The Prevalence of Cutaneous Manifestations in IDDM Patients and Their Association With Diabetes Risk Factors and Microvascular Complications

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OBJECTIVE — The aim of our study was to evaluate the frequency of skin manifestations, including the diabetic hand syndrome, in young IDDM patients. In addition, we studied the relation of the cutaneous manifestations to diabetes duration, glycemic control, and microvascular complications.

RESEARCH DESIGN AND METHODS — The frequency of skin manifestations, including the diabetic hand syndrome, were examined in 238 IDDM patients (disease duration >5 years) and 122 healthy control subjects in a cross-sectional study. In addition, we studied the relation of the cutaneous manifestations with diabetes duration, glycemic control, BMI, microvascular complications, and stratum corneum hydration using a stepwise logistic regression.

RESULTS — Diabetic skin manifestations were detected in 168 of 238 (71%) IDDM patients and in 18 of 122 (14%) of the control subjects. Ichthyosiform skin changes of the shins, scleroderma-like skin changes, tinea pedis, and dry scaly palms were detected in 48 vs. 7%, 39 vs. 0%, 32 vs. 7%, and 21 vs. 0.8% of the patients and control subjects, respectively. In the diabetic patients, a significant association was found between ichthyosis of the shins and scleroderma-like skin changes of the hand ($P < 0.001$) and between scleroderma-like skin changes and the skin dryness of the palms ($P < 0.0001$). When diabetic risk factors were considered, diabetes duration was significantly associated with scleroderma-like skin changes and ichthyosis of the shins ($P < 0.0001$). The latter was also found to be related to diabetic retinopathy ($P < 0.0001$). Keratosis pilaris was present in 21% of the patients versus 9% in control subjects and was found to be exclusively associated with high BMI.

CONCLUSIONS — Acquired ichthyosis is a common finding and the most prevalent skin manifestation in young IDDM patients. The development of several skin manifestations in insulin-dependent patients seems to be related to duration of diabetes and to development of diabetic microvascular complications.

Although the cutaneous manifestations of diabetes are well known and considered common (1), systematic surveys of the cutaneous findings in young diabetic patients with IDDM are sparse. Moreover, there is lack of distinction between prevalence among patients with IDDM and those with NIDDM. Although several reports suggest that some of the skin manifestations in diabetic patients may reflect the degree of long-term control of the disease and are associated with other diabetes complications, no confirmative data is available (1–5).

In this study, we examined the prevalence and types of skin lesions in young IDDM patients and studied their association with diabetes risk factors and with the development of microvascular complications. The results of our study suggest that the appearance of cutaneous manifestation in IDDM patients is not rare, with acquired ichthyosis being the most common finding. The development of skin manifestations is influenced by the duration of diabetes and associated with the development of diabetic microvascular complications.

RESEARCH DESIGN AND METHODS

— We examined 238 IDDM patients (117 men, 121 women) with disease onset at <30 years of age and with diabetes duration >5 years (Table 1). Each subject was questioned as to any history of skin disease and underwent a thorough dermatologic examination by two independent observers. We recruited 122 healthy volunteers (58 men and 64 women, aged 16–36 years, mean 23.3 ± 8.6 years) from hospital personnel and high schools and examined them for the prevalence of four common skin manifestations noted previously in our diabetes clinic: ichthyosiform changes, scleroderma-like skin changes, tinea pedis, and keratosis pilaris. Skin lesions were classified into three categories (4): *1*) skin disorders with direct association with diabetes; *2*) cutaneous infections; and *3*) skin reactions to insulin treatment. Skin lesions without a known association to diabetes were categorized separately as miscellaneous. Scleroderma-like skin change of the hand was diagnosed according to the criteria of Seibold (6). The limited joint mobility (LJM) reported to be common in young IDDM patients and often found in conjunction with scleroderma-like skin changes was assessed according to the criteria of Rosenbloom (7).

Stratum corneum hydration was measured on the shins and palms using a cm-820 PC Corneometer (Courage and Khazaka Electronie, Cologne, Germany) and compared to the normative data

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Received for publication 22 September 1997 and accepted in revised form 17 December 1997.

Abbreviations: AU, arbitrary units; LJM, limited joint mobility.

