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OBJECTIVE

The development of periarticular thickening of skin on the hands and limited joint mobility (cheiroarthropathy) is associated with diabetes and can lead to significant disability. The objective of this study was to describe the prevalence of cheiroarthropathy in the well-characterized Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) cohort and examine associated risk factors, microvascular complications, and the effect of former DCCT therapy (intensive [INT] vs. conventional [CONV]) on its development.

RESEARCH DESIGN AND METHODS

This cross-sectional analysis was performed in 1,217 participants (95% of the active cohort) in EDIC years 18/19 after an average of 24 years of follow-up. Cheiroarthropathy—defined as the presence of any one of the following: adhesive capsulitis, carpal tunnel syndrome, flexor tenosynovitis, Dupuytren's contracture, or a positive prayer sign—was assessed using a targeted medical history and standardized physical examination. A self-administered questionnaire (Disabilities of the Arm, Shoulder and Hand [DASH]) assessed functional disability.

RESULTS

Cheiroarthropathy was present in 66% of subjects (64% of the INT group and 68% of the CONV group; $P = 0.1640$) and was associated with age, sex, diabetes duration, skin intrinsic fluorescence, HbA_{1c}, neuropathy, and retinopathy ($P < 0.005$ for each). DASH functional disability scores were worse among subjects with cheiroarthropathy ($P < 0.0001$).

CONCLUSIONS

Cheiroarthropathy is common in people with type 1 diabetes of long duration (~30 years) and is related to longer duration and higher levels of glycemia. Clinicians should include cheiroarthropathy in their routine history and physical examination of patients with type 1 diabetes because it causes clinically significant functional disability.

Several musculoskeletal disorders of the upper extremities have been shown to be associated with type 1 diabetes (1–3) and can lead to painful and disabling limitations (4–6). Diabetic cheiroarthropathy is a condition characterized by thickened skin and limited mobility of the joints in the hands and fingers, leading to flexion contractures such as Dupuytren's contracture and flexor tenosynovitis, or trigger finger. Adhesive capsulitis of the shoulder also occurs more frequently in people with diabetes when compared with nondiabetic subjects (1,7,8) and may have a similar pathogenesis to the other musculoskeletal disorders being described.

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Accumulation of advanced glycation end products (AGEs) in collagen has been proposed as the underlying cause of these conditions (9,10). In addition, carpal tunnel syndrome has long been associated with diabetes and is thought to be related to both glycation of connective tissues and diabetic neuropathy. In this study we use the term *cheiroarthropathy* to encompass all of the musculoskeletal disorders of the upper extremities described above, including a positive prayer sign.

The Diabetes Control and Complications Trial (DCCT) (11) and its observational follow-up, the Epidemiology of Diabetes Interventions and Complications (EDIC) study (12), provide a unique opportunity to examine the prevalence of and factors associated with cheiroarthropathy in a well-characterized cohort of participants with type 1 diabetes that has been followed over an average of 24 years. The specific aims of the current cross-sectional study were to describe the prevalence of cheiroarthropathy in the DCCT/EDIC cohort, examine the effect of assigned therapy during DCCT (intensive [INT] vs. conventional [CONV]), describe predisposing risk factors including time-weighted HbA_{1c}, and explore the association with other diabetes-related microvascular complications such as retinopathy, nephropathy, and neuropathy.

RESEARCH DESIGN AND METHODS

Subjects

The DCCT (1983–1993) demonstrated the beneficial effects of INT insulin therapy on preventing the onset and delaying the progression of long-term complications of type 1 diabetes (11). At entry into the DCCT, the 1,441 subjects, aged 13–39 years with a duration of type 1 diabetes from 1 to 15 years, were generally healthy. The subjects were randomly assigned to CONV or INT therapy and were followed for a mean of 6.5 years; the specifics of this therapy have been previously described in detail (11). The DCCT comprised two cohorts: the primary prevention cohort had diabetes for 1–5 years, no retinopathy, and urinary albumin excretion $<$40 mg/24 h, and the secondary intervention cohort had diabetes for 1–15 years, very mild to moderate nonproliferative retinopathy, and urinary albumin excretion $\leq$200 mg/24 h at baseline (11).

