

The prevalence of cutaneous manifestations in young patients with IDDM

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Abstract

Objective. The aim of the study was to assess the prevalence of cutaneous disorders and their relation to disease duration, metabolic control, and microvascular complications in children and adolescents with IDDM.

Research design and methods. The presence and frequency of skin manifestations were examined and compared in 212 unselected IDDM patients (aged 2-22 years, diabetes duration 1-15 years) and 196 healthy sex- and age-matched control subjects. Logistic regression was used to analyze the relation of cutaneous disorders with diabetes duration, glycemic control, and microvascular complications.

Results. One hundred forty-two (68%) IDDM patients had at least one cutaneous disorder vs. 52 (26.5%) of controls ($P<0.01$). Diabetes associated skin lesions were found in 81 (38%) patients. Acquired ichthyosis, rubeosis faciei, diabetic hand and necrobiosis lipoidica were seen in 22 vs. 3%, 7.1 vs 0%, 2.3 vs. 0%, and 2.3 vs. 0% of IDDM and controls, respectively. The frequency of cutaneous reactions to insulin therapy was low – 2.7%. The prevalence of fungal infections in patients and controls was 4.7% and 1.5%, respectively. Keratosis pilaris affected 12% of our patients vs. 1.5% controls. Diabetic hand was strongly (OR=1.42; $P<0.001$; 95%CI =1.11-1.81), and rubeosis faciei weakly (OR=1.22; $P=0.0087$; 95%CI=1.04-1.43) associated with diabetes duration. Significant association was also found between acquired ichthyosis and keratosis pilaris (OR=1.53; $P<0.001$; 95%CI=1.09-1.79).

Conclusions. Cutaneous manifestations are common in IDDM patients, and some of them, like acquired ichthyosis and keratosis pilaris develop early in the course of the disease. Diabetic hand and rubeosis faciei are related to the disease duration.

Though it is well known that diabetes is associated with a number of cutaneous manifestations (1-3), there is a relative paucity of studies looking at the prevalence of skin changes in young patients with IDDM. Cutaneous manifestations generally appear subsequent to the development of the diabetes, but may be the first presenting sign or even precede the diagnosis by many years. The cutaneous findings can be classified into 4 major groups: (a) skin diseases associated with diabetes, such as scleroderma-like changes of the hand, necrobiosis lipoidica, and diabetic dermopathy; (b) cutaneous infections; (c) cutaneous manifestations of diabetic complications, such as neuropathic foot ulcers; and (d) skin reactions to diabetic treatment (1).

In order to understand the development of skin lesions and their relationship to diabetes complications, a useful approach would be either a long-term follow-up of IDDM patients and/or surveys of cutaneous disorders in younger IDDM subjects. Available data suggest that skin dryness and scleroderma-like changes of the hand represent the most common cutaneous manifestations of IDDM seen in up to 49% of the patients (3). They are interrelated, and also related to the diabetes duration. Timing of appearance of various cutaneous lesions in young patients with diabetes might be potentially useful for the research of their pathogenesis (i.e. derangement of epidermal lipid metabolism), therapeutic intervention (i.e. application of moisturizers or antifibrosing agents) or predicting microvascular complications.

We decided to examine an unselected young IDDM population to see what kind

of cutaneous manifestations develop at an earlier age and with a shorter duration of diabetes.

Research design and methods

Two hundred and twelve children, adolescents and young adults with IDDM (113 males, 99 females) with disease onset at ≤ 15 years of age (Table 1) consecutively attending the outpatient diabetic clinic at the Mother and Child Healthcare Institute of Serbia over a 5-month period (April-August 2005) was examined by two dermatologists. They took a medical history about skin diseases and performed the whole body cutaneous examination including visible mucosal surfaces. During the same time frame, 196 healthy children and adolescents (115 males and 81 females, aged 3-21 years, mean 11.5 ± 4.2) attending the dental medicine service of the Military Medical Academy for a routine dental check-up also underwent dermatological examination by the same physicians. All clinically definable cutaneous lesions were recorded in both populations. Scleroderma-like skin changes of the hand were diagnosed and assessed according to the criteria of Seibod (4). Xerosis (acquired ichthyosis) was diagnosed clinically based on the palpatory feeling of dry and rough skin accompanied by visible squames. The disorder was typically most severe over shins. In a few cases when diagnoses of the two examiners were discordant, they examined the patient together with a third dermatologist and reached a consensus. Medical files were reviewed for data on diabetes duration, HbA_{1c} levels, fasting triglycerides, cholesterol and thyroid stimulating hormone (TSH) levels, and renal function. Cumulative HbA_{1c} values as a measure of glucose control were

expressed as a mean of the yearly HbA_{1c} levels. Retinopathy was diagnosed by an experienced ophthalmologist using direct and indirect ophthalmoscopy, nephropathy was assessed by means of albumin excretion rate - 3 consecutive timed overnight urine collections (albumin excretion rate ≥ 20 $\mu\text{g}/\text{min}$ in at least two of three measurements), and peripheral neuropathy by means of a positive diabetic neuropathy index (5), and, when indicated electromyoneurography.