Table 1—*Characteristics of the study group of 238 IDDM patients*

Age (years)	23.5 ± 7.6 (12–44)
Age at IDDM onset (years)	10.65 ± 5.1
M/W	117/121
Duration of diabetes (years)	13 ± 2.5 (5–37)
Complications of diabetes	
Retinopathy	83
Nephropathy	56
Glucose control	
Cumulative HbA_1	11.3 ± 2
Insulin dosage ($U \cdot kg^{-1} \cdot day^{-1}$)	0.83 ± 0.2

Data are means ± SD (range) or *n*.

obtained from 80 healthy volunteers. All the subjects in this study were evaluated during the summer to eliminate the effect of seasonal variation.

Tinea pedis and bacterial infections were clinically evaluated, and the diagnosis of candidal intertrigo confirmed by laboratory culture, as well. The diagnosis of erythrasma was done using a Wood's Lamp.

Medical records were reviewed for information concerning diabetes duration, daily insulin requirement, glycemic control (estimated by the individual mean of the yearly HbA_1 levels using ion exchange chromatography; Isolab, Akron, OH), fasting triglycerides, cholesterol levels, and thyroid and renal function.

Assessment of retinopathy was performed yearly by a retinal specialist, using direct and indirect opthalmoscopy, with results graded as nonproliferative or proliferative retinopathy.

Twenty-four-hour urinary microalbumin excretion was used to detect diabetic nephropathy using a radioimmunoassay technique (8). The mean value of three determinations was used for statistical analysis, the upper limit of the normal range of this test being 22 mg/24 h. BMI was calculated by dividing the body weight by the height squared.

Statistical analysis

Statistical analysis was performed using step-wise logistic regressions using SAS (SAS Institute, Cary, NC). As several regressions were performed, with a well-known α inflation associated with stepwise logistic regression, a cutoff for significance level for variables in the model was set at $P \leq 0.01$.

Table 2—*Incidence of the various cutaneous lesions in 238 IDDM patients*

Manifestations	*n*	M/W	%
Category 1—skin manifestations associated with diabetes			
Ichthyosiform (shins)	115	51/64	48.0
Scleroderma-like changes of the hand	95	53/42	39.0
Dry scaly hands	49	21/28	21.0
Diabetic shin spots	16	7/9	7.0
Generalized thick skin	14	6/8	6.0
Rubeosis facei	7	1/6	3.0
Necrobiosis lipoidica	4	0/4	1.6
Yellow hands	4	4/0	1.6
Facial hyperhydrosis	4	2/2	1.6
Purpura hyperpigmentation	4	1/3	1.6
Acanthosis nigricans	2	2/0	0.8
Multiple skin tags	2	2/0	0.8
Diabetic ulcer	1	1/0	0.4
Granuloma annulare	1	0/1	0.4
Category 2—infections			
Fungal			
Tinea pedis (interdigitalis)	77	44/33	32.0
Onychomychosis	14	10/4	6.0
Candidal intertrigo	4	1/3	1.6
Candidal vaginitis	4	0/4	1.6
Bacterial			
Folliculitis	6	4/2	2.5
Erythrasma	6	3/3	2.5
Category 3—skin reactions to insulin therapy			
Insulin lypohypertrophy and lypoatrophy	15	8/7	6.5
Miscellaneous			
Keratosis pilaris	50	17/33	21.0
Acne	20	12/8	8.4
Tinea versicolor	8	3/5	3.3
Atopic dermatitis	4	1/3	1.6
Keloids	4	2/2	1.6
Dysplastic nevi	2	1/1	0.8
Contact dermatitis	2	1/1	0.8
Psoriasis	1	1/0	0.4
Generalized pruritus	1	0/1	0.4
Erythema nodosum	1	1/0	0.4
Buccal hyperpigmentation	1	0/1	0.4

RESULTS — The clinical data relating to diabetes are given in Table 1. A total of 168 of the 238 (71%) IDDM patients had skin manifestations considered to be associated with diabetes (Table 2). The findings of both examiners were compiled, except for six discordant findings, in which a second evaluation was repeated by both physicians. The most prevalent manifestation was ichthyosiform skin changes of the shins, which were detected in 48% of the patients and in only 6.5% of the control subjects. Only two patients with ichthyosiform skin changes of the shins had abnormal thyroid function tests. Dry scaly palms were detected in 21% of IDDM patients and 0.8% of control subjects.

Compared with 0 control subjects, 65 (27%) IDDM patients had mild to moderate scleroderma-like skin changes and 30 (12%) patients had severe changes. Of the 95 (85%) patients with scleroderma-like skin changes, 81 also had LJM. Overall, LJM was found in 100 (42%) patients, with mild changes in 38 (16%), moderate in 39 (16%), and severe in 23 (10%) patients. Fourteen patients presented with generalized thick skin, affecting mainly the upper back, arms, and thighs. Biopsy specimens obtained in two patients were negative for

mucin stain and showed no obvious abnormality using hematoxylin eosin staining. Thirteen of these patients had also scleroderma-like skin changes of the hands.

