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ORIGINAL ARTICLE

An overlooked rheumatologic manifestation of diabetes: diabetic cheiroarthropathy

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Abstract

Objectives The objectives of the study were to analyze the clinical characteristic of diabetic cheiroarthropathy (DCA) in patients with type 1 diabetes mellitus (DM), type 2 DM, and prediabetes and to evaluate the frequency of DCA among groups.

Method The cross-sectional study was conducted at the Division of Endocrinology and Metabolism outpatient clinic over a 14-month period. A total of 239 patients (160 female, 79 male), who had type 1 DM, type 2 DM, and prediabetes, were enrolled. The demographics, clinical variables, and laboratory outcomes were recorded. Diabetic cheiroarthropathy was defined according to physical examination. The functional disability of patients with DCA was assessed by the self-administered questionnaire (disabilities of the arm, shoulder and hand-DASH).

Results Diabetic cheiroarthropathy was determined in 35.1% of all patients. The frequency of DCA was higher in patients with prediabetes ($x^2 = 0.009$, post hoc power = 0.794). According to the logistic regression analysis, prediabetes (OR = 4.52, 95% CI 2.16–9.47, $p < 0.001$), presence of polyneuropathy (OR = 3.82, 95% CI 1.61–9.07, $p = 0.002$), and fasting glucose level (OR = 1.01, 95% CI 1.00–1.01, $p = 0.004$) found as the most effective risk factors in determining DCA. DASH disability scores were significantly higher in prediabetic patients than that in type 2 DM group ($p = 0.021$).

Conclusion High frequency of DCA and impaired hand function are observed in prediabetic patients. Musculoskeletal manifestations can emerge as an early sign of diabetic status. Also, people who suffer from hand involvement should be examined for diabetes along with rheumatologic diseases.

Keywords Diabetes mellitus · Diabetic cheiroarthropathy · Function · Hand · Prediabetes

Introduction

Diabetic cheiroarthropathy (DCA), a musculoskeletal involvement of diabetes, is characterized by limited joint mobility in the hand and a waxy appearance of the skin on the dorsal side [1, 2]. Among patients affected by DCA, hand function is decreased due to contractures, stiffness, and occasionally pain. Consequent of these manifestations, DCA is frequently confused with rheumatologic disorders such as acute arthritis and systemic sclerosis [3, 4].

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The accurate mechanism of how diabetes mellitus affects the musculoskeletal system is still unknown. The pathogenesis of DCA is multifactorial, with reasons including overuse, inflammation, trauma, mechanical impingement, genetics, and changes of immunologic, biochemical, and endocrinologic conditions [5, 6]. The underlying causes and effects vary from person to person [6]. The fundamental two theories regarding the cause of DCA are the accumulation of advanced glycation end products in collagen and microvascular deterioration [1, 5]. According to glycation theory, increased cross-links between collagen molecules and nonenzymatic collagen glycosylation emerging from long-lasting hyperglycemia may give rise to the strengthening of collagen, thus developing tightness and stiffness of skin [5]. In the microvascular deterioration theory, microvascular impairment causing tissue hypoxia may lead to the release of oxygen free radicals, which stimulate overproduction of growth factors and cytokines leading to cellular hyperplasia [5, 6].

DCA is diagnosed clinically using the following two clinical signs: prayer sign and table top sign. Laboratory and imaging findings are not determinative for diagnosis [7]. DCA is determined in patients with type 1 diabetes mellitus (type 1 DM), type 2 diabetes mellitus (type 1 DM), and prediabetes as well [2, 8]. In the literature, DCA is frequently detected in young patients with type 1 DM and this fact could be explained with the duration and severity of the diabetic disease [2]. Nevertheless, there is limited data to show an association with prediabetes and DCA compared to type 1 DM and type 2 DM. An intermediate state of hyperglycemia with glycemic parameters between the normal and diabetes threshold is described as prediabetes and all complications of diabetes such as early neuropathy, nephropathy, and retinopathy can be observed in prediabetes [9].

To the best of our knowledge, DCA has not been studied in patients with prediabetes in the literature. Therefore, the objectives of the present study were to evaluate the frequency of DCA and to investigate the potential effect of clinical parameters and types of diabetes on the development of DCA.

Methods

Study design and population

The study design was cross-sectional. Patients who met the diagnosis and classification criteria of diabetes as proposed by the American Diabetes Association (ADA) were enrolled in the study. According to the ADA, prediabetes represents impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG). The diagnosis was based on ADA criteria as follows: (i) for diabetes, fasting plasma glucose ≥ 126 mg/dL or postprandial plasma glucose ≥ 200 mg/dL or HbA1c ≥6.5% and (ii) for prediabetes, IFG defined as fasting plasma glucose = 100–125 mg/dL or IGT defined as postprandial plasma glucose = 140–199 mg/dL [10].

