (7.6%)	4 (5.1%)	0.732
Palmoplantar hyperhidrosis	4 (6.1%)	6 (7.6%)	0.756
Plantar hyperkeratosis/callus	5 (7.6%)	10 (12.8%)	0.319
Other dermatitis	3 (4.6%)	2 (2.5%)	0.659

Table 4. Factors associated with rubeosis faciei diabeticorum and xerosis cutis in children with type 1 diabetes mellitus

	Rubeosis faciei diabeticorum			Xerosis cutis		
	Children with T1DM (n=65)		p	Children with T1DM (n=65)		p
	Absent (n=59)	Present (n=6)		Absent (n=46)	Present (n=19)	
BMI	19.84±4.28	26.02±5.98	0.002*	21.03±4.55	18.90±5.02	0.100
Duration of diabetes (month) (mean ± SD)	43.50±39.58	70.00±45.16	0.128	41.30±39.69	57.21±41.22	0.151
HbA1c (mean ± SD)	8.07±1.59	8.33±1.99	0.713	8.02±1.68	8.27±1.49	0.580

T1DM: Type 1 diabetes mellitus, SD: Standard deviation, BMI: Body mass index

of rubeosis faciei diabeticorum has been found to be associated with extracutaneous complications of DM such as nephropathy, neuropathy, and retinopathy[10,13]. However, our study did not evaluate the patients' extracutaneous complications. Although no significant relationship could be demonstrated, patients with rubeosis faciei had longer disease duration and higher HbA1c levels than patients without rubeosis faciei. Additionally, the BMI of patients with rubeosis faciei diabeticorum was significantly higher than those without rubeosis. Based on this result, it can be stated that the prolongation of the disease duration, poor glycemic control, and increased BMI contribute to the development of rubeosis faciei diabeticorum. Studies with larger patient groups are needed to obtain precise results.

Fungal and bacterial cutaneous infections are among the common skin findings in patients with DM[5,6]. Kamel et al.[10] reported that the most common skin manifestation in children with T1DM was fungal infections (40%). The HbA1c value (10.98±1.6) and disease duration (8.07±3.8 years) were observed to be significantly higher in patients with fungal infection than those without fungal infection[10]. Other studies conducted on children with T1DM also found different rates of fungal infections. In these studies, the mean duration of the disease was reported to be between 4.2 and 13 years, and the mean of HbA1c values were reported to be between 9.1 and 11.3[7,8,11]. Our study did not observe any fungal infection in our patients. We believe that this result is related to the shorter disease duration (45.9±40.4 months) and lower HbA1c values (8.0±1.6%) detected in our patients as compared to previous studies.

In patients with T1DM, various skin reactions related to insulin therapy such as lipohypertrophy, lipoatrophy, bruising, erythema, blisters, scarring, or post-inflammatory hyperpigmentation may develop at the injection sites[6-8,14]. Lipohypertrophy is a salient complication because it causes suboptimal glycemic control. Different studies have demonstrated that the prevalence of lipohypertrophy ranged widely from 1.9% to 73.4%[15]. A study conducted in Turkey showed that lipohypertrophy was reported to be 48.8% in 215 patients with type 1-2 DM[16]. Additionally, in another study conducted in Turkey, lipohypertrophy has been determined as 61.1% in 95 patients with T1DM[17]. In our study, 83% of the patients had at least one skin reaction related to insulin therapy. The frequency of lipohypertrophy was found to be high (44.6%), which is consistent with the literature.

The most common dermatological complication associated with the insulin pump therapy (continuous subcutaneous insulin infusion) is different from those who are treated with multiple daily insulin injections[14,18-21]. Conwell et al.[14] reported that the most common dermatological complication of the insulin pump in children and adolescents with T1DM was observed to be scars (<3 mm in 94% of cases, ≥3 mm in 12% of cases). In the same study, other common dermatological complications were erythema (66%), subcutaneous nodules (62%), and lipohypertrophy (42%), whereas bruising (4%) was a rare dermatological complication[14]. Schober and Rami[18] also reported that the most common dermatological complication associated with the insulin pump was found to be scars <3 mm (50% in children aged under 6 years, 71% in children aged over 6 years). Binder et al.[19] showed that insulin pump-associated dermatological complications were mainly scars (24%), lipohypertrophy (20%), and eczema-like lesions (11%). Similar to these studies, scar (55%) was the most commonly observed complication in the patients using insulin pump in our study. In contrast to the previous studies, Ross et al.[20] reported that the most common cutaneous adverse event associated with insulin pump was skin irritation/reactions (31%). Berg et al.[21] found that the most common insulin pump-related dermatological complication was eczema (27.5%). In case reports, allergic contact dermatitis caused by insulin pump has been confirmed by patch test[22,23]. One of our patients had insulin pump-related contact dermatitis. However, the cause of the contact dermatitis could not be explained in our case, because the skin patch test was not performed. We believe that it is crucial to pay attention to the development of scars and contact dermatitis in the patients using insulin pump. Additionally, new pumps with suitable materials and practical methods should be developed to prevent these complications.

Study Limitations

Limitations of this study include its cross-sectional nature, the absence of the long-term follow-up of patients, and the shorter disease duration. Another limitation was the probability of not detecting some skin findings due to the small number of our cases. Furthermore, our study did not investigate the relationship between skin lesions and the extracutaneous complications of DM such as diabetic nephropathy and neuropathy. In pediatric patients with T1DM, studies including a long-term follow-up of skin lesions and investigating the relationship between skin lesions and extracutaneous complications will provide more valuable information.

Conclusion

We believe that significant benefits can be provided for the management and prevention of skin findings in children with T1DM through the training of the patients and caregivers as well as by increasing the awareness of physicians.

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2021;55:22-6

Ethics

Ethics Committee Approval: Ethical approval was received from the Aydın Adnan Menderes University Faculty of Medicine, Non-interventional Clinical Research Ethics Committee (approval number: 2017/1058, date: January 19, 2017).

Informed Consent: Written informed consent form was obtained from all the participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.G., Concept: M.G., Design: M.G., N.Ş., Data Collection or Processing: M.G., A.A., T.Ü., Analysis or Interpretation: M.G., Literature Search: M.G., Writing: M.G.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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