

Sclerodactyly and Diabetic Complications among Egyptian Adolescent Type 1 Diabetic Patient

Soha M. Abd El Dayem^{1*}, Abo El Magd El Bohy², Ahmed A. Battah³

¹*Pediatrics Department, National Research Centre, Cairo, Egypt;* ²*Radiology Department, Cairo University, Cairo, Egypt;* ³*Critical Care Department, Cairo University, Cairo, Egypt*

Abstract

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***Correspondence:** Soha M. Abd El Dayem, Pediatrics Department, National Research Centre, Cairo, Egypt. E-mail: S_eldayem@yahoo.com

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BACKGROUND: One of the common complications of diabetic patients is sclerodactyly which is considered as a part of limited joint mobility.

AIM: To assess sclerodactyly in adolescent type 1 diabetics and to detect its relation to other diabetic complications.

METHODS: Sixty-three diabetics and 60 controls were studied. Clinical, laboratory assessment, ultrasonography of the skin, carotid artery intima-media thickness (cIMT) & renal colour duplex were done for all participants.

RESULTS: Sclerodactyly was positive in 12 (19%) of diabetics. Patients with sclerodactyly had a significantly thickened skin compared to patients without sclerodactyly and controls, $P = 0.0001$. Male diabetics had significantly thickened skin ($p = 0.0001$). Diabetic patients with sclerodactyly had significant higher systolic blood pressure ($p = 0.03$), cholesterol ($p = 0.05$) and triglyceride ($p = 0.004$) and lower HDL-c ($p = 0.04$). Skin thickness had a significant positive correlation with age of diabetic patients ($p = 0.02$), waist/height ratio ($p = 0.04$), glycosylated hemoglobin ($p = 0.03$), albumin/creatinine ratio ($p = 0.03$), and cIMT ($p = 0.03$).

CONCLUSION: Ultrasound easily diagnoses sclerodactyly. Diabetic patients had a high prevalence of sclerodactyly with increased macrovascular and microvascular complications. Sclerodactyly may be a marker for diabetic vascular complications. Frequent follow up of diabetic patients for early detection of sclerodactyly in uncontrolled diabetic patients is recommended. It could be an alarming sign for microalbuminuria, hypertension, hyperlipidaemia and atherosclerosis.

Introduction

Type 1 Diabetes Mellitus (DM) is associated with significant morbidity due to microvascular and macrovascular complications as well as several cutaneous & musculoskeletal manifestations including sclerodactyly and limited joint mobility (LJM) syndrome [1], [2].

Diabetic musculoskeletal, connective tissue & cutaneous complications have not been paid attention as other diabetic microvascular and macrovascular complications. The hand is frequently affected, resulting in both disability and deformity, especially in longstanding diabetics with poor glycemic control. Progressive alterations in connective tissue due to glycosylation of proteins, microangiopathy and

peripheral neuropathy, along with collagen deposition in the skin and periarticular structures are the most likely explanations for the pathogenesis of these diabetic complications. Early diagnosis of these complications is of paramount importance in the routine care for diabetic patients as evidence indicate that diabetes control prevent progressive deformity and disability, prevent progression of associated diabetic microvascular and macrovascular complications and maintaining reasonable quality of life in diabetic patients [3], [4], [5], [6], [7].

Sclerodactyly, being a part of limited joint mobility syndrome (LJMS), or diabetic cheiroarthropathy, that is a condition characterised by hand stiffness resulting from flexion contractures of the fingers with thickened, tight, waxy skin [1]. However, these skin changes were also detected in

patients with DM who did not have LJM (and have been referred to as “diabetic sclerodactyly”). Seibold [8] detected skin changes in 34% of diabetic children compared with absent skin changes in healthy children; 20% of the diabetic patients had involvement limited to the proximal interphalangeal (PIP) joints, and distally, 10% had changes extending to the metacarpophalangeal (MCP) joints, and only 4% had skin changes proximal to the MCP joints. Skin thickness in the patient’s hands is assessed by attempting to tent the skin on the dorsum of the fingers between the examiner’s thumb and index finger. When skin changes are severe, loss of the transverse digital skin ridges on the dorsum of the fingers is obvious.

Collier et al., [6] used ultrasonography to study skin thickness in 92 patients with DM and 40 without. They found that skin thickness increases with the duration of DM and is closely related to the presence of LJM. Also, limited biopsy studies have revealed thickening of the dermis along with the accumulation of connective tissue in the lower dermis and a paucity of glands and hair follicles in diabetic patients [7], [9], [10].