The study was conducted at Cukurova University, Division of Endocrinology and Metabolism outpatient clinic over a 14-month-period. Written informed consent was obtained from each patient according to the Declaration of Helsinki. Exclusion criteria were as follows: (i) neurological disorders, (ii) rheumatologic disorders (hand osteoarthritis, rheumatoid arthritis, psoriatic arthritis, systemic sclerosis, etc.), (iii) musculoskeletal conditions (Dupuytren's contracture, trigger finger, etc.), (iv) diabetic ulcers on hands, and (v) amputation of fingers. The study protocol was approved by the Local Ethics Committee of Cukurova University.

Patients evaluation

The demographic features and clinical evaluations of patients including age, gender, body weights, heights, type of diabetes, diseases duration, medications, and comorbidity score were noted. Diabetic cheiroarthropathy was defined according to physical examination. The patients with positive table top sign or positive prayer sign were accepted as DCA. Prayer sign is described as the inability to close the gaps between palmar sides of opposite hands when the patient takes a praying position. Table top sign is defined as the inability to wholly contact the palmar side the hand on the table [3, 7, 11].

Laboratory outcomes including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), fasting and postprandial plasma glucose levels, and glycosylated hemoglobin (HbA1c) measurements were also recorded. A self-administered questionnaire (disabilities of the arm, shoulder and hand-DASH) was used to assess the functional disability of patients with DCA. This questionnaire includes 30 items evaluating the function of upper limbs using the 5-point scale. The total score is calculated within a range from 0 to 100. The higher scores represent a higher degree of functional disability [12].

Statistical analysis

The IBM SPSS version 20.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. Descriptive analysis was performed for the demographic variables. The normality of the variables was checked using the Shapiro-Wilk test. Non-parametric statistical methods (Mann-Whitney U test and Kruskall-Wallis test) were used to analyze data. Pair-wise comparisons were done by post-hoc analysis. The chi-square test was performed to compare the categorical parameters between groups. Post hoc power analysis was performed to find the observed power. Results with p values less than 0.05 were considered as statistically significant. Spearman's correlation test was used to analyze correlations.

Results

Two hundred and thirty-nine patients (160 female, 79 male) with diabetes were divided into three groups: (a) prediabetes ($n = 91$), (b) type 1 diabetes mellitus ($n = 59$), and (c) type 2 diabetes mellitus ($n = 89$). The demographic and clinical variables are given in Table 1. Accordingly, mean values for age, body mass index (BMI), and disease duration of the study population were 47.9 ± 15.4 years, 29.1 ± 5.6 kg/m^2, 80.5 ± 79.1 months, respectively.

DCA was determined in 35.1% of all patients. The distribution of DCA was similar in both genders ($x^2 = 0.097$). The frequency of DCA was higher in patients with prediabetes than in patients with type 1 and type 2 DM ($x^2 = 0.009$, post hoc power = 0.794). The comparison of demographic and clinical variables between patients with and patients without DCA are given in Table 2. According to the presence of DCA, there was no difference between groups in terms of diabetic nephropathy or diabetic retinopathy. However, the patients with DCA had higher rates of diabetic polyneuropathy ($x^2 = 0.005$).

The multinominal logistic regression analysis was performed to determine which variable played an important role for DCA. In the multivariable model, type of diabetes, presence of polyneuropathy, and fasting glucose level of the patient were found as the most effective risk factors determining DCA. The odds of DCA were 4.52 times higher (95% CI 2.16–9.47, $p < 0.001$) for patients with prediabetes, 3.82 times higher (95% CI 1.61–9.07, $p = 0.002$) for patients with polyneuropathy and 1.01 times higher (95% CI 1.00–1.01, $p = 0.004$) for each increased per unit of fasting glucose level after adjusting for age and sex.

DASH disability scores were different among diabetes groups having DCA ($p = 0.024$). Post-hoc analysis was performed to define the group that makes the analysis meaningful. According to the post-hoc analysis, DASH scores were significantly higher in prediabetic patients than that in type 2 DM group ($p = 0.021$) (Fig. 1). Additionally, in type 2 diabetes patients having DCA, a moderate-good correlation was found between HbA1c level and DASH scores ($r = 0.512$, $p = 0.010$). However, there was no correlation between other parameters and DASH scores.

When HbA1c levels were divided into three subgroups as normal (< 5.7%), prediabetes (5.7–6.4%), and diabetes (≥ 6.5%) proposed by the ADA, the frequency of DCA was greater in the normal HbA1c subgroup than that in prediabetes and diabetes subgroups ($x^2 = 0.001$). Therefore, the patients were evaluated in accordance with fasting glucose concentration dividing as normal, prediabetes, and diabetes defined by the ADA. DCA frequency was highest in prediabetes subgroup ($x^2 = 0.052$).