Statistical analysis

Statistical tests were performed using SPSS 8.0 for Windows (StatSoft Inc., 1997). χ^2 test was used to assess differences between the prevalence of cutaneous lesions in patients and control subjects (Table 2). *P* values were based on a two-sided test and considered significant if less than 0.01. Stepwise logistic regression was used to assess significant associations of cutaneous lesions with clinical and metabolic parameters of the patients with IDDM. Due to a well-known α inflation associated with stepwise logistic regression and several regressions performed, a cutoff for significance level for variables in the model was set at $P \leq 0.01$.

Results

The clinical data of the study population are given in Table 1. A total of 142 patients (68%) had at least one cutaneous disorder, and 81 patients (38%) had skin lesions considered to be associated with diabetes (Table 2). The most prevalent cutaneous manifestation was xerosis, found in 22% of IDDM patients. In control subjects, the ichthyosiform changes affected only in 3% of the children and adolescents. The difference was highly significant (Table 2; $P < 0.01$). TSH levels

were normal in all patients with ichthyosiform skin changes. Rubeosis, diabetic hand (scleroderma-like changes and/or limited joint mobility), and necrobiosis lipoidica were found only in patients with IDDM (Table 2). All 5 subjects with diabetic hand were boys and two of them also had Dupuytren's contracture. The prevalence of necrobiosis lipoidica in our IDDM population was 2.3%.

Though the prevalence of fungal, viral and bacterial infections was higher in the study population (4.3%, 4.3%, and 3.0%) than in control subjects, the difference was not significant and the numbers were generally low.

Keratosis pilaris, though not considered a diabetes-related cutaneous manifestation, was significantly more common (11.7%) in IDDM patients than in controls (1.5%) ($P < 0.01$). The prevalence of acne was comparable in both populations (Table 2). Other cutaneous disorders were uncommon and listed in Table 2.

Stepwise logistic regression was used to assess the influence of diabetes risk factors and late complications (disease duration, metabolic control, and nephropathy) on skin lesions. We found that diabetic hand was significantly related to the disease duration (OR=1.42; $P < 0.001$; 95%CI =1.11-1.81) with no evidence to relate it to either metabolic control or nephropathy. Rubeosis faciei was less strongly related to the disease duration (OR=1.22; $P = 0.0087$; 95%CI=1.04-1.43). Ichthyosiform skin changes were significantly related only to keratosis pilaris (OR=1.53; $P < 0.001$; 95%CI=1.09-1.79). There was no association of the mean values of triglycerides, fasting cholesterol, TSH

levels, or blood pressure with any of the cutaneous disorders.

Conclusions

This study was performed within a young population of IDDM patients. Disease duration and age of patients were lower than in two similar cross-sectional studies – 4 years vs 10 and 13 years, and 12 years vs 22 and 23 years, respectively. This is certainly a reason for the low prevalence of cutaneous disorders associated with diabetes. The exception is xerosis, found in 22% patients, vs 3% in control subjects. In the series of Romano et al. (2) only 6% of their patients had xerosis. Yosipovitch et al. (3) registered 48% patients with ichthyosiform skin changes in their series of patients. Despite possible definition discrepancies across the studies, it is clear that the skin dryness is one of the earliest and commonest manifestations of IDDM. The clinical observations are supported by objective findings of a reduced hydration state of the stratum corneum and decreased sebaceous gland activity in patients with diabetes, without any impairment of the stratum corneum barrier function (6). Even in the absence of clinically apparent xerosis, patients with diabetes mellitus have an impaired desquamation process (7). Similarly to a previous series of young patients with IDDM (3), ichthyosiform lesions in our patients were not associated with known causes of acquired ichthyosis, like atopic dermatitis, nutritional deficiencies or chronic renal failure.

The prevalence of rubeosis faciei in our patients with IDDM was rather high, 7%, twice as much as in a similar previous study (3), and it was found to be weakly ($P=0.0087$) related to the disease duration. The prevalence in most previous studies in patients with type 2 diabetes mellitus

was estimated at 21-59% (8,9). It is presumed that venular dilation in the cheeks of diabetic patients underlies rubeosis faciei, and caused by hyperglycemia-induced sluggish microcirculation (10). Hypertension may exacerbate the capillary damage (10). We could not demonstrate any relation of rubeosis faciei in our young patients with IDDM with metabolic control, and only one patient had concomitant hypertension. It is interesting that in the Italian series of 64 patients with IDDM, rubeosis faciei was not seen in any of the patients (2).