Lieberman et al., [11] showed that insulin pump treatment of juvenile diabetic patients diminished the skin thickness with a concurrent decrease in the levels of HbA1c, lending support to a metabolic rather than an underlying immunological cause. In sclerodactyly, laboratory and radiographic evaluation are usually unremarkable with normal erythrocyte sedimentation rate, negative antinuclear antibodies, negative rheumatoid factor and normal results of nail fold capillaroscopy [12], [13].

LJM, including sclerodactyly, is a common complication of DM, occurring in 8% to 58% of patients; most studies suggest a prevalence of about 30% to 40%. [10], [14], [15]. Recent studies [16], [17] revealed a reduced frequency of LJM compared with the frequency 2 decades ago. Lindsay JR et al., [17] stated that the incidence of LJMS & sclerodactyly has fallen from 43% to 23% between the 1980s and 2002 ($P < 0.0001$) and attributed this to improved glycemic control and diabetic care.

Rosenbloom and associates [10] reported that after 16 years of juvenile DM, patients with LJM had a more than 3-fold greater risk of clinically apparent microvascular disease (retinopathy and nephropathy) than those who did not have LJM. Also, Fitzcharles and coworkers [18] found a similar but less dramatic association of the microvascular disease with LJM in adult patients with DM.

The authors of the Oxford Regional Prospective Study tried to explore the temporal relationship between the development of LJM and microvascular complications [19] and stated that although the albumin to creatinine ratio was higher in patients with LJM than in those without LJM, there was no difference between the groups in the

prevalence of microalbuminuria, but after disease onset, the presence of microalbuminuria was increased in patients with LJM. The authors concluded that the presence of LJM confers a 1.9-fold increased risk of this complication.

Arkkila and associates [20] found a 3.1-fold higher risk of coronary heart disease and a 4-fold higher risk of cerebrovascular disease in patients who had type 2 DM with LJM.

So, sclerodactyly is one of the most important cutaneous manifestations of diabetes and was included as a part of the limited joint mobility syndrome (LJMS) in most previous studies while few studies focused on sclerodactyly as a separate entity.

In the current study, we focus on sclerodactyly as a separate entity and its relation to the duration of diabetes, diabetic control, lipid profile, microvascular & macrovascular diabetic complications.

Patients and Methods

Approval of ethical committee, National Research Centre, Registration number 11052 and written consent was taken from diabetics or their parents and controls of this cross-sectional observational study.

Sixty-three type 1 diabetic patients from the endocrine clinic, Medical Center of Excellence, National Research Centre and 60 age and sex-matched healthy normal volunteers were enrolled in the study.

Young diabetic patients (age > 14 and < 19 yrs) and more than 5 years duration of diabetes were selected to explore whether sclerodactyly starts at this early age shortly after the onset of diabetes or needs longer exposure to the diabetic milieu.

Patients suffering from acute diabetic complications, cardiac diseases, receiving metformin or multivitamins or Smokers were excluded from the study. Also, patients had any type of hand disorders like hand injury, Dupuytren’s contracture, flexor tenosynovitis and scleroderma (scleroderma diagnosed by history, physical examination, tapering, fingertips ulceration, calcinosis, dystrophy with necrosis of fingernails, Raynaud’s phenomena) were excluded from the study.

Demographic data of diabetic patients was taken. Also, data of the presence of any disease (cardiac, renal, neurological, scleroderma or any autonomic dysfunction) were obtained.

Clinical examination (general, cardiac, chest, neurological and hand) were done to all diabetics and controls.

Blood pressure was assessed three times, and the mean of second and third measurement was reported.

Weight, height, waist circumference (WC), and hip circumference (HC) were measured for diabetics and controls. Weight and height were measured by Seca Scale Standing Balance and a Holtain Portable anthropometer (Holtain, Ltd, Crymmych, Wales, U.K). Body mass index, waist/hip ratio and waist/height ratio (cm/cm) were calculated [21], [22]. After 12 hr fasting, venous blood was collected for measurement of lipid profile [23]. Also, in a sterile EDTA vacutainer tube, venous blood samples were obtained for measuring glycated haemoglobin (HbA1c). The mean value of HbA1c (HbA1c was assessed every 3 months, and the mean value was calculated for one year) was calculated.