Keratosis pilaris was more common in the diabetic patients (21%) than in control subjects (9%). Among the patients, the distribution of this manifestation was noted to be considerably more extensive than usual and mainly confined to the extensor aspects of the limbs.

Stratum corneum hydration of the shins in IDDM patients did not differ from that of control subjects (86 ± 12 vs. 87 ± 8 arbitrary units [AU]), but patients with ichthyosiform skin changes on the shins had significantly lower figures (83 ± 14 AU) than did those without such changes (89 ± 12 AU; $P < 0.0001$). Stratum corneum hydration on the palms was similar in IDDM patients and healthy control subjects (110 ± 15 vs. 109 ± 12 AU). The stratum corneum hydration did not differ between the diabetic patients with dry scaly palms and those without.

Using stepwise logistic regressions to examine the influence of diabetes risk factors on skin manifestations, we found that scleroderma-like skin changes of the hands were significantly related to duration of the diabetes ($P < 0.0001$), but no evidence was found to relate these skin changes to metabolic control. However, scleroderma-like skin changes were significantly associated with LJM as well as to dryness of the palms ($P < 0.0001$). As to the relation between the skin changes and development of secondary diabetic complications, ichthyosiform changes of the shins were found to be strongly associated with diabetic retinopathy ($P < 0.0001$). Keratosis pilaris was related only to high BMI ($P < 0.0001$), and tinea pedis only with age ($P < 0.001$). We found no association of the mean value of triglycerides, fasting cholesterol, thyroid levels, or blood pressure with any of the skin manifestations.

Of the 16 patients with diabetic shin spots, 12 had other microvascular complications, with 10 patients presenting severe complications, such as blindness, diabetic proteinuria, symptomatic neuropathy, and diabetic foot ulcer. Because of the small number of patients in this group, logistic regression was not performed.

CONCLUSIONS — The finding of greatest interest in this study is the fact that ichthyosiform skin changes of the shins, not previously mentioned in the literature in association with diabetes, were found to be the most prevalent manifestation, present in various degrees of severity in almost 50% of the young diabetic patients studied. The prevalence was similar in young men and women. With the exception of two patients having abnormal thyroid function, none of the conditions often associated with acquired ichthyosis—such as nutritional deficiency, atopic skin disease, and chronic renal failure—were present. Sweating disorders are considered to be common among diabetic patients, although their prevalence has not been investigated (9). Xerosis is considered to be related to an autonomic peripheral C fiber neuropathy (1,9). We failed, however, to find a significant relationship between the severity of xerosis and ichthyosis-like changes and the function of small C fibers by using thermal testing (unpublished results). It may be speculated that other factors, such as stratum corneum adhesion and accelerated aging of the skin, may be implicated in the development of ichthyosiform skin changes in IDDM patients. The strong relationship between ichthyosiform skin changes on the shins and scleroderma-like skin changes is of interest, and it could be explained by structural changes in skin proteins due to advanced glycosylation. The marked correlation between ichthyosiform skin changes on the shins and diabetic retinopathy suggests microvascular involvement in the pathogenesis of these skin changes. Histopathological investigation is needed to further clarify this relationship.

The dry scaly palms found in 21% of this group of patients is an additional finding that was not previously described. This finding did not reflect the presence of atopic dermatitis or contact dermatitis in our patients but was associated with scleroderma-like skin changes.

Scleroderma-like skin changes were next in frequency after ichthyosis, with a prevalence of 39% among our IDDM patients. The reported incidence of such changes in the literature ranges from 8 to 50%(1,6,10–12). A strong relationship was found between scleroderma-like skin changes and contractures of LJM, both of which are presumed to belong to the same spectrum of connective tissue abnormalities due to advanced glycosylation (13,14). There is controversy regarding the relation of LJM to the development of microvascular complications such as retinopathy and nephropathy (5,15,16). Our finding is in agreement with an extensive study on LJM that did not find any relationship to microvascular complications (17). Scleroderma-like skin changes were related to disease duration but not to parameters of diabetes control, similar to the findings of Seibold (6).

The generalized thickening of the skin in 6% of our patients has occasionally been noted in the literature (1) and is believed to result from alteration of the structural proteins by advanced glycosylation. Clinically, it differs from scleredema diabeticurom, which occurs in older and obese diabetic patients, mainly on the back, with peau d'orange appearance of the skin (3,18,19). The two biopsies we obtained clearly ruled out the diagnosis of scleredema diabeticurom.