Discussion

Musculoskeletal disorders accompanying diabetes mellitus are well-known conditions within the medical field. A number of papers have been studied on what musculoskeletal impairments are observed and which involvements are frequently seen in diabetic patients [1, 13]. DM affects not only the lower limb, but also upper extremity, especially hand and fingers [14]. Hand involvement might imitate the rheumatological disorders, such as arthritis and systemic sclerosis [3, 4, 15]. Therefore, patients suffering from hand disorders should also be evaluated in terms of diabetes seeing more frequently than the rheumatologic diseases [16, 17]. With this in mind, we evaluated the frequency and confounders of DCA in prediabetic and diabetic subjects.

In the current study, we found that the frequency of DCA was 47.3% in prediabetes, 28.8% in type 1 DM, and 27.0% in type 2 DM. Musculoskeletal involvement related to type 1 DM and type 2 DM is common [1, 18–20], and impairment

Table 1 The demographic and clinical variables of the study population

	Prediabetes $n = 91$	Type 1 diabetes mellitus $n = 59$	Type 2 diabetes mellitus $n = 89$	Total $n = 239$
Age (years)	53.1 ± 10.5 (24–75)	26.5 ± 7.6 (18–44)	56.7 ± 8.6 (36–85)	47.9 ± 15.4 (18–85)
BMI (kg/m^2)	30.6 ± 5.4 (21.3–46.9)	24.3 ± 4.0 (16.2–35.5)	30.8 ± 5.0 (20.6–43)	29.1 ± 5.6 (16.2–46.9)
Disease duration (month)	21.9 ± 25.7 (3–120)	131.6 ± 72.1 (12–276)	106.6 ± 82.7 (4–480)	80.5 ± 79.1 (3–480)
Fasting glucose level (mg/dL)	109.1 ± 16.8 (86.0–218.0)	200.7 ± 99.7 (64.0–500.0)	150.1 ± 55.4 (79.0–356.0)	147.0 ± 70.2 (64.0–500.0)
HbA1c (%)	5.9 ± 0.6 (5.0–6.3)	9.2 ± 2.3 (6.2–16.0)	7.4 ± 1.6 (5.2–13.6)	7.3 ± 2.0 (5.0–16.0)
CRP (mg/dL)	0.5 ± 0.4 (0.1–1.5)	0.6 ± 0.5 (0.1–2.1)	0.5 ± 0.4 (0.1–2.1)	0.5 ± 0.4 (0.1–2.1)
Comorbidity scores	4.9 ± 3.3 (1–15)	4.5 ± 2.7 (2–14)	7.3 ± 4.2 (2–21)	5.7 ± 3.8 (1–21)
DASH scores	19.7 ± 28.3 (0–155.8)	8.9 ± 17.9 (0–68.3)	6.4 ± 15.3 (0–78.3)	12.1 ± 22.4 (0–155.8)

Values are given as mean ± standard deviation (minimum−maximum)

BMI body mass index, *CRP* C-reactive protein, *DASH* disabilities of the arm, shoulder and hand

Table 2 The comparison of demographic and clinical variables between patients with and patients without DCA

	Patients with DCA	Patients without DCA	*p*
Age (years)	51.5 (39.3–61.8)	51.0 (36.0–60.0)	0.165
BMI (kg/m^2)	29.0 (25.3–32.1)	28.9 (25.0–32.5)	0.740
Disease duration (month)	36.0 (12.0–119.5)	60.0 (12.0–144.0)	0.093
Fasting glucose level (mg/dL)	112.0 (106.0–188.0)	121.0 (105.0–160.0)	0.995
HbA1c (%)	6.3 (5.6–7.6)	6.9 (6.0–8.4)	*0.010**
Comorbidity scores	5.0 (3.0–7.8)	5.0 (3.0–7.0)	0.554

Values are given median and interquartile range (Q1-Q3). *$p < 0.05$, *p* value for the comparison of between-group, Mann-Whitney *U* test

DCA diabetic cheiroarthropathy, *BMI* body mass index

of muscle, bone, and joint may also be observed in prediabetic patients. Fatemi et al. showed that musculoskeletal manifestations in prediabetic patients were as high as in patients with DM. Accordingly, knee osteoarthritis, carpal tunnel syndrome, and rotator cuff tendinitis were observed as the most common musculoskeletal findings in both prediabetes and DM, while DCA was found in neither group [21]. On the other hand, DCA is a usual involvement of diabetes. The prevalence of DCA in diabetes is different among studies. According to the literature, the prevalence of DCA has been found to be between 8 and 66% in type 1 DM and 8–76% in type 2 DM [1, 22]. Moreover, DCA could be seen in the normal population and its prevalence might reach up to 26% [22]. To the best of our knowledge, there is no data about the prevalence or frequency of DCA in prediabetes.