Screening for microalbuminuria was assessed in fresh morning urine samples by measuring albumin/creatinine ratio. Microalbuminuria was measured 3 times (separated every 2 months), and it considers positive if 2 from 3 samples were positive [24]. Antinuclear antibodies (ANA), anti-Scl-70 and anti-centromere antibodies were also assessed in all people with diabetes included in the study.

Ultrasonographic assessment of skin thickness: Epidermis plus dermis layers thickness was defined as skin thickness by using an ATL HDI 5000 ultrasound machine (Phillips Healthcare, Best, Netherlands) equipped with a 12-5 MHz linear array transducer [25], [26]. Assessment of Carotid intima-media thickness (cIMT) was done by using General Electric medical ultrasonographic machine model: Vivid 7 Pro, GE Vingmed ultrasound AS-NI90, Horton-Norway equipped with 7.5-10 MHz linear-array transducer) [27].

Renal colour duplex

The renal colour duplex scan was done by using 3-6 MHz convex array transducer (Toshiba, Xario ultrasound machine). We measured in both renal arteries the peak systolic velocities and excluded renal artery stenosis in all patients by evaluation of different segments starting from their origins to renal hila. After that, resistivity indices were assessed in both sides in the segmental, interlobar and arcuate arteries [28].

Statistical Analysis

Statistical analysis was conducted using Statistical Package for Social Science (SPSS) program version 20.0 (Chicago, Illinois, USA), t-test or Mann Whitney – U test (for non-symmetrically distributed data) for quantitative variables was done. One-way ANOVA test was done for analysis of more than 2 quantitative data followed by post HOCC test for detection of significance. Pearson's or spearman

correlation was also done.

Results

Antinuclear antibodies (ANA), anti-Scl-70 and anti-centromere antibodies were negative in all people with diabetes included in the study.

Comparison between diabetic patients and controls was shown in Table 1.

Table 1: Comparison between diabetic patients and controls

Variables	Patients		Controls		P-value
	Mean	SD	Mean	SD	
<i>Demographic data</i>					
Age of patients (yrs)	17.99	2.59	17.50	2.67	0.60
Duration of the disease (yrs)	10.91	3.54	--	--	--
Onset of disease (yrs)	7.00	3.28	--	--	--
Insulin dose (U/kg)	1.26	0.44	--	--	--
<i>Blood pressure</i>					
Systolic blood pressure (mmHg)	118.45	13.33	123.75	10.61	0.30
Diastolic blood pressure (mmHg)	76.55	10.06	80.00	10.69	0.40
<i>Anthropometric data</i>					
Midarm circumference (cm)	75.14	379.53	25.79	4.41	0.30
Waist circumference (cm)	82.83	11.21	74.56	11.23	0.04
Hip circumference (cm)	94.60	10.32	85.19	13.32	0.02
BMI (kg/m ²)	24.44	3.89	21.86	6.47	0.20
Waist/hip ratio	0.88	0.08	0.88	0.07	0.90
Waist/height ratio	0.51	0.07	0.48	0.10	0.30
<i>Laboratory data</i>					
HbA1c (%)	9.20	1.93	5.43	0.65	0.0001
#Albumin/ creatinine ratio (µg/g creatinine)	71.94	73.49	20.53	26.27	0.02
Cholesterol (mg/dl)	194.86	63.65	100.54	20.41	0.0001
Triglyceride (mg/dl)	106.59	53.12	68.89	28.39	0.03
HDL-c (mg/dl)	49.31	16.35	52.21	11.12	0.90
LDL-c (mg/dl)	116.49	39.10	62.50	19.88	0.0001
<i>Image study</i>					
cIMT (mm)	0.52	0.06	0.41	0.03	0.0001
Resistivity index (RI)	0.67	0.04	0.59	0.02	0.03

T-test for independent variables; # Mann Whitney U test was used; Median, mean ± SD (range); BMI: body mass index; HbA1c: glycosylated haemoglobin; LDL: Low-density lipoprotein; HDL: high-density lipoprotein; cIMT: carotid intimal medial thickness.

Sclerodactyly was positive in 12 (19%) of patients (Table 2).

Table 2: Frequency distribution of skin thickness in type 1 diabetic patients

Variables	N	%
Diabetic Sclerodactyly		
Negative	51	81
Positive	12	19

Patients with sclerodactyly have significantly thickened skin with skin thickness of 0.9 + 0.09 mm compared to patients without sclerodactyly and controls (skin thickness was 0.69 + 0.07 mm and 0.68 + 0.11 mm respectively, P = 0.0001 (Table 3).