Diabetic shin spots, reported to be pathognomonic and among the most common skin findings in diabetic patients (1,20), were found in only 7% of our patients. This could result from the evaluation of two different populations of diabetic patients, as implied by their different mean ages, 23 years in our patients, and >55 years in other reports. The finding that 12 of the 16 patients with diabetic shin spots had severe microvascular complications is in accordance with other studies (4,20), indicating that these skin manifestations are closely associated with individuals at high risk to develop accelerated diabetes complications. Further studies should be performed to determine whether appearance of shin spots in this population could serve as an alarming sign of development of severe diabetes complications, necessitating intensive follow-up and treatment.

The incidence of necrobiosis lipoidica, which is considered to be almost pathognomonic for diabetes, was somewhat higher in our group than that reported in the literature (0.6–1.2%) (1,4,21,22). Microangiopathy has been included among proposed causative factors for necrobiosis lipoidica, but in our group only one of the four patients with this phenomena had evidence of retinopathy.

Four patients had facial hyperhydrosis, a phenomenon previously described in diabetic patients by Watkins (23). In these patients, this phenomenon appeared to be in response to ingestion of certain foods.

The prevalence of yellow skin of the hand, rubeosis facei, and pigmented purpura in our study was much lower (1.6–3%) than that reported (21–59%) in the literature; again, difference in the populations (IDDM vs. NIDDM) studied could explain different frequency of these manifestations (1–3).

Only one patient in our study presented with granuloma annulare, a lesion believed to be related to abnormal carbohydrate metabolism (1).

Regarding the prevalence of skin infections, we found that the prevalence (32%) of tinea pedis in our group is within the normal range according to the numbers reported by Lugo-Somolinos and Sanchez (24). Still, such frequency is relatively high when one considers the young age of our group and the much lower prevalence (7%) in our healthy control subjects. Tinea pedis was significantly associated with age, and in agreement with data reported by Lugo-Solomonis and Sanchez (24), duration of the disease and glucose control did not predict its appearance.

Of our IDDM patients, 6% had lypohypertrophy and lypoatrophy. These reactions are considered rare (1,4,25). However, we did not find any epidemiological study regarding their true prevalence.

Although keratosis pilaris is considered to be a common skin disorder reportedly affecting up to 40% of the population (26), it was present in 21% of our diabetic subjects, an incidence above that found in our healthy control subjects (9%); moreover, it was more extensive than usual. Several studies have shown a relationship between keratosis pilaris, skin xerosis, and atopic skin diseases (27). Others found an association between this skin disease and obesity and hyperandrogenism (28). Furthermore, keratosis pilaris was reported to be more prevalent in adolescent girls (26), whereas in our study most of the affected patients were of older age. In the current study, keratosis pilaris was only related to high BMI, which may implicate insulin-resistant states on the evolution of keratosis pilaris.

In summary, this cross-sectional study has shown a high prevalence of cutaneous lesions in young IDDM patients, with the most common being ichthyosiform skin changes. Given the high prevalence of the latter and in the absence of other conditions associated with acquired ichthyosis, IDDM should be added to the list of diseases associated with this phenomenon. Although the pathogenesis of most of the skin lesions remains unclear, a number of the skin manifestations appear to be related to other microvascular complications and to duration of diabetes. Further studies should be performed to determine whether the detection of these skin lesions may serve as predictor markers of imminent diabetes complications, necessitating intensive follow-up and treatment.

