Musculoskeletal Complications in Type 1 Diabetes

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Musculoskeletal Complications in Type 1 Diabetes

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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, HbA1c, 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.
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 HbA1c, 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 ≤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-administered 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 ≥15 degrees in the shoulder or ≥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 (HbA1c, 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 χ2 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 HbA1c, 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 (nephropathy, nephropathy, and retinopathy) after adjusting for age,
sex, duration of diabetes, and time-weighted DCCT/EDIC HbA1c.

Mean functional disability scores from the DASH were presented for selected characteristics. The differences between sex, DCCT treatment group, tertiles of time-weighted HbA1c, 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 HbA1c; 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 HbA1c measured between 1983 and 2011 showed the proportion of each cheiroarthropathy to be progressively higher with higher mean HbA1c levels (Fig. 1).

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

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**Table 1—Characteristics of subjects with and without cheiroarthropathy**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (n = 1,217)</th>
<th>Cheiroarthropathy present (n = 807)</th>
<th>Cheiroarthropathy absent (n = 410)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52.2 ± 6.9</td>
<td>52.7 ± 6.6</td>
<td>51.3 ± 7.3</td>
<td>0.0017</td>
</tr>
<tr>
<td>Female sex</td>
<td>584 (48)</td>
<td>430 (53)</td>
<td>154 (38)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Menopause*</td>
<td>300 (55)</td>
<td>232 (57)</td>
<td>68 (48)</td>
<td>0.0494</td>
</tr>
<tr>
<td>Married or remarried</td>
<td>880 (73)</td>
<td>584 (73)</td>
<td>296 (73)</td>
<td>0.9724</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>31.1 ± 4.9</td>
<td>31.9 ± 5.0</td>
<td>29.5 ± 4.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.8 ± 5.5</td>
<td>28.7 ± 5.5</td>
<td>28.8 ± 5.4</td>
<td>0.9931</td>
</tr>
<tr>
<td>Obese (BMI ≥30 kg/m²)</td>
<td>411 (35)</td>
<td>281 (36)</td>
<td>130 (33)</td>
<td>0.3422</td>
</tr>
<tr>
<td>DCCT INT therapy</td>
<td>616 (51)</td>
<td>397 (49)</td>
<td>219 (53)</td>
<td>0.1640</td>
</tr>
<tr>
<td>Primary cohort†</td>
<td>607 (50)</td>
<td>351 (43)</td>
<td>256 (62)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Current smoker</td>
<td>136 (11)</td>
<td>95 (12)</td>
<td>41 (10)</td>
<td>0.3567</td>
</tr>
<tr>
<td>Hba1c [% (mmol/mol)]</td>
<td></td>
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<tr>
<td>Time-weighted DCCT/EDIC</td>
<td>8.0 ± 1.0 (63.8 ± 10.5)</td>
<td>8.1 ± 1.0 (64.5 ± 10.5)</td>
<td>7.9 ± 0.9 (62.3 ± 10.3)</td>
<td>0.0004</td>
</tr>
<tr>
<td>During DCCT</td>
<td>8.1 ± 1.4 (64.8 ± 15.3)</td>
<td>8.1 ± 1.4 (65.3 ± 15.4)</td>
<td>8.0 ± 1.4 (63.9 ± 15.0)</td>
<td>0.1356</td>
</tr>
<tr>
<td>During EDIC</td>
<td>8.0 ± 1.0 (63.4 ± 11.1)</td>
<td>8.0 ± 1.0 (64.2 ± 11.1)</td>
<td>7.8 ± 1.0 (61.8 ± 11.0)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Skin intrinsic fluorescence (AU)§</td>
<td>22.6 ± 4.7</td>
<td>22.9 ± 4.7</td>
<td>22.1 ± 4.7</td>
<td>0.0052</td>
</tr>
<tr>
<td>Neuropathy‡</td>
<td>327 (29)</td>
<td>250 (34)</td>
<td>77 (21)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Nephropathy¶</td>
<td>168 (14)</td>
<td>112 (14)</td>
<td>56 (14)</td>
<td>0.9162</td>
</tr>
<tr>
<td>Retinopathy¶</td>
<td>255 (21)</td>
<td>201 (25)</td>
<td>54 (13)</td>
<td>&lt;0.0001</td>
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</table>

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 χ² 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 prevention 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. ‡ 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.
of cheiroarthropathy and age, sex, duration of diabetes, or HbA1c 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 HbA1c.