Table 3: Comparison between maximal skin thickness in people with diabetes (with and without clinical symptoms) and controls

Variables	Patients				Controls		P-value
	Negative clinically		Positive clinically		Mean	SD	
	Mean	SD	Mean	SD			
Sclerodactyly	0.69	0.07	0.90	0.09	0.68	0.11	0.0001

One-way ANOVA test is used followed by post HOCC test; Patients with clinical symptoms have significantly higher skin thickness than control, and patient without waxy skin while no difference between patients without waxy skin and control.

Male diabetic patients had significantly higher skin thickness (Table 4).

Table 4: Comparison between skin thicknesses in diabetic patients about sex

Variables	Males		Female		P-value
	Mean	SD	Mean	SD	
Skin thickness	0.77	0.10	0.65	0.08	0.0001

Systolic blood pressure, albumin/creatinine ratio, cholesterol, triglyceride, cIMT were significantly higher, while HDL-c was significantly lower in people with diabetes with positive skin thickness (Table 5).

Table 5: Comparison between diabetic patients about skin thickness

Variables	Skin thickness				P-value
	Negative N = 51		Positive N = 12		
	Mean	SD	Mean	SD	
Demographic data					
Age (yrs)	15.59	1.95	16.10	1.39	0.40
Duration of disease (yrs)	8.63	3.11	9.15	2.46	0.60
Insulin dose (u/kg)	1.49	0.47	1.39	0.41	0.50
Blood pressure					
Systolic blood pressure (mmHg)	116.57	11.36	125.45	12.93	0.03
Diastolic blood pressure (mmHg)	82.71	9.95	83.18	7.17	0.90
Anthropometric data					
Waist circumference (cm)	83.57	10.53	84.36	8.69	0.80
Hip circumference (cm)	92.34	8.99	92.18	6.47	0.90
Waist/hip ratio	0.90	0.07	0.92	0.07	0.70
waist/height ratio	0.52	0.07	0.49	0.06	0.20
BMI (SDS)	1.26	1.09	1.35	1.00	0.80
BMI (kg/m ²)	25.11	4.89	24.62	3.63	0.80
Laboratory data					
HbA1c %	9.08	1.68	9.72	1.73	0.30
Albumin/creatinine ratio (µg/g creatinine)	17.73	14.25	63.44	201.40	0.05
Uric acid (mg/dl)	4.17	1.09	3.84	0.77	0.50
OXLDL (mg/dl)	17.91	5.82	18.19	6.27	0.90
Cholesterol (mg/dl)	168.83	42.20	202.55	70.35	0.05
Triglyceride (mg/dl)	73.67	21.95	124.29	93.64	0.004
HDL-c (mg/dl)	56.85	23.14	46.25	10.77	0.04
LDL-c (mg/dl)	107.90	40.18	119.72	51.35	0.40
VLDL-c (mg/dl)	12.95	3.74	19.12	8.26	0.07
Image study					
Common carotid intimal medial thickness (mm)	0.48	0.08	0.51	0.05	0.03
Resistivity index (RI)	0.60	0.03	0.62	0.06	0.20

T-test for independent variables; # Mann Whitney U test was used; Median, mean ± SD (range); BMI: body mass index; HbA1c: glycosylated haemoglobin; LDL: Low-density lipoprotein; HDL: high-density lipoprotein; cIMT: carotid intimal medial thickness.

Sclerodactyly had a significant positive correlation with age of diabetics, waist/height ratio, HbA1c, albumin/creatinine ratio, triglyceride and cIMT (Table 6).

Table 6: Correlation between skin thickness with demographics, laboratory data and carotid intimal medial thickness in type 1 diabetic patients

Variables	Skin thickness	
	r	P-value
Demographic data		
Age (yr)	0.29	0.02
Duration of disease (yr)	0.24	0.06
Insulin dose (u/kg)	0.13	0.40
Anthropometric data		
Waist/hip ratio	0.03	0.83
Waist/height ratio	0.31	0.04
Blood pressure		
Systolic blood pressure (mmHg)	0.33	0.03
Diastolic blood pressure (mmHg)	0.02	0.91
Laboratory data		
HbA1c %	0.3	0.03
Albumin/creatinine ratio (µg/g creatinine)	0.3	0.03
Uric acid (mg/dl)	0.07	0.78
Cholesterol (mg/dl)	-0.25	0.08
Triglycerid (mg/dl)	0.35	0.01
HDL-c (mg/dl)	-0.16	0.26
LDL-c (mg/dl)	0.13	0.38
Image study		
Carotid intimal medial thickness (mm)	0.20	0.01
Resistivity index (RI)	0.17	0.31

BMI: body mass index; HbA1c: glycosylated haemoglobin; LDL: Low-density lipoprotein; HDL: high-density lipoprotein; cIMT: carotid intimal medial thickness.