At the end of the DCCT, subjects in the CONV treatment group were taught INT therapy and all subjects were encouraged to perform INT therapy. In 1994, 1,375 (95%) of the surviving DCCT subjects enrolled in the EDIC study, the DCCT's observational follow-up study (1994 to the present). At EDIC years 18/19 (2011–2012), 1,217 of the 1,281 active EDIC participants (95%) enrolled in this cheiroarthropathy study, which was approved by the institutional review boards of all participating centers.

Study Design

This cross-sectional study was conducted during an annual examination for the EDIC study. Cheiroarthropathy was assessed by a targeted clinical history, self-administered questionnaire, and physical assessment. The targeted history was obtained by trained study staff using an investigator-designed questionnaire (Supplementary Data). The questions addressed symptoms and/or diagnosis, treatment, and treatment response related to adhesive capsulitis, carpal tunnel syndrome, tenosynovitis, and Dupuytren's contracture.

A self-administrated and previously validated questionnaire, Disabilities of the Arm, Shoulder and Hand (DASH) (13), was completed by the subjects. This 30-item questionnaire measures function of the upper limbs using a 5-point scale, with a total score ranging from 0 to 100. Higher values represent more functional disability (14). DASH questions also assess physical health, pain, and social/emotional health (14).

The physical assessment included visual screening for a positive prayer sign (limited joint mobility preventing palmar surfaces of the hands from lying flat against each other in opposition). Subjects with a positive prayer sign also had finger extension measured with goniometry unless excluded by a history of injury (e.g., fractured fingers) with residual deformity, stroke with persistent physical limitations, or deformities from rheumatoid arthritis. All subjects had bilateral shoulder flexion measured unless there was a history of stroke, shoulder surgery, or shoulder injury with residual limitations. Hand and shoulder measurements were performed using two standard plastic goniometers (Patterson Medical, Bolingbrook, IL). Study coordinators were trained and certified to perform the measurements by a board-certified hand therapist. To determine intrarater reliability, goniometer measurements were performed twice for each shoulder and twice for each digit. Differences between the first and second measurements at each location were compared. If the first and second measurements differed by $\geq$15 degrees in the shoulder or $\geq$10 degrees in the fingers, third and fourth measurements were obtained. The average of the first two measurements (or the third and fourth, when taken) were used for analysis.

Biomedical Evaluations and Assessment of Diabetes Complications

Biomedical evaluations such as physical examination, medical history, routine laboratory tests (HbA_{1c}, lipids), and assessment of diabetes complications have been described elsewhere in detail (12,15).

The degree of collagen glycation was measured as skin autofluorescence (16,17). Skin autofluorescence measurements were obtained on the underside of the forearm near the elbow using a skin fluorescence spectrometer (18).

Statistical Methods

Demographic and clinical characteristics were compared between those with and without cheiroarthropathy using the Wilcoxon rank sum test for ordinal and numeric variables and the χ^2 test for categorical variables. Similarly, the clinical characteristics associated with the individual components of cheiroarthropathy were analyzed. The prevalence of any cheiroarthropathy and of the individual elements was expressed as a percentage of the total cohort of subjects who participated in this cheiroarthropathy study. The coprevalence of the individual elements is described in the RESULTS and Supplementary Table 2.

The characteristics of interest for further risk factor analyses were age, sex, duration of diabetes, cohort assignment, time-weighted DCCT/EDIC HbA_{1c}, and the degree or presence of retinopathy, nephropathy, or neuropathy. Logistic regression models were used to assess the association among risk factors, microvascular complications, and the presence of cheiroarthropathy. Three separate multivariable logistic regression models were used to assess the effect of each microvascular complication (neuropathy, nephropathy, and retinopathy) after adjusting for age,

sex, duration of diabetes, and time-weighted DCCT/EDIC HbA_{1c}.

