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Ethnicity and Prevalence of Scleroderma-Like Syndrome: A Study of Arab and Jewish Israeli Insulin-Dependent Diabetic Children

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ABSTRACT

Scleroderma-like syndrome (SLS) may represent the earliest apparent diabetes complication in insulin-dependent diabetic (IDDM) patients. To evaluate the frequency of SLS and its association with other diabetes-related pathology in our diabetic population, we studied 153 (127 Jewish and 26 Arab) IDDM patients and 45 healthy age- and gender-matched controls (25 Jewish, 20 Arab). The mean age and diabetes duration of the patients were 14.09 ± 5.1 years and 51 ± 45 months, respectively. While no diabetes-related pathology was found in the controls, SLS was detected in 47% of all patients (skin, 31.4%; arthropathy, 37.9%; both, 22%), and nephropathy, neuropathy, and retinopathy were present in 10.5%, 5.2%, and 4.6%, respectively. Independent of age, SLS directly correlated with diabetes duration ($p < 0.01$) and with the presence of either nephropathy or neuropathy ($p < 0.009$ and $p < 0.005$, respectively). One or more features of systemic diabetic involvement were present in 22% of patients with SLS, compared to only 7.2% in patients without SLS ($p < 0.009$). When patients were analyzed according to ethnicity, the frequency of skin involvement and neuropathy were found to be higher among Arab patients, particularly males ($p < 0.002$ and $p < 0.005$, respectively), and detection of one was significantly associated with the presence of the other ($p < 0.001$). In conclusion, our results suggest that SLS is the most common diabetic complication among Jewish and Arab IDDM patients, and its presence may reflect an inherited tendency to develop other serious diabetic complications. Ethnicity (Arab) by itself, particularly when associated with male gender, seems to accelerate neurological and dermatological diabetic involvement. (Journal of Diabetes and Its Complications 11;6:323–327, 1997.) © 1997 Elsevier Science Inc.

INTRODUCTION

Scleroderma-like syndrome (SLS), also termed "Syndrome of Limited Joint Mobility (LJM)" or "cheiroarthropathy," was first described in diabetic children by Rosenbloom and Frias,[1] and is presently considered the earliest clinically apparent long-term diabetic complication in children and

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adolescents.[2] In the three initially described young patients with type I diabetes of long duration,[1] LJM of fingers and large joints were associated with growth retardation, thick and waxy skin, delayed sexual maturation, and early microvascular complications. Following that report, larger series appeared describing in more detail a wide range of manifestations in children with insulin-dependent diabetes mellitus (IDDM) and indicating a frequency of LJM that varied between 8% and 50% of the cases.[3–8] Such variability could be explained by differences in the populations studied, their age, duration of diabetes, and by the use of various examination techniques.[2–9] The association of LJM with other secondary diabetic manifestations and its value in the prediction of microvascular complications, specifically retinopathy and nephropathy, is still a matter of debate.[10–12] The incidence of IDDM has been reported to differ among Arabs and Jews in Israel,[13] suggesting a role of genetics in the various aspects of this disease, including the development of long-term diabetic complications.

The aim of the present study was to assess the prevalence of SLS among our IDDM patients, and its relationship to various parameters such as ethnicity, disease duration, long-term glycemic control and insulin requirement, and the presence of other diabetic complications.

METHODS

Study Design. The study subjects were 153 young IDDM patients regularly attending the Juvenile Diabetes Outpatient Clinic at the Lynn Clinic and the Rambam Medical Center in Haifa were studied. The diagnosis of IDDM was made according to the National Diabetes Data Group criteria.[14] Patients suffering from other diseases, such as thalassemia major, celiac, or autoimmune disease were excluded from the study. Twenty-five age- and gender-matched healthy Jewish and 20 Arab subjects with no family history of diabetes served as a control group. The patients were examined during their routine visits to the clinic at 3-month intervals, and the following variables were recorded: age, gender, age at onset of disease, duration of diabetes, ethnic background (Jewish, Arab, other) and glycemic control. Glycemic control was determined using measurements of glycosylated hemoglobin (G-Hb) by affinity chromatography (normal range, 4%–8%) using Glyc-AffinGHb Kit (ISOLAB, Inc, Akron, OH, USA). The mean of the last 4 analyses done over the last year was calculated and considered to represent recent glycemic control of each patient in the study. The mean daily insulin requirement and the ratio of insulin units/kg weight were calculated using the previous 12 months recorded data at follow-up visits. All patients were routinely examined for the presence of diabetic complications, as follows:

1. *Nephropathy* was assessed by the albumin excretion rate in three 24-h urine collections using a radioimmunoassay technique. The mean value of three tests was used for statistical analysis. Microalbuminuria was defined when excretion ranged from 25 to 300 mg/24 h, and macroalbuminuria as albumin excretion greater than 300 mg/24 h.[15]
2. *Retinopathy* was assessed by the degree of retinal involvement, using direct and indirect ophthalmoscopy, in every patient, by a retinal specialist who had been blinded as to the glycemic control and other clinical parameters of the patient. Grading was done according to a variation of the modified Airlic House classification.[16] with grades greater than 1 and less than 5 being classified as nonproliferative retinopathy, and grades greater than 6 as proliferative retinopathy.
3. *Neuropathy* was screened for by a complete neurological examination by the same neurologist, who looked in particular for evidence of neuropathy. The diagnosis of diabetic neuropathy was based on the criteria established by Dyck et al.[17] The laboratory tools included in the examination were: (1) electrodiagnosis (EMG); (2) thermal testing, a relatively new technique aimed at assessment of small sensory fibers;[18] (3) vibratory sensory thresholds; and (4) autonomic tests, recording heartbeat variations and drops in blood pressure. At least two abnormal laboratory tests were required for a diagnosis of diabetic polyneuropathy.[17]
4. *Scleroderma-like syndrome* was assessed by examination of skin and joints involvement by the same pediatric rheumatologist, who was not informed at the time of examination as to the duration of diabetes, daily insulin requirement, G-Hb level and presence of diabetic complications. The extent of involvement of the skin and of the joints was determined according to the criteria established by Rosenbloom et al.[9] The degrees of severity were scored as follows: (1) For skin involvement, grade 1, thick; grade II, thick and tight; and grade III, thick, tight and waxy. (2) For joint mobility, stage 1: mild limitation: involvement of one or two interphalangeal joints, one large joint, or only the metacarpal-phalangeal joint bilaterally; stage 2: moderate limitation: involvement of three or more interphalangeal joints, or one finger joint and one large joint, bilaterally; stage 3: severe limitation: moderate limitation plus cervical spine involvement or obvious hand deformity at rest.

Statistical Analysis. Stepwise logistic regression analysis was used in order to determine which of the risk factors (age, gender, age at onset of disease, duration of diabetes, ethnicity, and glycemic control) are independently and significantly related to diabetic complications. In order to remain in the model, each independent variable must be significantly ($p < 0.05$) related to the dependent response probability in the optimal model. The relationship between complications was tested by χ^2 tests of the frequencies of pres-

TABLE 1. DIFFERENT DEGREES OF SKIN INVOLVEMENT AND LIMITED JOINT MOBILITY IN DIABETIC SUBJECTS

		Skin Involvement					Limited Joint Mobility				
				Severity Score					Severity Score		
Patients	*n*	*n*	%	I	II	III	*n*	%	I	II	III
Jewish	127	33	22	30	3	—	47	37	30	11	6
Arab	26	15	58[a]	7	6	2	11	42	6	2	3
Total	153	48	31.4	37	9	2	58	37.9	36	13	9

n, number of patients; severity score, for severity scoring, see Methods.

[a] $p < 0.002$.

ence or absence of each complication. A p value less than 0.05 was regarded as denoting a significant relationship between the tested complications.

RESULTS

The mean age ± SD of the 153 diabetic patients was 14 ± 5.2 (range, 2.5–36 years) and 14.07 ± 2.4 years (range, 5–22 years) in the control group. The male/female ratio in the diabetic patients and the controls was 67/86 and 18/27, respectively. One hundred and twenty-seven patients were Jewish and 26 were of Arab origin, with an overall mean diabetes duration of 51 ± 44.6 months (range, 1–205 months). The mean dose of insulin requirement was 0.82 ± 0.3 U/kg/day and the mean level of G-Hb over the last 12 months of follow-up was 12.8% ± 3.5%.