Diabetic hand, a variety of sclerodermoid lesions in diabetic patients, was seen in only 2.3% of our patients but was strongly related to diabetes duration ($P<0.001$). In young patients with IDDM with a three times longer disease duration, the prevalence of scleroderma-like changes of the hand was 39% (3). All of our 5 patients with diabetic hand were boys, older than 14 years with mean diabetes duration of 9 years. Previous studies showed a correlation of these changes with the duration of diabetes and increasing age (10). The association with microvascular complications could not be assessed as they were extremely rare in our young patient population. It seems that scleroderma-like lesions of the hand are a late complication of IDDM, at least if compared to ichthyosiform skin changes. Advanced glycosylation is believed to underlie the connective tissue changes in this disorder (3,11).

We found necrobiosis lipoidica in 2.3% ($n=5$) of our patients with IDDM (mean age 14 years, mean disease duration 7 years; 4 girls), but no significant relationship to disease duration, age or metabolic control was confirmed. Studies indicated the prevalence of 0.3-1.2%

among diabetic patients, two thirds of them with IDDM (8,12-14). In young subjects with IDDM, necrobiosis lipoidica was found in 1.6% of the patients (3). We cannot account for the higher prevalence of necrobiosis lipoidica in our population of IDDM patients, and although microangiopathy has been proposed as a causative factor for necrobiosis (10), neither of our patients had retinopathy or nephropathy.

The prevalence of cutaneous infections, though somewhat higher in the population of IDDM patients was not statistically different from the healthy subjects (Table 2). Dermatophyte infections (tinea pedis and onychomycosis) were diagnosed in 2.8%, and candidosis in 1.9% of our diabetic patients. The figures are very close to those found among 64 IDDM patients of Romano et al. (2), where the prevalence of tinea infections was 3% and of candida infections 5%. The figures were higher for their type 2 diabetes patients – about 20% (2). Two larger studies in non-selected adult diabetic patients demonstrated mycologically proven dermatophyte infections in 4% and 31% patients, respectively, but the prevalence was similar or higher in control subjects (15,16). However, Yosipovitch et al (3) reported tinea pedis in 36% of their young IDDM patients vs only 7% in control subjects. On balance, contrary to a common belief, it seems that dermatophyte and candida infections are not more common in patients with diabetes in general as compared with healthy persons.

Cutaneous reactions to insulin therapy (lipoatrophy and lipohypertrophy) were observed in only 6 patients in our series (4 with lipohypertrophy, 1.8%). In the largest study of skin disorders in young

IDDM patients, these changes were seen in 6.5% of patients (3). The prevalence of lipohypertrophy in IDDM patients in two studies specifically looking at the disorder was very high, 29% and 48% (17,18). De Villiers (19) in his 33 young patients with IDDM, using careful palpation, not only visible lesions, found the prevalence of 52%, and even 80% when only patients examined on several occasions were counted. On the other hand, Romano et al. (2) in his series of IDDM patients did not mention a single patient with either lipohypertrophy or lipoatrophy. Lipohypertrophy is a consequence of repeated insulin injections at same sites, and may complicate treatment leading to delayed insulin absorption. The low number of patients with lipohypertrophy in our series may result from a failure to recognize subtle changes amenable only to careful palpation, but still the prevalence of visible lesions should range from 15% to 50% according to previous studies (18,19). The low prevalence of cutaneous reactions to insulin therapy in our patients might be a result of regular education of our patients and their parents about adequate injection technique with a division of main injection areas in several zones (e.g. abdomen in 6-9 zones).

Keratosis pilaris proved to be significantly more prevalent among our IDDM patients than in control subjects (11.7% vs 1.5%; $2P < 0.01$). This disorder showed in a stepwise logistic regression analysis a highly significant association with ichthyosiform skin changes. This is in line with findings of the Israeli group (3,20) linking keratosis pilaris to a high body mass index (BMI), dry skin, and atopic eczema. In our series only one patient had atopic eczema, and, unfortunately, we did not calculate BMI of our patients. The age of a majority of our IDDM patients with

keratosis pilaris (21 of 27) was >10 years. There was no preponderance of adolescent girls in our patients with keratosis pilaris as suggested in some studies (21). It seems that skin xerosis plays a significant role in the development of pilar keratosis.

Frequencies of other dermatologic conditions, unrelated to diabetes, were not different between patients and control subjects (Table 2). When, like with halo nevi, a condition was present only in IDDM patients, the numbers were too small to draw any conclusion.