Mean functional disability scores from the DASH were presented for selected characteristics. The differences between sex, DCCT treatment group, tertiles of time-weighted HbA_{1c}, cheiroarthropathy status, and total number of cheiroarthropathies was evaluated using the Wilcoxon rank sum test. The Kruskal-Wallis test was used for characteristics that were divided into two or more groups. The same characteristics and methods were used to evaluate group differences in mean shoulder flexion.

RESULTS

The characteristics of the study cohort at the time of the cheiroarthropathy assessment are shown in Table 1. The study population had an average age of 52 years, and mean duration of type 1 diabetes was 31 years. Cheiroarthropathy, defined as any one of the following abnormalities: adhesive capsulitis, carpal tunnel syndrome, tenosynovitis, Dupuytren's contracture, or a positive prayer sign, was present in 807 of the subjects (66%). The most common type of cheiroarthropathy was adhesive capsulitis, found in 372 of the subjects (31%), followed by carpal tunnel syndrome (n = 362; 30%), flexor tenosynovitis (n = 340; 28%), positive prayer sign (n = 251; 22%), and Dupuytren's contracture (n = 105; 9%). Of the participants, 400 (33%) had one type of cheiroarthropathy by report or had a positive prayer sign based on examination; 241 participants (20%) had two types of cheiroarthropathy, 124 (10%) had three, and 42 (3%) had four or five. Among those with two types of cheiroarthropathy, the most common combinations were carpal tunnel syndrome and flexor tenosynovitis (31%) followed by the combination of carpal tunnel syndrome and adhesive capsulitis (17%).

The demographic and clinical characteristics of those with and without cheiroarthropathy are presented in Table 1. Subjects with cheiroarthropathy were older (52.7 ± 6.6 vs. 51.3 ± 7.3 years old; P = 0.0017) and more likely to be female (53% vs. 38%; $P < 0.0001$). The presence of cheiroarthropathy also was associated with a longer duration of diabetes; higher mean DCCT/EDIC HbA_{1c}; the presence of other diabetes-related complications, specifically neuropathy and retinopathy ($P < 0.0001$); and higher levels of skin intrinsic fluorescence (P = 0.0052).

Cheiroarthropathy was examined by DCCT treatment group (INT vs. CONV therapy). Adhesive capsulitis, flexor tenosynovitis, and Dupuytren's contracture were more frequent in the CONV group (P = 0.05), whereas there was no difference by treatment group in the frequency of carpal tunnel syndrome or the presence of a positive prayer sign. Cheiroarthropathy was less likely to occur in the primary prevention cohort than in the secondary intervention cohort ($P < 0.0001$) (Table 1). Examination of the prevalence of the types of cheiroarthropathy by tertiles of time-weighted DCCT/EDIC HbA_{1c} measured between 1983 and 2011 showed the proportion of each cheiroarthropathy to be progressively higher with higher mean HbA_{1c} levels (Fig. 1).

Table 2 presents the odds of cheiroarthropathy for various risk factors and microvascular complications. The association between the presence