Combined LJM and increased skin thickness were detected in 72/153 (47%) of the patients, while isolated LJM or skin changes were observed in 58/153 (38%) and 48/153 (31.4%), respectively. When the whole group of patients was evaluated according to their ethnic origin, 15/26 (58%) of the Arab diabetic patients displayed skin involvement, compared to only 33/127 (26%) of the Jewish patients ($p < 0.002$) (**Table 1**). None of the 45 controls had any systemic signs of long-term diabetes.

Systemic diabetic complications at the time of the study were observed in 22 (14.3%) patients, of whom 17 (11%) had evidence of nephropathy, 8 (5.2%) had neuropathy, and 7 (4.6%) had retinopathy. Four patients suffered from more than one complication. Microvascular complications were detected in 22% of patients who had evidence of SLS, compared to only 7.2% of those without such involvement ($p < 0.0009$).

No significant difference was noted between the Jewish and Arab diabetic patients regarding factors such as age, duration of diabetes, age of disease onset, insulin requirement, and mean level of G-Hb (**Table 2**). A significant direct correlation was found between the presence of SLS and diabetes duration ($p < 0.001$), but not with age or glycemic control.

The correlation between the various risk factors (age, gender, ethnicity, duration of diabetes, and glycemic control) and the various modes of microvascular diabetic injury was studied by stepwise logistic regression (**Table 3**). The results indicate the following: (1) The presence of albuminuria correlated positively with disease duration ($p < 0.01$), age ($p < 0.01$), and level of HbA_{1c} ($p < 0.03$). In addition, a significant association was found between urinary albumin excretion and presence of SLS ($p < 0.009$). (2) A direct correlation was found between diabetic neurological dysfunction and either diabetes duration ($p < 0.01$) or age ($p < 0.03$); such associations were particularly significant in Arab males ($p < 0.005$). Although statistical analysis did not establish a significant association between the presence of skin involvement and neuropathy, there was a trend toward such association reflected by $p = 0.05$. (3) Eye involvement correlated only with the patient's age ($p < 0.003$), but not with other variables or with the presence of SLS.

DISCUSSION

In the present study, we found manifestations of scleroderma-like syndrome in 47% of our IDDM patients and in none of the controls. We apply the term SLS in

TABLE 2. CLINICAL CHARACTERISTICS OF JEWISH AND ARAB IDDM PATIENTS

	Jewish *n* = 127	Arab *n* = 26
Age (years)	14.01 ± 5.9	14.4 ± 4.4
Age at onset (years)	9.7 ± 4.9	10.1 ± 5.1
Duration (months)	51.0 ± 45.8	52.1 ± 39.5
G-Hb level[a] (%)	12.4 ± 3.4	14.6 ± 3.1
Insulin requirement (U/kg/day)	0.82 ± 0.28	0.84 ± 0.2

IDDM, insulin-dependent diabetes mellitus; G-Hb, glycosylated hemoglobin.

[a] *Mean of values measured over the 12 months prior to study.*

No significant differences between groups regarding any of these clinical characteristics.

TABLE 3. *p* VALUES REGARDING THE ASSOCIATION OF DIABETIC COMPLICATIONS WITH DIVERSE RISK FACTORS

Microvascular Complications	Duration of Diabetes (years)	Age (years)	Gender M/F	G-Hb (%)	Ethnic origin J/A
Nephropathy	<0.01	<0.01	NS	<0.03	NS
Retinopathy	NS	<0.03	NS	NS	NS
Neuropathy	<0.01	<0.03	<0.02 (M)	NS	<0.002 (A)
Skin	<0.01	NS	NS	NS	<0.02 (A)
Joints	<0.0001	NS	NS	NS	NS
SLS (skin + joints)	<0.001				

M/F, male/female; G-Hb, glycosylated hemoglobin; J/A, Jewish/Arab; NS, not significant.

There was no significant difference between Jewish and Arab diabetic patients as to the occurrence of the overall scleroderma-like syndrome, but skin manifestations alone were more frequent among Arab patients.