Discussion

Sclerodactyly is a part of limited joint mobility (LJM), appear in the form of hand stiffness with flexion contractures of the fingers with thickened tight waxy skin. Diabetic patients had skin changes without LJM, and it is known as “diabetic sclerodactyly” [8].

In the present study, people with diabetes had higher HbA1c, albumin/creatinine ratio, cholesterol, triglyceride, LDL-c, cIMT and renal arterial resistivity indices as well as the waist circumference & hip circumference.

Our patients with sclerodactyly have significantly thickened skin with skin thickness of 0.9 ± 0.09 mm, compared to patients without sclerodactyly and controls (skin thickness of 0.69 ± 0.07 mm and 0.68 ± 0.11 mm respectively, ($P = 0.0001$)). No significant difference was detected between patients without thickened waxy skin and control. Our findings are comparable to results of Seibold [8] who found skin changes in 34% of diabetic children compared with no skin changes in healthy children.

In the current study, the incidence of sclerodactyly was 19%, and this is in line with recent studies [16], [17] that revealed a decreased frequency of LJM and sclerodactyly in comparison with the frequency 2 decades ago. Lindsay JR et al., [17], revealed that the presence of LJM and sclerodactyly has decreased from 43% to 23% between the 1980s and 2002 ($P < 0.0001$) and related this to better glycemic control and care of diabetics. On the other hand, most old studies reported incidences of LJM and sclerodactyly ranging from 8% to 58% of patients and average prevalence was about 30% to 40% [10], [14], [15].

In the present study, people with diabetes with sclerodactyly showed a significant positive correlation with age of diabetic patients and HbA1c. These findings are in agreement with those of Derraik et al., [25] who found a relationship between poor glycemic control and thickness of the dermis ($p = 0.015$), with an estimated thickening of 87 µm with every 1% increase in HbA1c ($p < 0.0001$). On the other hand, Lo et al., [29] and Tüzün et al., [30] reported that there is no relation between HbA1c and skin thickness or diabetic sclerodactyly, respectively.

In the current study, male diabetic patients had significantly higher skin thickness. Systolic blood pressure, cholesterol, triglyceride and cIMT were significantly higher, while HDL-c was significantly lower in people with diabetes with positive skin thickness. These agree with Arkkila et al., [20] who reported that type 2 diabetic patients with LJM had 3.1 and 4 fold higher risk of coronary heart disease and cerebrovascular disease, respectively. Another study revealed that type 1 diabetic women with LJM were associated with subclinical macroangiopathy (greater cIMT and a higher risk of plaques). On the contrary,

diabetic men with LJM were more likely to have proteinuria, retinopathy, and hypertension [31].

In our study, people with diabetes with sclerodactyly had a relationship with microalbuminuria and no relation with resistivity index (RI). Amin et al., [19], reported that albumin to creatinine ratio was insignificantly higher in patients with LJM and microalbuminuria increase with increasing duration of the disease by 1.9 fold and Rosenbloom et al., [9] reported that patients had an increased risk of clinically apparent microvascular disease (retinopathy and nephropathy) by more than 3 fold. Fitzcharles et al., [18] found a similar but less dramatic association of the microvascular disease with LJM in adult patients with DM.

Sclerodactyly has the same pathogenetic link with systemic diabetic complications and ultrasound on the hand is easy, early detection of diabetic macrovascular and microvascular diseases which may be used as a screening method.

In conclusion, ultrasound is an easy method for diagnosis of sclerodactyly. Increased prevalence of sclerodactyly in diabetic patients is high, and it is related to the presence of macrovascular and microvascular complications. Sclerodactyly may be used as a marker for early detection of diabetic vascular complications.

We recommend frequent follow up of diabetic patients for early detection of sclerodactyly in uncontrolled diabetic patients that could be an alarming sign for microalbuminuria, hypertension, hyperlipidaemia and atherosclerosis.

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