Table 1—Characteristics of subjects with and without cheiroarthropathy

Characteristics	Total (n = 1,217)	Cheiroarthropathy present (n = 807)	Cheiroarthropathy absent (n = 410)	P value
Age (years)	52.2 ± 6.9	52.7 ± 6.6	51.3 ± 7.3	0.0017
Female sex	584 (48)	430 (53)	154 (38)	<0.0001
Menopause*	300 (55)	232 (57)	68 (48)	0.0494
Married or remarried	880 (73)	584 (73)	296 (73)	0.9724
Duration of diabetes (years)	31.1 ± 4.9	31.9 ± 5.0	29.5 ± 4.3	<0.0001
BMI (kg/m^2)	28.8 ± 5.5	28.7 ± 5.5	28.8 ± 5.4	0.9931
Obese (BMI ≥30 kg/m^2)	411 (35)	281 (36)	130 (33)	0.3422
DCCT INT therapy	616 (51)	397 (49)	219 (53)	0.1640
Primary cohort†	607 (50)	351 (43)	256 (62)	<0.0001
Current smoker	136 (11)	95 (12)	41 (10)	0.3567
HbA_{1c} [% (mmol/mol)]				
Time-weighted DCCT/EDIC	8.0 ± 1.0 (63.8 ± 10.5)	8.1 ± 1.0 (64.5 ± 10.5)	7.9 ± 0.9 (62.3 ± 10.3)	0.0004
During DCCT	8.1 ± 1.4 (64.8 ± 15.3)	8.1 ± 1.4 (65.3 ± 15.4)	8.0 ± 1.4 (63.9 ± 15.0)	0.1356
During EDIC	8.0 ± 1.0 (63.4 ± 11.1)	8.0 ± 1.0 (64.2 ± 11.1)	7.8 ± 1.0 (61.8 ± 11.0)	0.0002
Skin intrinsic fluorescence (AU)‡	22.6 ± 4.7	22.9 ± 4.7	22.1 ± 4.7	0.0052
Neuropathy§	327 (29)	250 (34)	77 (21)	<0.0001
Nephropathy||	168 (14)	112 (14)	56 (14)	0.9162
Retinopathy¶	255 (21)	201 (25)	54 (13)	<0.0001

Data are mean ± SD or n (%). The P value evaluates the difference between subjects with and without cheiroarthropathy using the Wilcoxon rank sum test for ordinal and numeric characteristics or the contingency χ^2 test for categorical characteristics. *Data on menopause were available for 546 women (404 with cheiroarthropathy present and 142 with cheiroarthropathy absent). †The primary prevention cohort consisted of subjects with type 1 diabetes for 1–5 years and no diabetes-related complications (no microaneurysms on fundus photography and urine albumin excretion <40 mg/day). The secondary intervention cohort consisted of subjects with type 1 diabetes for 1–15 years, mild to moderate nonproliferative retinopathy, and a urinary albumin excretion rate <200 mg/day. ‡AU represents arbitrary relative fluorescence units as a function of excitation wavelength measured in 1,145 subjects at EDIC years 16/17. §Neuropathy is defined as the presence of confirmed clinical neuropathy, measured in 1,119 subjects at EDIC years 13/14. ||Nephropathy is defined as an albumin excretion rate ≥30 mg/24 h at 2 consecutive visits. ¶Retinopathy is defined as a self-reported history of scatter laser treatment to one or both eyes.