A significant positive correlation was found between neuropathy and the prevalence of SLS skin manifestations in Arab patients.

our work both for scleroderma-like skin changes and for the LJM condition, as we agree with the premise that, similarly to scleroderma, digital flexion contractures in IDDM are secondary to thickening of periarticular skin and subcutaneous tissue.[19] Our study agrees with other reports in that the duration of diabetes constitutes the main variable that determines the development of SLS.[2] Indeed, several investigators estimate that approximately 50% of patients with a diabetes duration of more than 5 years are affected.[8] In contrast, a prospective study by Rosenbloom et al. found LJM in over 90% of patients who were 10–20 years of age, suggesting that, although LJM may well be related to the duration of diabetes exposure, it appears to be also age dependent.[20] In our own series of young patients (mean age, 14.09 ± 5.1; range, 2.5–36 years), most of whom had diabetes of a relatively recent mean onset (less than 5 years), the occurrence of SLS was associated only with a longer duration of diabetes, although very early onset of SLS was noted in some children of Arab extraction.

Overall, involvement of the skin or the joints or a combination of both was detected in 44% of the Jewish diabetic patients compared to 61.5% of the Arab, but these differences did not reach statistical significance. Only when skin involvement was analyzed separately from arthopathy, was significance clearly obtained. The influence of ethnicity on the predisposition to develop SLS is as yet unclear. It seems that in most populations, microvascular disease is predominantly dependent on hyperglycemia and duration of diabetes, whereas macrovascular disease patterns might reflect those of the background community. Most of the reports on the prevalence of SLS in IDDM patients have addressed mainly Caucasian subjects. In contrast, studies from Italy,[5] Nigeria,[21] and the present series suggest that ethnic background may affect the prevalence of SLS. In our study, when the incidence of SLS was analyzed according to ethnic origin, the frequency of skin involvement was found to be significantly higher among Arab than among Jewish diabetic patients; there were no differences in therapeutic compliance or glycemic control to explain such a difference. The different occurrence of skin involvement in Arab and in Jewish patients may conform with the concept of genetic heterogeneity of type I diabetes,[22–24] and racial or genetic factors may thus also determine the susceptibility to SLS. The glycosylated hemoglobin concentrations measured in all our patients over the last 12 months showed no appreciable individual fluctuations, thereby reflecting overall adequate glycemic control. Moreover, during the last 12–15 years, our medical center has provided comprehensive management for the diabetic children in the total community, Arab and Jewish alike, attaining a remarkable homogeneity as regards counseling, compliance, and metabolic control. This may support the likelihood that ethnicity rather than sociocultural factors is responsible for the differences between the groups.

The importance of SLS detection in young diabetic patients lies in its possible relationship to the serious microvascular complications of diabetes, especially retinopathy and nephropathy. In our group of young diabetics with a disease duration of less than 5 years, the incidence of microvascular complications was low (14.3%), as expected. However, patients who did manifest SLS showed by far a higher frequency of microvascular complications than those without the condition (22.2% versus 7.4%). These finding support the reported life-table analysis which assigns an 83% risk for development of microvascular complications after 16 years of diabetes in the presence of LJM, in contrast to a risk of only 25% in its absence.[2]

Regarding the influence of ethnicity in diabetic complications, Leibovici et al.,[25] in a study of Israeli Jewish IDDM patients, showed an increased risk for developing diabetic nephropathy and retinopathy in non-Ashkenazi diabetics. In contrast, we did not find ethnic

origin to be a risk factor for development of microvascular complications. This discrepancy could be due to either differences in the population studied: namely, Jewish versus Arab and Ashkenazi versus Sephardic Jewish patients, and to differences in disease duration, as our population consisted mainly of patients with diabetes of relatively recent onset.

Interestingly, both SLS and diabetic neuropathy were more frequent among Arab patients, particularly males, with a significant correlation between the two manifestations. It could be speculated that an advanced rate of glycosylation of proteins in the nervous system and in the skin could be responsible for the development of such diabetic injuries, particularly when the common ectodermal origin of these two systems is considered.

In conclusion, our study indicates that the presence of SLS in diabetic patients is associated with duration of disease, and that it is more likely to be observed in patients with microvascular complications. Ethnicity, Arab origin in our case, seems to predispose to development of both SLS and neuropathy, while male gender seems to accentuate such predisposition.

Our results suggest, that the extent of skin involvement may be regarded as reflecting a cumulative influence of diabetes on the structure and function of connective tissue. The evaluation of the predictive value of such changes among diverse diabetic populations requires further studies that are standardized for degree of metabolic control, perhaps by parameters than can assess earlier measures of metabolic control. A better understanding of genetic determinants that may contribute to the development of SLS in juvenile diabetics might thereby be attained.

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