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 HbA1c 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 HbA1c, 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 glycaemia: those with higher HbA1c levels had higher DASH scores (P < 0.0001). Similar to the relationship between HbA1c levels and cheiroarthropathy, higher HbA1c 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 HbA1c 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

Figure 1—Association of prevalence of cheiroarthropathy by tertiles of time-weighted HbA1c during the DCCT/EDIC (1983–2011). Subjects could report more than one type of cheiroarthropathy. The P values estimate the HbA1c group differences calculated using the contingency \( \chi^2 \) test for categorical variables. Twenty subjects were missing an HbA1c measurement at EDIC year 18.
Cheiroarthropathy was present in 65% of patients with type 1 diabetes, mean duration of diabetes was 30 years. A recent epidemiological review of conditions causing limited joint mobility in the general population (15) showed no evidence of increased prevalence of frozen shoulder, stiff hand, and trigger finger when compared with the general population (15). A recent epidemiological review of conditions caused by diabetes and new onset rheumatoid arthritis (16) also showed no increased prevalence.

Table 2—Modeling associations among factors, macrovascular complications, and the presence of cheiroarthropathy.

<table>
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<th>Characteristics</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
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<tbody>
<tr>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
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</table>

Adjusted models.
In previous studies, advanced age, longer duration of diabetes, worse glycemic control, and the presence of diabetic microvascular complications have been observed as risk factors for the development of microvascular complications (1). In type 1 diabetes, we have identified factors associated with the risk of developing neuropathy and retinopathy, but not nephropathy, that we examined. These factors include the presence of microvascular complications, which reflect shared pathogenesis, and the prevalence of retinopathy. The prevalence of retinopathy was marginally significant (P = 0.01), and marginally significant for retinopathy (P = 0.005) in the adjusted analyses (Table 2). The adjusted analyses (Table 2) suggest that diabetes duration, glycemic control, and microvascular complications are associated with the risk of developing retinopathy. In addition to these factors, we have identified female sex as a risk factor for retinopathy. The adjusted analyses (Table 2) show that diabetes duration, glycemic control, and microvascular complications are associated with the risk of developing retinopathy. In conclusion, diabetes duration, glycemic control, and microvascular complications are associated with the risk of developing retinopathy.
can potentially provide a positive influence on the participants’ health. On the other hand, the prevalence of chiroarthropathy documented herein may be an underestimation, 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 chiroarthropathy 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 chiroarthropathy 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 glycosuria 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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The DASH Outcome Measure and the QuickDASH are the property of the Institute for Work & Health (IWH). These instruments were jointly developed by the IWH and the American Academy of Orthopaedic Surgeons. The project was supported by the American Association for Hand Surgery, the American Orthopaedic Society for Sports Medicine, American Shoulder and Elbow Surgeons, the American Society for Surgery of the Hand, the Arthroscopy Association of North America, and the American Society of Plastic Surgeons. The DASH is currently administered by the IWH. Permission for use in this study was granted on 6 October 2010.

Industry contributors have had no role in the DCCT/EDIC study but have provided free or discounted supplies or equipment to support participants’ adherence to the study: Abbott DiabetesCare (Alameda, CA); Animas (Westchester, PA); Bayer Diabetes Care (North America Headquarters, Tarrytown, NY); Becton Dickinson (Franklin Lakes, NJ); CanAm (Atlanta, GA); Eli Lilly (Indianapolis, IN); LifeScan (Milpitas, CA); Medtronic Diabetes (Minneapolis, MN); Nova DiabetesCare (Billericia, MA); Omron (Shelton, CT); OmniPod Insulin Management System (Bedford, MA); Roche Diabetes Care (Indianapolis, IN); and Sanofi (Bridgewater, NJ).

Duality of Interest. No potential conflicts of interest relevant to this article were reported. Author Contributions. M.E.L., A.B., J.H., P.G., E.G., J.L., and G.L. wrote the manuscript. B.B.H. researched data, performed analyses, and wrote the manuscript. P.A.C., C.M., and D.M.N. researched the data and wrote the manuscript. L.D. researched the data. M.E.L. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Portions of these data were presented in poster form at the 72nd Scientific Sessions of the American Diabetes Association, Philadelphia, PA, 8–12 June 2012.

References