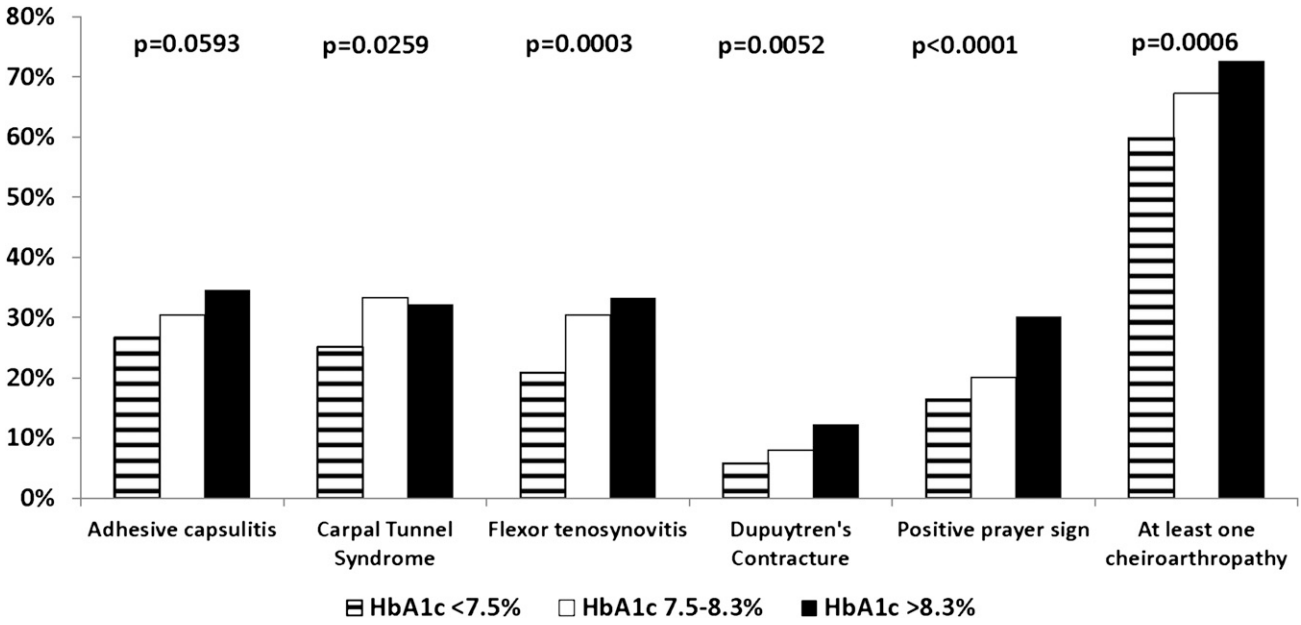

Figure 1—Association of prevalence of cheiroarthropathy by tertiles of time-weighted HbA_{1c} during the DCCT/EDIC (1983–2011). Subjects could report more than one type of cheiroarthropathy. The *P* values estimate the HbA_{1c} group differences calculated using the contingency χ^2 test for categorical variables. Twenty subjects were missing an HbA_{1c} measurement at EDIC year 18.

of cheiroarthropathy and age, sex, duration of diabetes, or HbA_{1c} did not change substantially and remained significant after adjustment for retinopathy, neuropathy, or nephropathy. The associations of cheiroarthropathy with neuropathy remained significant in a multivariable model adjusting for the other significant risk factors, whereas the association with retinopathy remained nominally significant ($P = 0.0547$). The odds of cheiroarthropathy were 1.60 times higher (95% CI 1.14–2.24) for subjects with neuropathy and 1.45 times higher (95% CI 0.99–2.11) for subjects with retinopathy after adjusting for age, sex, duration of diabetes, and time-weighted DCCT/EDIC HbA_{1c}.

A subgroup analysis was performed to determine whether the demographic and clinical characteristics differed among the individual components of cheiroarthropathy (Supplementary Table 1). Although there were some differences in clinical characteristics among the components of cheiroarthropathy, the trend of the associations was more consistent than not. As with the combined definition, the presence of the individual components was generally associated with older age, longer duration of diabetes, female sex, and higher HbA_{1c} and skin fluorescence levels. Not all of the associations in the analysis of the components were statistically significant, possibly because of the smaller number of cases and reduced power.

In addition, we examined the demographic and clinical characteristics of those subjects with one, two or three, and four or five components of cheiroarthropathy (Supplementary Table 2) Analyses were limited by the relatively small number of subjects with four or five components ($n = 42$). However, subjects with longer duration of diabetes, assignment to CONV therapy during DCCT, higher HbA_{1c} and skin fluorescence, and the occurrence of retinopathy and neuropathy all were associated with an increased frequency of these cheiroarthropathy components, in a graded fashion.

DASH disability scores were higher in women than in men (13.5 vs. 8.3; $P < 0.0001$) (Table 3). The presence of any cheiroarthropathy was associated with higher DASH scores, reflecting more functional limitation, and there was a progressive effect on functional limitation with the presence of more elements of cheiroarthropathy ($P < 0.0001$). DASH scores also were associated with glycemia: those with higher HbA_{1c} levels had higher DASH scores ($P < 0.0001$). Similar to the relationship between HbA_{1c} levels and cheiroarthropathy, higher HbA_{1c} levels were associated with worse DASH scores. There were no differences in DASH scores between the DCCT INT and CONV treatment groups. Cheiroarthropathy had an adverse effect on DASH work capacity, similar to the effect on overall DASH scores. Cheiroarthropathy also adversely affected other activities such as sports and performing arts, as indicated by the DASH sports and performing arts scores.