We have not observed many of other skin disorders associated with diabetes, like generalized thick skin, diabetic dermopathy, yellow hands, acanthosis nigricans, granuloma annulare, multiple skin tags, or ulcers. The most likely explanation is the relatively short duration of diabetes in our pediatric and adolescent patients with IDDM as compared to previous cross-sectional studies (2,3).

Results of the cross-sectional study confirm that the most prevalent cutaneous manifestation in young patients with IDDM is dry skin. As suggested by Yosipovitch et al. (3), keratosis pilaris is also a condition disproportionately represented in IDDM population. Both conditions appear early in the course of

the disease and do not correlate with its duration. Our IDDM patient population was younger and with shorter diabetes duration than those described in previous studies, without patients with retinopathy and neuropathy, and with a very low prevalence of nephropathy and hypertension. This may explain the rarity of other diabetes-associated cutaneous manifestations. Comparing mean disease duration in our and the Israeli population (3) of IDDM patients (4.2 vs 13 yrs) it may be supposed that many of the diabetes related skin disorders begin to develop after the fifth year of diabetes (in 71% of our patients, the duration of diabetes was <5 years).

A prospective arm of the study analysing cutaneous manifestations in the same cohort of young patients after several years would offer additional data on the natural history of skin lesions in patients with type 1 diabetes in relation to the disease duration and microvascular complications. The frequency and type of cutaneous lesions justify the early inclusion of a dermatologist in the management of IDDM patients in order to recognize and treat the disorders, and direct further research into prevention some of the lesions, especially those with an underlying fibrosing process.

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Table 1. Characteristics of the study population of 212 young patients with IDDM.

Age (years)	12.5±3.7 (2-22)
Males/females	113/99
Duration of diabetes (years)	4.2±3.0 (1-15)
Age at onset (years)	8.3±3.6 (0.5-15)
Diabetic complications	
	Nephropathy 15 (7)
	Retinopathy 0 (0)
	Neuropathy 0 (0)
	Hypertension 4 (1.9)
Cumulative HbA1c	9.1±1.6

Data are mean ± SD (range) or *n* (%).

Table 2. Distribution of cutaneous lesions in 212 young IDDM patients, and 196 age- and sex-matched controls.

Lesions		Patients (<i>n</i> = 212)			Controls (<i>n</i> = 196)		
		<i>n</i>	%	M/F	<i>N</i>	%	M/F
<i>Skin manifestations associated with diabetes</i>							
Xerosis (acquired ichthyosis)		47	22.2*	24/23	6	3	3/3
Diabetic hand		5 [§]	2.3	5/0	0	0	0
Rubeosis		15	7.1	6/9	0	0	0
Necrobiosis lipoidica		5	2.3	1/4	0	0	0
<i>Infections</i>							
Fungal		10	4.7	3/7	3 [†]	1.5	3/0
	Tinea pedis	4	1.9	2/2	1	0.5	1/0
	Onychomycosis	2	0.9	2/0	0	0	0/0
	Candidosis	4	1.9	1/3	0	0	0/0
Viral	Warts	8	3.7	4/4	4	2	2/2
Bacterial		7 [‡]	3.3	5/2	2	1	0/2
	Impetigo	3	1.4	1/2	1	0.5	0/1
	Folliculitis	3	1.4	2/1	1	0.5	0/1
<i>Skin reactions to insulin therapy</i>							
Lipohypertrophy		4	1.8	2/2	0	0	0/0
Lipoatrophy		2	0.9	0/2	0	0	0/0
<i>Other skin disorders</i>							
Acne		41	19.3	20/23	31	15.5	17/14
Keratosis pilaris		27	11.7*	13/14	3	1.5	3/0
Pityriasis versicolor		2	0.8	2/0	5	2.5	4/1
Café-au-lait macules		6	2.6	4/2	0	0	0/0
Halo nevi		4	1.7	2/2	0	0	0/0
Eczema		8	3.5	3/5	2	1	1/1
Atopic dermatitis		1	0.4	1/0	1	0.5	1/0
Psoriasis		2	0.9	1/1	0	0	0/0
Vitiligo		1	0.4	1/0	2	1	2/0
Alopecia areata		2	0.9	2/0	0	0	0/0
Seborrheic dermatitis		6	2.6	3/3	7	3.5	5/2
Striae dystensae		3	1.3	0/3	0	0	0/0
Dermatitis herpetiformis/ gluten enteropathy		1	0.4	0/1	0	0	0/0
Purpuric dermatosis		1	0.4	1/0	0	0	0/0

[†]Two patients had tinea corporis (*M. canis*) and tinea capitis (*M. canis*), respectively; [‡]A patient with an ingrowing toenail; [§]two patients also had Dupuytren contracture; **P*<0.01 vs. control patients