The results of the present study showed that the distribution of DCA in prediabetic patients was detected higher than that in type 1 and 2 DM. According to the laboratory outcomes, DCA frequency was highest in patients with the normal HbA1c level and prediabetic fasting glucose concentration. This result was considered compatible with prediabetes. Moreover, a few risk factors including types of DM, the presence of polyneuropathy and fasting glucose level were found as an enhancing factor for DCA. The most accepted theory for the impairment of hand in patients with DM is that increased AGEs in collagen trigger the deterioration by preventing function of enzymes and glycated macromolecules and by accelerating oxidative stress and inflammatory responses [1, 5, 21, 23]. Production of AGEs by nonenzymatic glycation reaction is initiated by hyperglycemia, hyperlipidemia, and oxidative stress [23]. Also, AGEs are associated with age, serum uric acid, creatinine concentration, and decreased glomerular filtration rate [24]. The accumulation of end products is correlated with the duration of diabetes, serum glucose, and HbA1c levels [21]. The increased frequency of hand involvement in prediabetes could be explained by insidious high level of blood glucose causing AGEs accumulation. In their study, Jimenez et al., found that both prediabetes and DM had increased AGEs, which is accepted as a fundamental product causing their chronic complications [24]. Thus, the close relationship between musculoskeletal involvement and chronic complications can be elucidated by accumulation of AGEs.

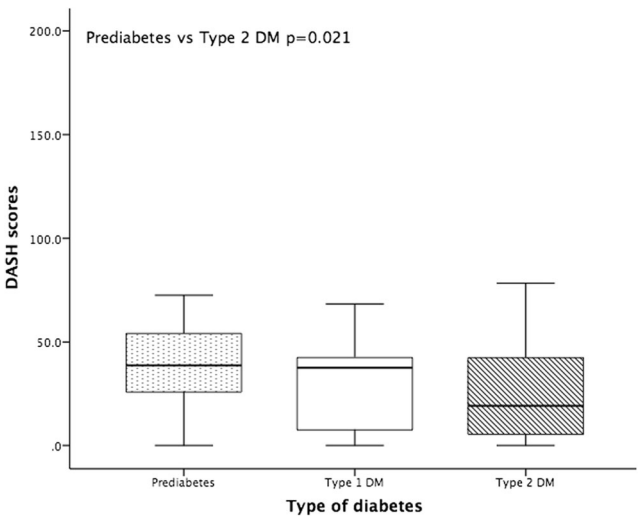

Fig. 1 Comparison of DASH scores among groups

In the current study, we also found that the functional impairment of hand accompanied by DCA was higher in prediabetes. The study by Larkin et al. observed the functional limitation of hand represented by high DASH scores in participants with DCA caused by type 1 DM [1]. Redmond et al. compared the hand function between patients with type 1 and 2 DM. Both groups revealed reduced grip strength. DASH scores were higher particularly in women [25]. In another study, Ramchurn et al. showed that the hand function assessed by Health Assessment Questionnaire was getting worse with the increasing number of musculoskeletal involvement in type 1 and type 2 DM [26].

The treatment of DCA includes non-pharmacological, pharmacological, and surgical therapy. Non-pharmacological treatment includes lifestyle changing, physical therapy, occupational therapy, and assistive devices [3, 27]. Lifestyle changing (cessation of cigarette smoking, weight reduction, etc.) is a cornerstone treatment to decrease the modifiable risk factors

of prediabetes and DM. Active and passive range of motion, joint mobilization, and daily stretching exercises are recommended in order to prevent contractures [3, 9, 27]. Orthosis may be useful in case of pain and impaired joint mobility. Pharmacological therapy is fundamentally based on the treatment of prediabetes and DM. Additionally, analgesics, nonsteroidal anti-inflammatory drugs and corticosteroid injections can be tailored. Moreover, recent animal studies have found that Alagebrium (ALT-711) could reduce the accumulation of AGEs by breaking AGE cross-links [3, 28]. Surgical therapy is recommended for certain cases with severe flexion contractures [3].

The limitations of the study include the nonhomogeneous spreading of gender and the lack of imaging modalities. On the other hand, the strength of the study is the sample size that was large enough to compare the results among groups.

In conclusion, in the current study, the frequency of DCA was analyzed, and deterioration of hand function was assessed in participants with prediabetes, type1, and type 2 DM. The higher rates of DCA and impaired hand function are found in prediabetes. In light of the results, it can be suggested that DCA could be an early sign of diabetic status. Prediabetes and/or diabetes mellitus should be kept in mind when assessing a patient with hand involvement, particularly cheiroarthropathy of the hands.

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Compliance with ethical standards

Disclosures None.

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