The goniometer measurements of shoulder flexion revealed generally less flexibility in the right shoulder (right hand dominance in 90%) (Table 3). The CONV therapy group had reduced right shoulder flexion when compared with the INT group. Higher HbA_{1c} levels were associated with reduced flexion in both shoulders. Finally, the presence of any cheiroarthropathy and the number of cheiropathic abnormalities were associated with significantly less flexion.

CONCLUSIONS

Musculoskeletal disorders involving the hands and shoulders that may result from the accumulation of AGEs have been shown in previous studies to occur more frequently in individuals with diabetes compared with those without diabetes (1,2,19). Compared with hyperglycemia-associated complications affecting the eyes, kidneys, peripheral and autonomic nervous system, heart, and brain, this constellation of long-term complications has received

almost no attention in clinical research and likely is underappreciated in clinical care. Using this well-phenotyped cohort of patients with type 1 diabetes, we have demonstrated that cheiroarthropathy affecting the hands and shoulders is extremely common and possibly exceeds the prevalence of retinopathy, nephropathy, neuropathy, and cardiovascular disease. These musculoskeletal disorders often cause pain and functional limitations, as we have shown with the validated, self-administered DASH Disability and Symptom score, and may affect the ability to perform routine daily activities (4–6); however, patients and health care providers may not be aware of these potentially treatable complications (3). For example, clinical care guidelines such as the American Diabetes Association's Clinical Practice Recommendations (20) recommend regular and frequent assessments of the eyes, kidneys, and cardiovascular and nervous systems, but there is little mention of musculoskeletal disorders and no recommendations for routine monitoring of signs or symptoms suggestive of cheiroarthropathy.

Cheiroarthropathy was present in 66% of the DCCT/EDIC participants after a mean diabetes duration of 30 years. Adhesive capsulitis in the shoulder occurred most frequently (31%), followed by carpal tunnel syndrome (30%), flexor tenosynovitis (28%), positive prayer sign (22%), and Dupuytren's contracture (9%). Of the participants, 33% had two or more musculoskeletal disorders; the most common combination was carpal tunnel syndrome plus flexor tenosynovitis. In a prior study of 100 patients with type 1 diabetes (mean duration 22 years), 43% had cheiroarthropathy, and 10% had both hand and shoulder disorders (1). The relative frequency of musculoskeletal disorders in this smaller study differed from our findings in that Dupuytren's contracture and trigger finger were most common and occurred with equal frequency, followed by adhesive capsulitis and carpal tunnel syndrome. A recent epidemiological review of conditions causing limited joint mobility in patients with diabetes shows higher prevalence of frozen shoulder, stiff hand syndrome, Dupuytren's contracture, and trigger finger when compared with the general population (19).

Table 2—Modeling associations among risk factors, microvascular complications, and the presence of cheiroarthropathy

	Univariate models		Adjusted models*					
			Model 1		Model 2		Model 3	
Characteristics	OR (95% CI)	Wald χ^2	OR (95% CI)	Wald χ^2	OR (95% CI)	Wald χ^2	OR (95% CI)	Wald χ^2
Age (per 10 years)	1.36 (1.14–1.62)	11.73	1.30 (1.07–1.59)	6.83	1.38 (1.14–1.66)	11.33	1.38 (1.14–1.66)	11.23
Sex (female vs. male)	1.90 (1.49–2.42)	26.61	2.07 (1.58–2.70)	27.77	1.91 (1.47–2.47)	23.70	1.97 (1.52–2.54)	26.72
Duration of diabetes (per 10 years)	2.87 (2.19–3.76)	58.49	2.53 (1.89–3.38)	39.19	2.81 (2.12–3.72)	52.29	2.60 (1.95–3.47)	42.37
Cohort assignment (primary vs. secondary)‡	0.46 (0.36–0.59)	38.37	—	—	—	—	—	—
Time-weighted DCCT/EDIC HbA_{1c} (per 1%)	1.25 (1.10–1.43)	11.58	1.25 (1.07–1.46)	8.22	1.37 (1.18–1.59)	17.56	1.26 (1.09–1.46)	9.40
Neuropathy (yes vs. no)§	1.95 (1.45–2.61)	19.87	1.60 (1.14–2.24)	7.51	—	—	—	—
Nephropathy (yes vs. no)‖	1.02 (0.72–1.44)	0.01	—	—	0.85 (0.57–1.26)	0.68	—	—
Retinopathy (yes vs. no)¶	2.19 (1.58–3.04)	21.90	—	—	—	—	1.45 (0.99–2.11)	3.69