References

1. Huntley AC: Cutaneous manifestations of diabetes mellitus. *Dermatol Clin* 7:531–546, 1989
2. Huntley AC: Cutaneous manifestations in diabetes general considerations. In *The Skin in Diabetes*. Jelinek JE, Ed. Philadelphia, Lea & Febiger, 1986, p. 23–30
3. Jelinek JE: The skin in diabetes. *Diabet Med* 10:201–213, 1993
4. Perez MI, Kohn SR: Cutaneous manifestations of diabetes mellitus. *J Am Acad Dermatol* 30:519–531, 1994
5. Yosipovitch G, Mukamel M, Karp M: Diabetic hand syndrome in juvenile diabetics. *Harefuah* 119:63–66, 1990
6. Seibold JR: Digital sclerosis in children with insulin dependent diabetes mellitus. *Arth Rheum* 25:1355–1361, 1 982
7. Rosenbloom AL: Skeletal and joint manifestations of childhood diabetes in symposium on juvenile diabetes. *Pediatr Clin North Am* 31:579–601, 1984
8. Kalter-Leibovici O, Van-Dyk D, Leibovici L, Loya N, Erman A, Kremer I, Boner G, Rosenfeld JB, Karp M, Laron Z: Risk factors for the development of diabetic nephropathy and retinopathy in Jewish IDDM patients. *Diabetes* 40:204–210, 1991
9. Navarro X, Kennedy WR, Fries TJ: Small nerve dysfunction in diabetic neuropathy. *Muscle Nerve* 12:498–507, 1989
10. Buckingham B, Prejeda AJ, Sandborg C, Kershnar A, Uitto J: Skin joint, and pulmonary changes in type I diabetes mellitus. *Am J Dis Child* 140:420–423, 1986
11. Buckingham B, Uitto J, Sandborg C, Keens T, Roe T, Costin G, Kaufman F, Bernstein B, Landing B, Castellano A: Scleroderma-like skin changes in insulin-dependent diabetes mellitus: clinical and biochemical studies. *Diabetes Care* 7:163–169, 1984
12. Jelinek JE: Collagen disorders in which diabetes and cutaneous features coexist. In *The Skin in Diabetes*. Jelinek JE, Ed. Philadelphia, Lea & Febiger, 1986, p. 155–174
13. Monnier VM, Vishwanath V, Frank KE, Elmets CA, Dauchot P, Kohn R: Relation between complications of type I diabetes mellitus and collagen linked fluorescence. *N Engl J Med* 314:403–408, 1986
14. Lyons TJ, Kennedy L: Non enzymatic glycosylation of skin collagen in patients with type I (insulin dependent) diabetes mellitus and limited joint mobility. *Diabetologia* 28:2–5, 1985
15. Rosenbloom AL, Silverstein JH, Lezotte DC, Richardson K, McCullum M: Limited joint mobility in childhood diabetes mellitus indicates increased risk for microvascular disease. *N Engl J Med* 305:191–194, 1981
16. Garg SK, Chase HP, Marshall G, Jackson W, Holmes D, Hoops S, Harris S: Limited joint mobility in subjects with insulin dependent diabetes mellitus: relationship with eye and kidney complications. *Arch Dis Child* 67:96–99, 1992
17. Schulte L, Roberts MS, Zimmerman C, Kelter J, Simons LS: A quantitative assessment of limited joint mobility in patients with diabetes. *Arthritis Rheum* 36:1429–1443, 1993
18. Hanna W, Friesen D, Bombardier C, Gladman D, Hanna A: Pathologic features of diabetic thick skin. *J Am Acad Dermatol* 16:546–553, 1987
19. Cole GW, Headley J, Skowsky R: Scleroderma diabeticurom: a common and distinct cutaneous manifestation of diabetes mellitus. *Diabetes Care* 6:189–192, 1983
20. Melin H: An atrophic circumscribed skin lesion in the lower extremities of diabetic. *Acta Med Scand* 176 (Suppl. 423):1–75, 1964
21. Muller SA, Winkelman RK: Necrobiasis lipoidica diabeticorum, a clinical and pathological investigation of 171 cases. *Arch Derm* 93:272–281, 1966
22. Shall L, Millard LG, Stevens A, Tattersall RB, Peacock I: Necrobiosis lipoidica: the foot print not the footstep (Abstract). *Br J Derm* 123 (Suppl. 37):47, 1990
23. Watkins PJ: Facial sweating after food: a new sign of diabetic autonomic neuropathy. *Br Med J* 1:583–587, 1973
24. Lugo-Somolinos A, Sanchez JL: Prevalence of dermatophytosis in patients with diabetes. *J Am Acad Dermatol* 26:408–410, 1992
25. Jegasothy B: Cutaneous complications of diabetic treatment. In *The Skin in Diabetes*. Jelinek JE, Ed. Philadelphia, Lea & Febiger, 1986, p. 217–226
26. Poskitt L, Wilkinson JD: Natural history of keratosis pilaris. *Br J Dermatol* 130:711–713, 1994
27. Mevorah B, Marazzi A, Frenk E: The prevalence of accentuated palmoplantar markings and keratosis pilaris in atopic dermatitis autosomal dominant ichthyosis and control dermatological patients. *Br J Dermatol* 12:679– 685, 1985
28. Barth JH, Wojnaroswka F, Dawber RP: Is keratosis pilaris another androgen dependent dermatosis. *Clin Exp Dermatol* 13:240–241, 1988