Data are odds ratios (95% CIs) and Wald χ^2 statistics. *Data are from eight separate univariate logistic regression models. †Models 1–3 represent three separate multivariable logistic regression models. Model 1 uses the presence vs. absence of neuropathy as a predictor of cheiroarthropathy after adjusting for age, sex, duration of diabetes, and time-weighted DCCT/EDIC HbA_{1c}. Models 2 and 3 use nephropathy and retinopathy, respectively. ‡Cohort assignment is defined by diabetes duration, as described in the RESEARCH DESIGN AND METHODS. The effect of diabetes duration is the same in both the primary and secondary cohorts. Since cohort assignment and diabetes duration are highly correlated and the effect of diabetes duration is diluted in the presence of cohort assignment, only diabetes duration was included in the three multivariable regression models. §Neuropathy is defined as the presence of confirmed clinical neuropathy measured in 1,119 subjects at EDIC years 13/14. ‖Nephropathy is defined as an albumin excretion rate ≥30 mg/24 h at 2 consecutive visits. ¶Retinopathy is defined as self-reported history of scatter laser treatment to one or both eyes.

Table 3—DASH functional disability scores and mean shoulder flexion (degrees) by selected characteristics of type 1 diabetes

Characteristics	DASH functional disability scores						Shoulder flexion*			
	Disability & symptom module (n = 1,203)		Work module† (n = 1,024)		Sports & performing arts module† (n = 483)		Right shoulder (n = 1,170)		Left shoulder (n = 1,153)	
	Mean ± SD	P value	Mean ± SD	P value	Mean ± SD	P value	Mean ± SD	P value	Mean ± SD	P value
Patients, n	10.8 ± 13.2		7.3 ± 13.9		13.7 ± 22.8		146.58 ± 16		148.26 ± 16	
Sex										
Males	8.3 ± 10.6	<0.0001	6.2 ± 12.3	0.0202	12.7 ± 21.5	0.3434	146.61 ± 15	0.5642	148.23 ± 16	0.9639
Females	13.5 ± 15.0		8.6 ± 15.4		15.6 ± 25.2		146.55 ± 18		148.29 ± 16	
Treatment group										
INT	10.3 ± 12.5	0.1287	7.5 ± 14.0	0.9409	14.1 ± 23.3	0.9232	147.55 ± 16	0.0391	148.42 ± 16	0.6425
CONV	11.4 ± 13.8		7.1 ± 13.7		13.3 ± 22.4		145.56 ± 17		148.09 ± 16	
Time-weighted DCCT/EDIC HbA_{1c} (%)										
<7.5	7.3 ± 9.7	<0.0001	5.0 ± 11.1	<0.0001	10.5 ± 19.9	0.0245	148.84 ± 16	0.0033	150.57 ± 15	0.0003
7.5–8.3	11.5 ± 14.4		7.0 ± 13.2		15.4 ± 23.4		146.12 ± 17		148.69 ± 16	
>8.3	13.6 ± 13.9		10.1 ± 16.4		16.5 ± 25.8		144.94 ± 17		145.60 ± 17	
Cheiroarthropathy status										
Absent	6.4 ± 10.3		4.0 ± 9.9		9.1 ± 19.7		149.74 ± 17	<0.0001	150.98 ± 16	<0.0001
Present	13.1 ± 13.9	<0.0001	9.1 ± 15.2	<0.0001	16.5 ± 24.2	<0.0001	144.98 ± 16		146.89 ± 16	
Total cheiroarthropathies (n)										
0	6.4 ± 10.3	<0.0001	4.0 ± 9.9	<0.0001	9.1 ± 19.7	<0.0001	149.74 ± 17	<0.0001	150.98 ± 16	<0.0001
1	9.7 ± 10.8		6.1 ± 11.3		12.7 ± 20.2		145.72 ± 16		147.94 ± 16	
≥2	16.4 ± 15.7		12.2 ± 18.0		20.6 ± 27.3		144.25 ± 16		145.86 ± 16	

The P values evaluate the group differences using the Wilcoxon rank sum test for quantitative variables. The Kruskal-Wallis test is used for time-weighted DCCT/EDIC HbA_{1c} and the total number of cheiroarthropathies. *Lower values reflect less shoulder flexion, that is, a limited range of motion. Subjects with a history of stroke, shoulder surgery, or previous shoulder injury with residual limitations were excluded. Subjects with out-of-range values (<35 or >180 degrees) also were excluded. †This module was completed only by subjects who worked and/or who participated in sports or performing arts.

In previous studies, advanced age, longer duration of diabetes, worse degree of glycemic control, and the presence of microvascular complications have been observed as risk factors for cheiroarthropathy in type 1 diabetes (2). We have confirmed these observations and with our large DCCT/EDIC cohort have been able to quantify the risk associated with these factors (Table 2). In addition, we have indentified female sex and the occurrence of neuropathy and retinopathy, but not nephropathy, as being associated with cheiroarthropathy ($P < 0.0005$ for all) (Table 1). These same risk factors apply fairly consistently across the individual components of cheiroarthropathy that we examined.

Whether the coprevalence of microvascular and musculoskeletal complications reflects shared pathogenesis ("common soil"), such as the role of HbA_{1c} levels in both, or is confounded by factors such as longer duration is not clear. The adjusted analyses (Table 2) support the independent effects of duration of diabetes, HbA_{1c} levels, and microvascular complications on the prevalence of cheiroarthropathy. The effects of neuropathy and retinopathy were slightly reduced in the adjusted models but still significant for neuropathy ($P = 0.01$) and marginally significant for retinopathy ($P = 0.0547$).

Of note, although the musculoskeletal disorders were associated with glycemic control (time weighted during DCCT/EDIC and during EDIC), INT therapy during the DCCT was not consistently significantly associated with the elements of cheiroarthropathy. Whether the absence of an effect of previous INT treatment on aggregate cheiroarthropathy was secondary to heterogeneity among the elements and their relationship with INT therapy or to other factors is unknown. However, the more consistent relationship of aggregate cheiroarthropathy and its elements with HbA_{1c} levels suggests an important relationship with glycemic control.

The limitations of our study include the possibility that the DCCT/EDIC cohort is too unique to be generalizable to the nonstudy population with type 1 diabetes; a careful selection process was used at the time of enrollment, and subjects who commit to longitudinal clinical trials tend to be more highly motivated and engaged than the general population. These factors

can potentially provide a positive influence on the participants' health. On the other hand, the prevalence of cheiroarthropathy documented herein may be an underestimate, to the extent that the DCCT/EDIC cohort, and especially the INT treatment group during the DCCT, may have been more aggressively managed than the general population with type 1 diabetes, thereby preventing this complication in some subjects. In addition, our study was cross-sectional, so we can only describe prevalence after substantial exposure to diabetes, not incidence. Finally, use of a positive prayer sign as an indicator of cheiroarthropathy may have introduced some inaccuracy into our classification since prior treatment for Dupuytren's contracture or flexor tenosynovitis may render a previously positive prayer sign negative. The strength of the study is the large number of the subjects, who were carefully phenotyped with standardized and validated methods.

Previous small studies have demonstrated that cheiroarthropathy is a complication of type 1 diabetes (1). This study establishes the high prevalence of specific musculoskeletal disorders and risk factors and their adverse effect on functionality. Lower levels of glycemia should reduce the risk of developing these sometimes disabling complications, as it has reduced other type 1 diabetes complications (21). Surveillance for musculoskeletal disorders should be added to the recommendations for the routine care of people with type 1 diabetes.

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